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Mechanistic insight into the protective and pathogenic immune-responses against SARS-CoV-2

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ABSTRACT

COVID-19 is a severe respiratory illness that has emerged as a devasting health problem worldwide. The disease outcome is heterogeneous, which is most likely dependent on the immunity of an individual. Asymptomatic and mildly/moderate symptomatic (non-severe) patients likely develop an effective early immune response and clear the virus. However, severe symptoms dominate due to a failure in the generation of an effective and specific early immune response against SARS-CoV-2. Moreover, a late surge in pathogenic inflammation involves dysregulated innate and adaptive immune responses leading to local and systemic tissue damage and the emergence of severe disease symptoms. In this review, we describe the potential mechanisms of protective and pathogenic immune responses in "mild/moderate" and "severe" symptomatic SARS-CoV-2 infected people, respectively, and discuss the immune components that are currently targeted for therapeutic intervention.

1. Introduction

The Coronavirus disease 2019 (COVID-19) has emerged in December 2019 in Wuhan City of China and is caused by a novel coronavirus, named as "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) based on its genetic similarity with the previously emerged SARS-CoV. Previously, the SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have created epidemics in 2002 and 2012, respectively (Xu et al., 2020b). SARS-CoV-2 causes severe acute respiratory syndrome and other clinical symptoms that are similar to the previous coronaviruses. However, due to its higher rate of human-to-human transmission, SARS-CoV-2 has created a devastating pandemic with a much higher toll on human lives and the economy (Hirano and Murakami, 2020). As per the World Health Organization (WHO), the number of confirmed cases and deaths worldwide are 756, 291,327 and 6,841,640, respectively, and the impact is still pressing with evolving subvariants and COVID-19 breakouts (Smith et al., 2022). The vital clinical symptoms of COVID-19 include fever, dry cough, fatigue, sputum production, dyspnea, myalgia, sore throat, and chills; while a small percentage of patient exhibits gastrointestinal infection-related symptoms (Li et al., 2020). There is a substantial prevalence of clinically asymptomatic infections, whereas a varying level of symptoms is associated with symptomatic COVID-19. Based on the disease severity, COVID-19 patients can be classified roughly into two categories, non-severe (asymptomatic and mild/ moderate) and severe. The mild/ moderate category includes patients with less severe clinical symptoms, including low-grade fever, cough, discomfort with no/ mild evidence of pneumonia, and not requiring ICU admission (Xu et al., 2020d; Yang et al., 2020; Zhao et al., 2020b; Zhu et al., 2020). The severe category includes patients with high viral load, severe pneumonia, acute respiratory distress syndrome (ARDS), other systemic symptoms such as organ failure, and may or may not need an ICU admission (Zhao et al., 2020c). Asymptomatic, mild/ moderate, and severe patients are all associated with viral shedding and human-to-human transmission. Most of the SARS-CoV-2 infected people (~ 80%) are non-severe that get recovered on their own or with

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conventional medications (Ma et al., 2021). Severe symptoms are observed mostly in older people and patients with pre-existing medical conditions, including cardiovascular disease, chronic respiratory diseases, and diabetes. Approximately 15% of patients exhibited symptoms of progressive pneumonia, and approximately 5% of patients develop ARDS and multiple-organ failure (Cao, 2020; Xu et al., 2020c). Some COVID-19 patients also exhibit persistent clinical manifestations for several months beyond the onset of recovery, a condition recognized as the "long COVID" or post-acute sequelae SARS-CoV-2 infection (PASC) (Davis et al., 2023). These observations raise an important question; why do some individuals develop severe disease whereas many others do not?

Frequent battles between viruses and their hosts lead to the evolution of both hosts and virus species in a manner that can benefit their survival (Enard et al., 2016). Although viral pandemics could activate the process of natural selection and species evolution, they often cause mass casualty and economic loss. Coronaviruses have co-existed with animals, possibly for millions of years (Wertheim et al., 2013), and diverse species of bats and birds act as natural hosts. When viruses, including coronaviruses, undergo cross-species transmission, they cause more severe pathogenesis (Ziegler et al., 2020). The chronology of the SARS-CoV-2 evolution is discussed in detail in many reviews (Jin et al., 2020; Rothan and Byrareddy, 2020). The immune system, of the alternative host, is a vital defense mechanism to fight against viruses. The jaw vertebrates have evolved a specialized adaptive immune system in addition to the more ancient innate immune system to combat such infections. The innate and adaptive immune system of the host co-ordinates with each other to orchestrate a cascade of immune reactions leading to the effective elimination of the pathogen and generation of immune memory (Cooper and Alder, 2006). The primary strain, which started in China's Wuhan city, underwent significant evolution of its genome (via random mutations), leading to mutants or genetic variants. The development of new SARS-CoV-2 strains and subvariants has exacerbated the problem. As per the CDC, the strains that became concerning includes, B.1.1.7 [Alpha (α) – 2020, United Kingdom], B.1.351 [Beta (β) - 2020; South Africa], P.1 [Gamma (γ) - 2020; Brazil], B.1.617.2 [Delta (δ) - 2020; India], and B.1.1.529 [Omicron (O) - 2021; South Africa. The other important variants are B.1.427/B.1.429 [Epsilon (ε) – 2020; USA)], P.2 [zeta (ζ) – 2020; Brazil], B.1.525 (Eta (η) - 2020; Multiple countries), P.3 [Theta (θ) – 2021; Phillipines], B.1.526 [Iota (ι) – 2020; USA], B.1.617.1 [Kappa (κ) – 2020; India], C.37 [Lambda (λ) – 2022, Peru) (Aleem et al., 2022). As of January 2023, Omicron subvariants accounts for > 98% of variant of concern (VOC), as per SARS-CoV-2 genomic sequencing data submitted to "Global Initiative on Sharing Avian Influenza Data (GISAID, gisaid.org)" during February 2022 through January 2023. The current concerning omicron subvariants are XBB.1.5, CH.1.1, and BF.7 and exhibits strong immune evasion (Callaway, 2023). Numerous mutations, particularly in the S protein, are present in the novel strains, augmenting the virus-angiotensin-converting enzyme-2 (ACE-2) binding efficiency, resulting in high infections, mortality rates, and new waves of illness worldwide (Malik et al., 2022).

SARS-CoV-2 induces acute inflammation and dysregulation of innate and adaptive immune systems of the human host, leading to local and systemic tissue damage in severe COVID-19 patients. The symptoms are either absent or diminished in asymptomatic and mild/moderate disease conditions (Huang et al., 2020; Xu et al., 2020d). A comprehensive understanding of the roles of innate and adaptive immune responses during the "mild/ moderate" and "severe" disease conditions is lacking (Huang et al., 2020). Therefore, understanding the host-pathogen interactions, immune-mediated clearance, and immuno-pathogenesis of SARS-CoV-2 infection can help hypothesize, design experiments, and strategize effective solutions to combat the COVID-19 pandemic or similar pandemics in the future. This review explores the potential immunological events in the human host during "effective clearance" as well as during the "establishment of severe clinical symptoms" of SARS-CoV-2 infection. We also summarize potential therapeutic strategies targeting immune components to control the severity of COVID-19.

2. The infection process of SARS-CoV-2

COVID-19 is highly contagious, and human-to-human transmission occurs when a patient's respiratory droplets get deposited in the nasal, oral, and conjunctival mucosa of an uninfected person via droplets, aerosol, and physical contact (Banerjee et al., 2021; Sanyal and K. Paul, 2021). SARS-CoV-2 mainly targets the respiratory tracts, but other organs like the gut, heart, blood vessels, kidney, brain, and the central nervous system are also affected. Epithelial cell lining of the nasal passage, upper respiratory tract, and lungs (especially the goblet, ciliated, and type II alveolar cells) are the primary infection targets due to the higher expression of SARS-CoV-2-interacting host proteins (Roy et al., 2021; Salian et al., 2021; Sungnak et al., 2020; Xu et al., 2020a). Other cell types like endothelial cells, fibroblast, myeloid cells, lymphocytes, and epithelial cells in many organs are also potential infection targets. (www.covid19cellatlas.org.) (Akhmerov and Marban, 2020; Asadi-Pooya and Simani, 2020; Cheng et al., 2020; Henry and Lippi, 2020; Lukassen et al., 2020; Muus et al., 2020; Wang et al., 2020). Further spread of the coronavirus from the lung to other organs may involve circulating infected immune cells (e.g., lymphocytes, monocytes, macrophages) (Gu et al., 2005; Muus et al., 2020; Roy et al., 2021). Infection and associated immunopathology of other organs need further investigation. The target-cell entry mechanisms of SARS-CoV-2 is critical in host-immune monitoring and is briefly discussed in the following section.

SARS-CoV-2 is a positive-sense single-stranded enveloped RNA (+ssRNA) virus. The genome is annotated to encode as many as 14 open reading frames (ORFs) and encodes proteases, RNA-dependent RNA polymerase, and several structural proteins (Fig. 1). The essential SARS-CoV-2 structural proteins are the Spike (S) glycoprotein, Envelope (E) protein, Membrane (M) glycoprotein, and Nucleocapsid (N) protein. The SARS-CoV-2's S protein attaches to the entry receptor angiotensin-converting enzyme 2 (ACE2) on the host cell surface, followed by its proteolytic activation. Cell surface Transmembrane protease serine 2 protein (TMPRSS2) and lysosomal cathepsin protease-mediated proteolytic cleavage of viral S protein is important for viral endocytosis and infection (Hoffmann et al., 2020). The internalized SARS-CoV-2 undergoes the viral replication cycle (Fig. 1) (Li et al., 2020; Zhou et al., 2020a).

3. Immune response to SARS-CoV-2

The anti-SARS-CoV-2 immune response is most likely initiated in the infected respiratory cells by the activation of various immune components to ameliorate disease progression. COVID-19 disease severity seems to largely depend on the hosts' immunity against SARS-CoV-2. Asymptomatic and mild/ moderate symptomatic patients, who likely develop a compelling early immune response, exhibit successful viral clearance. While patients with severe symptoms (especially the elderly and those with pre-existing health conditions) generate a dysfunctional early immune response against SARS-CoV-2 leading to life-threatening complications (Huang et al., 2020; Xu et al., 2020d). Inadequate early immune response allows immune evasion, viral propagation, the spread of infection and subsequently cell death, and the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These signals trigger late uncontrolled inflammation (local and then systemic) and substantial tissue damage.

The immune system of mammals has been sub-grouped into innate and adaptive immune systems. The innate and adaptive systems are different in terms of their response time, specificity, and type of immune cells involved, but both the systems coordinate with each other in generating effective anti-viral immunity. In the subsequent sections, we

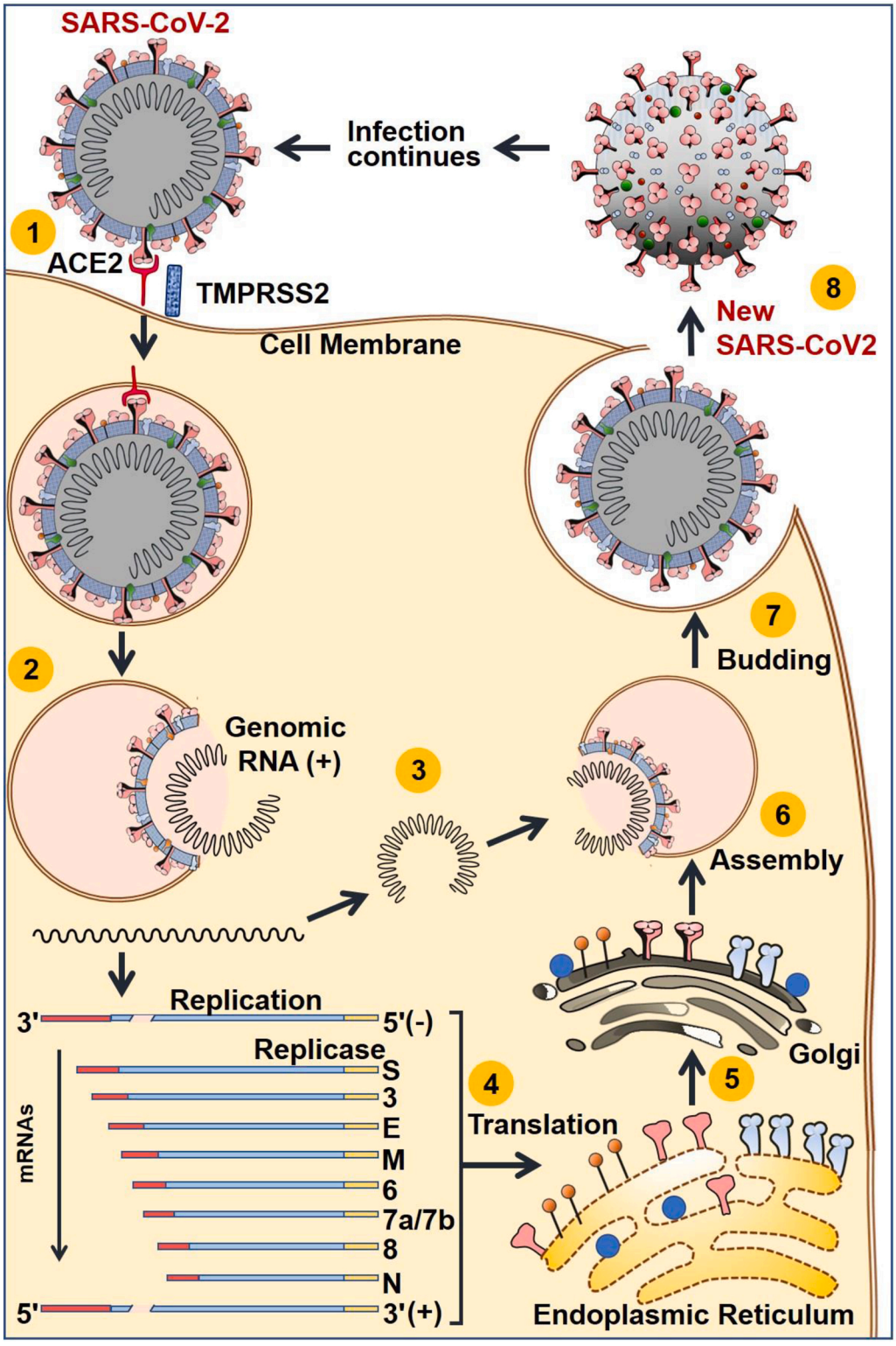

Fig. 1. The infection cycle of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). 1. The key to the coronavirus infection is its binding to the receptor angiotensin-converting enzyme 2 (ACE2) on the host cells. SARS-CoV-2 spike protein (S) is primed by the transmembrane protease, serine 2 (TMPRSS2), leading to the interaction with the membrane-bound form of ACE2. This interaction is a critical step in viral internalization. The routes employed by SARS-CoV-2 include endocytosis and membrane fusion. 2. After the viral entry into the host cell, followed by peeling off the viral envelope, the viral genomic RNA is released in the cytoplasm. 3. The virus hijacks the host machinery to transcribe, replicate, and translate. ORF1a and ORF1b of the genomic RNA are translated into nonstructural proteins. Some nonstructural proteins form a replication/transcription complex (RNA-dependent RNA polymerase, RdRp), which use the (+) strand genomic RNA as a template. The (+) strand genomic RNA produced through the replication process becomes the genome of the new virus particle. SARS-CoV-2 virus sub genomic RNA encodes four major structural proteins: The S protein, the nucleocapsid (N) protein; the membrane (M) protein; and the envelope (E) protein. 4. The synthesized proteins are trafficked from the endoplasmic reticulum (ER) to the Golgi. Furthermore, the nucleocapsid protein is combined with the (+) strand genomic RNA. 5. The protein and RNA assemble into the complete virus particle in the Endoplasmic Reticulum-Golgi apparatus compartment. 6. The viral particles are finally excreted to the extracellular region for new infections.

will discuss innate and adaptive immune responses to SARS-CoV-2 infection.

3.1. Innate Immune Response to SARS-CoV-2

Innate defense against SARS-CoV-2 initiates at the level of physical barriers and mucociliary clearance in the upper respiratory tract. As the SARS-CoV-2 breaches the physical barriers and infects its target cells, a coordinated host innate immune response is rapidly mounted upon the recognition of viral PAMPs (Saksena et al., 2023). Although the innate immune response is considered as non-specific, a limited specificity is generated by the engagement of the types of receptors and sensors present at the cell surface, endosome, and cytoplasm for the detection of PAMPs (Reikine et al., 2014). Besides receptor and sensors-mediated innate immune signaling, the host's complement systems also target the virus and virus-infected cells to aid the innate-immune cell response

(discussed in Section 3.3). The generation of an effective innate immune response is essential to facilitate the development of a more specific adaptive immune response that involves lymphocytes (discussed in Section 4). SARS-CoV-2 infection-associated outcome can be attributed to an appropriate host innate immune response. This review features type-I interferon (IFN-I) and pro-inflammatory cytokines, innate immune cells, and complement activation.

3.1.1. IFN-I and pro-inflammatory cytokines in SARS-CoV-2 infected patients

To successfully combat and generate immune memory, the host's cells generate an early innate immune response that includes the production of antiviral IFN-I and proinflammatory cytokines soon upon viral detection (Kikkert, 2020). Based on preclinical and clinical data from coronavirus epidemics, it is apparent that a large proportion of the human population can generate such an early innate immune response despite virus-mediated subverting mechanisms (discussed in Section 3.1.1.). However, a significant proportion of patients fail to do so, which leads to uncontrolled immune cell-mediated inflammation and severe symptoms (discussed in Section 3.1.2.). Therefore, depending on the host's immunity, this innate immune response to SARS-CoV-2 could be protective or detrimental, which is primarily determined by the timing of its onset. (Kikkert, 2020). There are limited reports about the nature and composition of early IFN-I and proinflammatory cytokines production in patients who have recovered from a SARS-CoV-2 infection. At the late stage, a decreased level of IFN-I (IFNα, Interferon-stimulated genes (ISGs)) and IFN-II (IFN-γ) along with an elevated level of many pro-inflammatory cytokines and chemokines (such as IL-6, Tumor, necrosis factor (TNF), IL-8, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, CXCL10, MCP1, and CCL3) has been documented in the severe COVID-19 patients as compared to the non-severe COVID-19 patients (Cao, 2020; Magro et al., 2020; Prompetchara et al., 2020; Smith et al., 2022). The elevated cytokines level is characterized as a cytokine storm, which seems to be significantly contributed by the innate immune cells and to some extent by the adaptive immune cells as well.

3.1.2. Effective early innate immune response against SARS-CoV-2

A study of 10 mild/ moderate symptomatic COVID-19 patients has indicated generation of an early pro-inflammatory (TNFα, IL6, IL10, and IFN-γ) response that subsided as the infection resolved (Diao et al., 2020a). However, a shortcoming with this study is that IFN-I and many other inflammatory cytokines (IL-1β, MCP-1, CCL2, CXCL10, etc.) were not monitored. Smith et al. employed multi-IFN subtypes digital ELISA to demonstrate poor activation and modulation of type I interferon immunity in COVID-19 patients who were critically sick, as compared to uninfected and moderate group (Smith et al., 2022). A recent report with 100 mild and sever patients in Tehran suggests that the reduced levels of IFN-I signaling and higher autoantibody against IFN-α may be associated with the severity of the COVID symptoms in patients (Soltani-Zangbar et al., 2022). Although, higher autoantibody against IFN-α may potentially dampen the antiviral role of IFN-I and making life threatening condition of the patient (Bastard et al., 2020), a detailed time-course, (especially at early time points) monitoring of IFN-I and important cytokines would be needed to stratify patients for better therapeutic intervention.

IFN-I acts in a paracrine manner on many cell types (e.g., virally infected cells, alveolar macrophages, neutrophils, dendritic cells, etc.) expressing interferon receptors "IFNAR". IFN-I binds to IFNAR and activates the JAK-STAT pathway, which induces a battery of Interferon-stimulated genes (ISGs) with diverse antiviral and immune-modulating functions. SARS-CoV-2 being a (+)ssRNA virus, may induce IFN-I and other proinflammatory cytokines in the infected cells and surrounding innate immune cells similar to other RNA viruses (Hoffmann et al., 2020; Prompetchara et al., 2020; Zhou et al., 2020a). The generation of anti-viral early innate immune response including IFN-I by RNA virus should ideally engage sensors in endosomes (Toll-like receptors "TLR-3" and "TLR-7")], cytoplasm (Retinoic acid-inducible gene-I "RIG-I", Melanoma differentiation-associated protein 5 "MDA-5")] and potentially other sensors (Takeuchi and Akira, 2009) (Fig. 2). A couple of SARS-CoV and MERS-CoV infections studies in the mouse model, have noted a difference in sensing of coronavirus derived RNA in lung epithelial cells (key target cells) and other innate immune cells (Channappanavar et al., 2019b). For example, to sense MERS-CoV derived RNA, innate immune cells such as macrophages can engage both RIG-I/ MDA5 and TLR7 pathways, whereas epithelial cells engage the TLR7 pathway only. Recent studies involving modeling of early SARS-CoV-2 infection using primary lung epithelial cells, epithelial cell lines (Calu-3) and induced pluripotent stem cell-derived airway epithelium cells, suggest that SARS-Cov-2 infection triggers interferon response via MDA5, LGP2 and NOD1 sensor proteins but not the TLR3. Contradictory results about the involvement of RIGI is also published (Thorne et al., 2021; Yin et al., 2021). IRF3, IRF5 and NF-kB/p65 transcription factors seems to induce the interferon production (Yin et al., 2021). The interferon and cytokine produced by infected cells supernatant can strongly activate macrophages. They argue that inflammatory state of the lungs' macrophages and epithelial cells may determine the disease severity as SARS-CoV-2 infection drives higher inflammatory response when macrophages and epithelial cells are pre-exposed to inflammatory signals in vitro (Thorne et al., 2021). However, it remains to be determined how this recent zoonotic virus adapted to evade the innate immune response of a new host (humans) and the mechanisms that render it insensitive to the IFN signaling induced by the infection. Questions that remains unanswered are, first, whether severe patients have defects in eliciting IFN-I response, second, which components of sensing mechanism contributes to this defect, associated genetic mutations (e.g. TLR3, TLR7) and finally, whether young adults mount stronger IFN-I response as compared to older people? Characterizing the mechanistic differences of these early innate immune response in young adults and older people may help devise strategies to save severe COVID-19 patients.

3.1.3. SARS-CoV-2 may limit the host's early IFN-I response

SARS-CoV-2, like other viruses, has evolved mechanisms to impair the early anti-viral IFN-I response to evade the host's immunity by implementing multiple potential mechanisms. SARS-CoV-2 may interfere with IFN-I response by the following mechanisms. First, SARS-CoV-2 may limit the generation of the viral-PAMPs (RNA) by endoribonuclease activity of non-structural protein "NSP15" (Hackbart et al., 2020). Second, the impaired ubiquitination-mediated activation of RNA-sensor "RIG-I" by nucleocapsid (N) protein might cause a shift in the RNA-sensing (Hu et al., 2017). Third, ORF of SARS-CoV-2 may limit IFN-I production, similar to SARS-CoV. SARS-CoV encoded proteins, such as ORF6, and ORF3b that may dampen IFN-I effect by acting on signaling up/ downstream of the IFNAR receptor (Lokugamage et al., 2020). Fourth, delayed exposure of PAMPS to induce the IFN-I signaling. Indeed, recent findings suggest that ORF6 of SARS-CoV-2 inhibit the interferon response by directly interacting with proteins involved in cytokine signaling. For example, ORF6 is shown to interact with STAT1, an important mediator of cytokine signaling, to prevent STAT1 localization in the nucleus, thereby preventing the interferon response (Miyamoto et al., 2022), or by directly interacting with the cellular trafficking protein-Rae6 to block the export of mRNAs encoding IRF1 (interferon regulatory factor 1) and the sensor protein- RIG1 (Haagmans et al., 2022). Delayed mounting of IFN-I response by infected cells is evident by several studies (Thorne et al., 2021). Therefore, possibly, an early IFN-I therapy may ameliorate SARS-CoV-2 infection (Lokugamage et al., 2020). The model of early IFN-1 theory is further evaluated by screening of all 12 IFN-1 subtypes against SARS-CoV-2 infection which identified a group of effective IFN subtypes that can be therapeutically useful to treat acute infection upon SARS-Cov-2 exposure (Schuhenn et al., 2022).

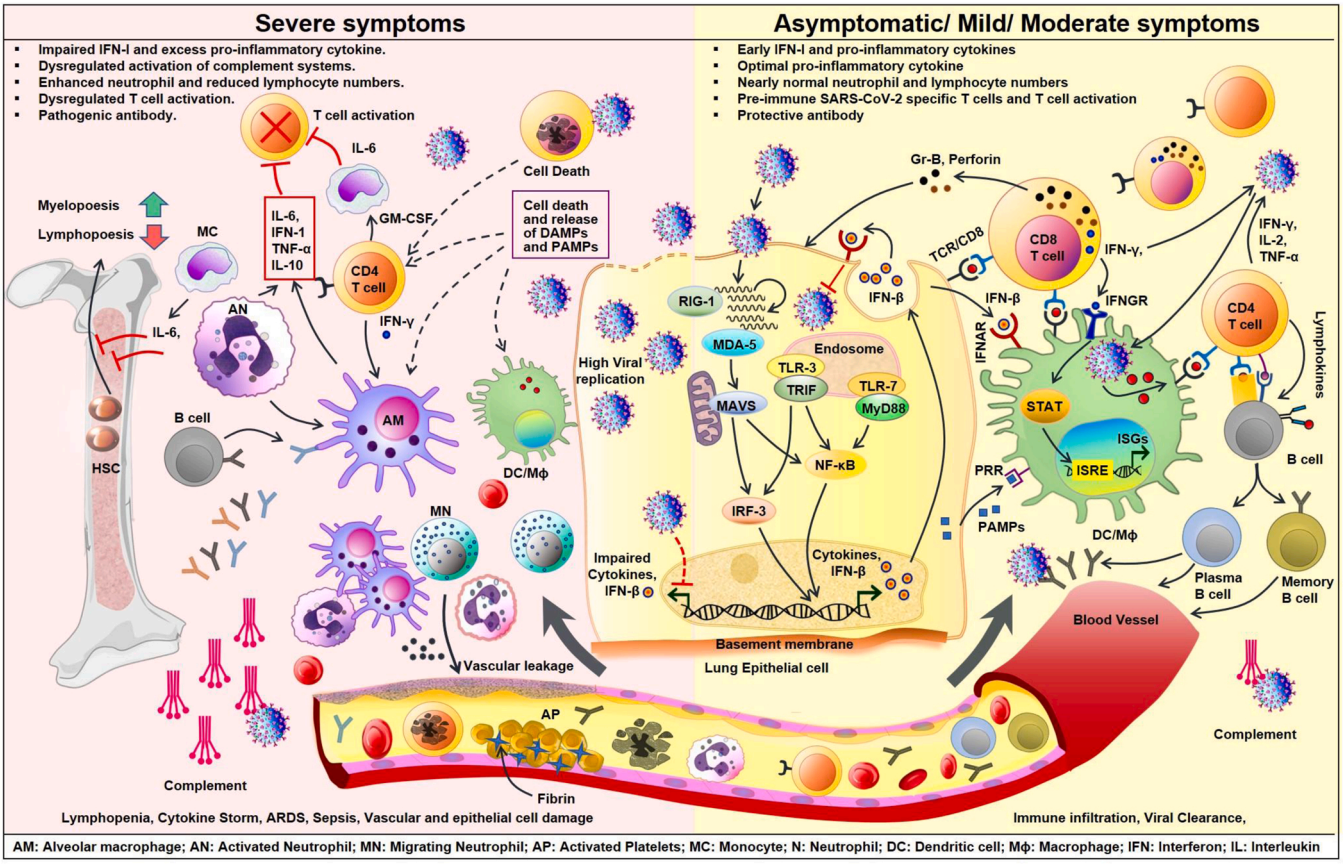

Fig. 2. Mechanistic insight into the immune-responses against SARS-CoV-2 during non-severe (asymptomatic/ mild/ moderate) and severe condition. SARS-CoV-2 infects lung epithelial cells as the primary target. Intracellular sensing of viral RNAs by cytosolic RIG-I/ MDA5/ and membrane-bound TLR-3 and TLR-9 can lead to antiviral signaling. RIG-I/MDA5 acts through MAVS, and TLR-3 and TLR-7 act through TRIF and MYD88, respectively, to activate IRF3 and NF-kB to produce host defense molecules such as IFNs, proinflammatory cytokines, and chemokines. The secreted IFNs induce the expression of interferon-stimulated genes (ISGs) that play crucial roles in inhibiting the viral propagation and activation of innate and adaptive immune responses. Moreover, secreted cytokines, viral PAMPs, and DAMPs can activate innate immune cells and cause local inflammation. Left side (immune response in severe condition): In an inadequate early immune response, uncontrolled viral propagation and aberrant host cell death can release higher amounts of DAMPs and PAMPs. Elevated levels of DAMPs and PAMPs can initiate and perpetuate resident immune cell activation and promote infiltration of innate (DC, MQ, 2 AM cells) and adaptive (CD4 + T cells) immune cells to produce a higher amount of pro-inflammatory cytokines, chemokines and IFNs. The released chemokines and cytokines can recruit more immune cells to the site of infection by blood vessel leakage and chemotaxis and further perpetuate the production of cytokines to aggravate the inflammation further. This elevated positive pro-inflammatory feedback loop is characterized as a cytokine storm (IL-6, IP-10, MIP1α, MIP1β and MCP1, TNF, IL1-β, etc.) that can lead to the damage of infected and distant organs. Elevated cytokines levels and excess cell death-released antigens may cause continuous, unrestricted stimulation of memory cells. Stimuli-activated memory B cells can trigger polyclonal antibody production (likely non-neutralizing) that may further enhance SARS-CoV-2 infection through antibody-dependent enhancement (ADE) and contribute to multi-organ damage. Higher cytokine (likely IL-6) levels may lead to inhibition of T cell activation and lymphopoiesis. Right Side (immune response in non-severe condition): The optimal local inflammation attracts dendritic cells (DCs), macrophages (Mϕ) and virus-specific lymphocytes to the site of infection. Antigen-presenting cells (DC, Mϕ, B cell) can present viral antigen to CD8 + T cells and CD4 + T cells. Activated CD8 + T cells can eliminate the infected cells by secreting granzyme B, perforin, and IFN-γ. Activated CD4 + T cells can produce IFN-γ, proinflammatory cytokines, and trigger differentiation of viral antigen-specific B cells. B cells differentiated into plasma cells and memory B cells are specific to viral antigens. The plasma cells produce optimal antibodies (higher titer of neutralizing antibodies), which can lead to the clearance of the virus. These timely, regulated, and coordinated immune responses effectively clear the virus without causing any damage to the organ (lung) and provide long term immunity.

3.1.4. Pathogenic delayed pro-inflammatory cytokines production in severe COVID-19 patients

Approximately 15–20% of COVID-19 patients with severe symptoms are unable to mount an early efficient innate immune response, which leads to uncontrolled viral propagation, aberrant cell death and release of virus-associated PAMPs, and cellular DAMPs (including nuclear DNAs). Aberrant cell deaths may induce acute lung injury (ALI) and danger signal-triggered immune responses, inflammation, and associated immunopathology in COVID-19 patients via multiple mechanisms (discussed in Section 3.1) (Rock and Kono, 2008). Briefly, the release of PAMPs and DAMPs from infected lung epithelium can engage many sensors/ receptors in the resident and infiltrated innate immune cells, leading to massive production of pro-inflammatory cytokines that may have various effects at the local and systemic level (Fig. 2). The surge in cytokines and chemokines can stimulate the infiltration of neutrophils, monocytes-macrophages, dendritic cells, T cells, B cells, antibodies, and activated complement proteins in the lung parenchyma. The infiltrated immune cells can ultimately aggravate the patient's condition by contributing to the overproduction of a variety of cytokines (cytokine storm), and immune-mediated tissue and vasculature damage. Systemically, some of the cytokines may act on the hematopoietic stem/ progenitor cells to trigger an increased production of neutrophils and other myeloid cells along with a concomitant decrease in lymphocyte production (leading to lymphopenia). Many of the cytokines can also exert a pathogenic effect on distant organs such as blood vessels, hearts, liver, kidney, and intestine (Zaim et al., 2020). Experimentally, similar phenomena were also reported in a mouse model of the MERS-CoV study (Channappanavar et al., 2019a). Fig. 3 describes the kinetics of clinical

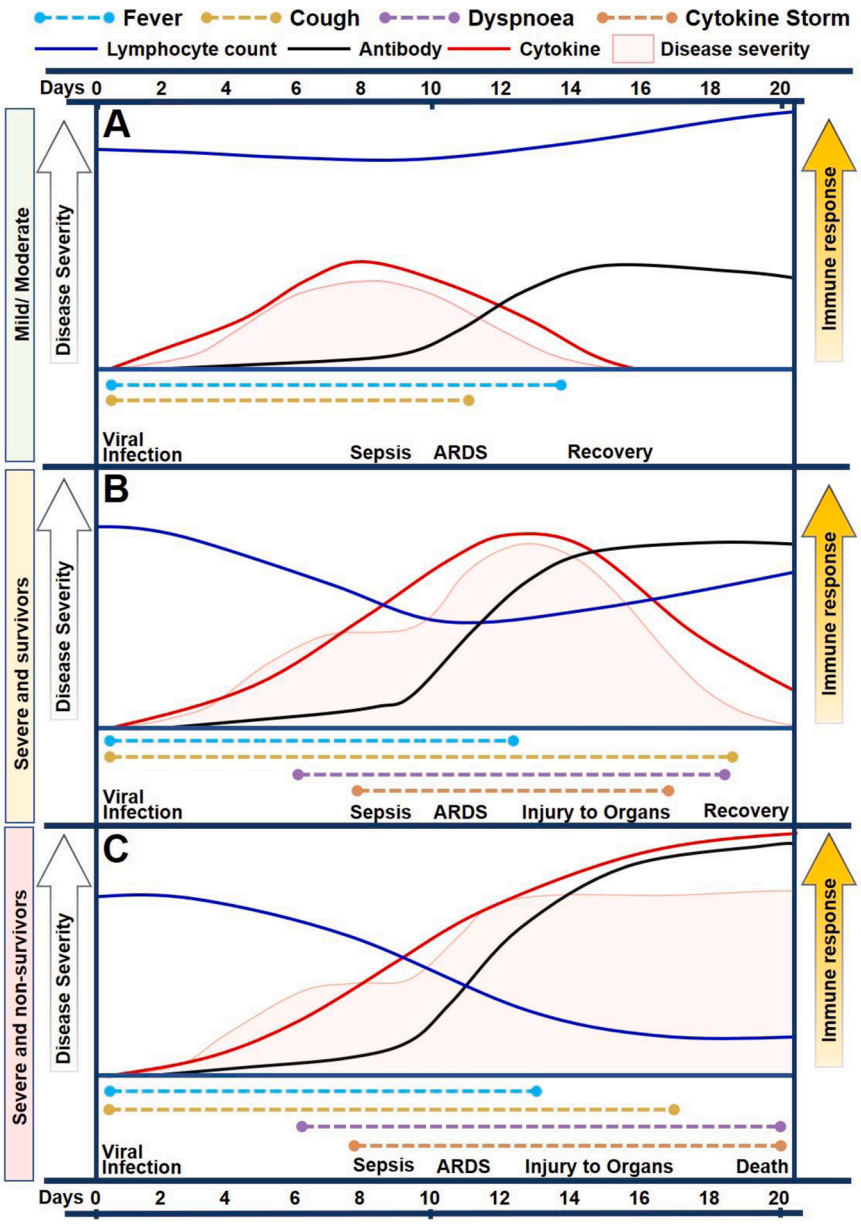

Fig. 3. Proposed kinetics of immune responses and their relationship with the severity of the SARS-CoV-2 infection in non-severe (mild/ moderate) vs. severe patients (survivors and nonsurvivors). Graphical representation of various immune responses kinetics and disease pathology in different categories of COVID-19 patients based on the current understanding. Panels A, B, and C represent the kinetics of immune responses and disease pathology in mild/ moderate, severe survivor and severe non-survivor patients, respectively. The x-axis in each panel represents the progression of the disease symptoms/ pathology with a tentative timeline in days (Zhou et al., 2020). The left y-axis represents the severity of the disease for each patient category. The right y-axis represents the relative immune responses (arbitrary representation) of IFNs and proinflammatory cytokines (Red line), SARS-CoV-2 specific antibody (black line), and 3 lymphocytes count (blue line). The scales on the y-axis are relative to the maximum amplitude in non-survivors and the comparison among the panels is qualitative. The kinetics of antibody production in severe and non-severe cases are described by Thevarajan et al. (2020) and Zhou et al. (2020a). The kinetics of lymphocytes number in nonsevere and severe is described by Tan et al. (2020) and Wang et al. (2020). The IFNs and proinflammatory cytokine production kinetics are compiled from SARS-CoV-2, SARS-CoV and MERS-CoV infection (Zhou et al., 2020c, Oberfeld et al., 2020). Data reported in multiple articles are combined to recapitulate the kinetics of disease progression and immune response and may not accurately represent all patients (Zhou et al., 2020).
tables.

courses of major symptoms and cytokine response in mild/ moderate and severe COVID-19 patients. At this stage of the disease, it will be essential to identify each of the detrimental immune components (cell types and cytokines) for better management of COVID-19.

3.2. *Innate immune cells in SARS-CoV-2 infected people*

Limited data exists about the kinetics of innate immune cell number and activity changes in asymptomatic and mild/ moderately symptomatic SARS-CoV-2 infected people. Non-severe COVID-19 patients show a near-normal number of circulating neutrophils, NK cells, and monocytes but a drastically lower percentage of inflammatory monocytes as compared to the normal healthy control. In contrast, the severe COVID-19 patients exhibit drastically enhanced neutrophils, normal NK cells and marginally reduced monocytes in their blood as compared to the non-severe patients (Chan et al., 2020; Qin et al., 2020; Tan et al., 2020; Wang et al., 2020). Severe patients have a relatively higher percentage of inflammatory monocytes (CD14 +CD16 +) as compared to non-severe patients (Zhou et al., 2020b). The time course study shows an increase of neutrophil count in non-survivor as the disease progresses, whereas surviving patients exhibit a near-normal level of neutrophil counts as they recover (Chan et al., 2020; Qin et al., 2020; Tan et al., 2020; Wang et al., 2020).

Additionally, the patient's lungs may also exhibit increased infiltration of innate immune cells, including neutrophils, activated monocytes, dendritic cells, and mast cells (Chen et al., 2020). Neutrophilia may result due to an increased myelopoiesis in response to cytokines produced during the onset of uncontrolled inflammation (Qin et al., 2020). Moreover, the increased lung-specific immune-infiltration could be due to cytokine-induced increased vascular permeability and blood stasis (Magro et al., 2020; van de Veerdonk et al., 2020). The ALI-associated increased circulating and lungs infiltrated innate immune cells can cause a cytokine storm, which is strongly associated with the ARDS and poor outcome of COVID-19 patients.

3.3. *Complement activation in SARS-CoV-2 infected people*

Complement activation is one of the innate immune mechanisms that

is involved in the clearance of viruses (Agrawal et al., 2017). There are three described complement activation pathways, the classical pathway, alternative pathway, and the lectin pathway (LP). LP is initiated by binding of mannose-binding Lectins (MBL) to mannose residues on the viruses and virus-infected cell surface. MBL, in turn, binds to the SARS-CoV infected cells and the SARS-CoV spike protein resulting in the activation of the complement system (Lau et al., 2005). Activation of these pathways converges on a common signaling cascade that includes the production of complement components, such as C3a and C5a, that are inflammatory mediators and initiates pathogen opsonization and lysis of the virus-infected cells (Campbell and Kahwash, 2020).

The role of activated complement is not yet reported during the development of an effective immune response leading to viral clearance in mild/ moderate symptomatic patients. Clinical studies have shown that pulmonary tissues and sera from the severe COVID-19 patients have a significantly higher level of terminal complement components (such as C5b-9, C4d, MASP2, and C5a), suggesting systemic activation of some of the complement pathways (Gao et al., 2020b; Magro et al., 2020). Aberrant activation of the complement system leads to immune-mediated severe symptoms in various virus infections, including coronaviruses (Campbell and Kahwash, 2020; Gralinski et al., 2018; Sun et al., 2013). The elevated level of activated complement proteins in COVID-19 patients (both in tissues and circulation) could be due to first, the abundantly produced SARS-CoV-2 N-protein, which binds and potentiate MBL-mediated activation of MASP-2 (an essential component of lectin pathway) (Gao et al., 2020b; Zhang et al., 2020). Second, SARS-CoV-2 S-protein, which co-localizes with the complements, C4d, and C5b-9 in many severe patients (Magro et al., 2020). Third, autoantibodies might be produced in the severe COVID-19 patients similar to SARS-CoV infection, which is known to trigger the complement activation in the autoimmune diseases (Chang et al., 2021; Thurman and Yapa, 2019) (discussed in Section 4.2). The role of activated complement in severe lung disease is supported by a study using a complement protein mutant mice ($C3^{-/-}$) model of SARS-CoV infection (Gralinski et al., 2018). Activated complement contributes to the lung disease severity by various mechanisms that are described elsewhere (Markiewski and Lambris, 2007; Stoermer and Morrison, 2011). The complement C3a, C4a, and C5a proteins can act as anaphylatoxins with potent proinflammatory properties and can contribute to inflammatory cell recruitment and neutrophil activation in COVID19 (Afzali et al., 2021; Bosmann and Ward, 2012).

Considering the role of Complement-activation in COVID-19 patients, targeted therapy has emerged as an effective treatment modality and several clinical trials have been designed to target C3, C4, and C5. The ITHACA trial (NCT04382755) randomized C3 inhibitor AMY-101 in COVID-19 patients with severe hypoxemia. AMY-101 reduced oxygen dependence, CRP, ferritin, thrombin, and 28-day survival, but was not statistically significant (Skendros et al., 2022). In the phase 2 experiment PANAMO (NCT04333420), severe COVID-19 patients were administered the anti-human C5a monoclonal antibody IFX-1. Nevertheless, no statistically significant improvements in clinical endpoints were seen in severe COVID-19 patients treated with IFX-1 (De Leeuw et al., 2022). Eculizumab, a monoclonal antibody targeting C5, may increase survival and minimize hypoxia in severe COVID-19 patients (Annane et al., 2020).

4. Adaptive immune response to SARS-CoV-2

The adaptive immune response is relatively delayed (usually takes 3–5 days) and mostly pathogen-specific. The lymphocytes (B and T cells) are critical components of the adaptive immune system. Co-ordinated actions of various types of lymphocytes help maintain inflammatory response and provide specific and robust protection against a pathogen. SARS-CoV-2 infection-associated outcome could be attributed to a regulated or dysregulated adaptive immune response in the host. The aspects of adaptive immune components discussed in this review include lymphocytes number, B cell and antibody function, T cell function, and memory lymphocyte generation.

4.1. Number of lymphocytes in SARS-CoV-2 infected people

Non-severe COVID-19 patients show a near-normal number of circulating lymphocytes whereas severe COVID-19 patients exhibit drastically reduced number of lymphocytes in their blood, a condition termed as Lymphopenia (Chan et al., 2020; Qin et al., 2020; Tan et al., 2020; Wang et al., 2020). Analysis of lymphocyte subsets in severe cases shows a significant reduction in the number of T cells, mainly the $CD4^{+}$ T and NK cells, but without any significant changes in B cell number (Qin et al., 2020; Wang et al., 2020). The detailed time-course analysis shows that non-severe patients-maintained lymphocytes $> 20\%$ and severe patients who died show a gradual reduction of lymphocytes to reach $< 5\%$. Whereas severe patients who got cured initially show reduction ($<10\%$) followed by recovery to near-normal level (15–20%) of lymphocytes (Tan et al., 2020).

The cellular mechanism of observed lymphopenia and increased neutrophil-lymphocyte-ratio in severe COVID-19 patients could be due to the following reasons and beyond. First, severe patients may be characterized by higher infiltration of the lymphocytes over neutrophil at the site of infection. Proinflammatory cytokine (such as IL-6) and chemokine (MCP1, CXCL-10) may preferentially recruit lymphocytes and monocytes at the site of infection (McGonagle et al., 2020). Second, reduced lymphocyte production by skewed hematopoietic lineage specification and/ or by inhibition of lymphocyte proliferation. Inflammation can skew hematopoietic fate decision towards the myelopoiesis with a concomitant decrease in lymphopoiesis (Chan et al., 2020; Duggan et al., 2017; Pietras, 2017; Qin et al., 2020; Tan et al., 2020; Wang et al., 2020). Besides, severe patients are also associated with pre-existing conditions like diabetes and hypertension (Yang et al., 2020). Metabolic molecules, such as elevated blood lactic acid levels may inhibit lymphocyte proliferation in severe COVID-19 cases (Fischer et al., 2007; Tan et al., 2020). Third, severe patients may have higher lymphocyte death. The potential mechanism of lymphocyte death could be due to direct infection of lymphocytes, cytokine storm, damage of lymphatic organ, and metabolic disorder (Tan et al., 2020); (Sefil et al., 2014; Shen et al., 2022). Further investigation is warranted to decipher the role of COVID-associated cause of lymphopenia in severe COVID-19 cases.

4.2. B cells and antibodies function in SARS-CoV-2 infected people

Patients who recover from COVID-19 infection have SARS-CoV-2 binding antibodies in their sera, suggesting a role of B cells and virus-specific antibodies in providing protective immunity against SARS-CoV-2 (Thevarajan et al., 2020; Zhou et al., 2020a). The interaction of antigen with the naïve (or memory) B cells generates activated B cells, which then differentiate into antibody secreting cells (ASCs) with the help of T follicular helper (T_{FH}) cells. The ASC produces antibodies that are critical for viral clearance. Detailed kinetic analysis of antibody production, ASCs, and T_{FH} cell generation and the state of a disease condition was studied in a 47-year-old mild symptomatic patient who recovered (Thevarajan et al., 2020). Viral clearance started on day 7, and symptoms were resolved on day 13. The SARS-CoV-2 specific antibodies were detected on day 7, followed by an increase in titer until day nine that remained elevated on day 20. ASC and T_{FH} cell proportion also followed the same kinetics as that of the virus-specific Abs. This study, although limited to one patient, suggests that effective and timely B cell-mediated antibody response might be critical in the recovery of most patients. This is supported by a few reports suggesting that about 70% of non-severe COVID-19 patients have high and persistent SARS-CoV-2 neutralizing antibodies after their recovery (Wu et al., 2020). Larger longitudinal cohort studies by Achiron et al. (289 males and 108 females) and Cohen et al. (254 COVID-19 patients) also

reported that SARS-CoV-2 neutralizing antibodies persist beyond 9 months post infections, with the persistence of long-lived plasma cells (ASC) and memory B cells (estimated half-life >200 days) conferring long term protective immunity against the re-infection (Achiron et al., 2021; Cohen et al., 2021). The antibody-mediated protective immunity against SARS-CoV-2 could be due to the following: blocking the binding of the pathogen to the host cells, neutralization of the pathogen, cytotoxicity, and phagocytosis of infected cells (Fig. 3). The potential role of the SARS-CoV-2-specific antibody in viral elimination is confirmed by a few *ex-vivo* studies that showed neutralization of the virus by patient-generated antibodies (Wolfel et al., 2020; Zhou et al., 2020a). Future in-vivo studies would be required to find out the importance and potency of antibody-mediated neutralization of SARS-CoV-2 at different populations and phases of the disease.

Several studies show longitudinal changes in antibody response to SARS-CoV-2 in multiple patients and found significantly elevated levels of Abs during the course of the disease (Achiron et al., 2021; Long et al., 2020; Zhao et al., 2020a). SARS-CoV-2-specific antibodies were detected in < 40% of patients in the first week after onset of the symptoms, and the level rapidly increased to 100% of patients within 15 days (late stage of infection) (Zhao et al., 2020a). Virus-specific antibodies peak appears in 3–4 weeks post-infection (Burnett et al., 2021). Higher level of ASC and virus specific antibodies were observed in many severe patients compared to non-severe patients at late stages of infection (Burnett et al., 2021). Surprisingly, the disease worsens as the antibody level increases in the severe group; on the contrary, the disease symptoms improve with increasing antibody levels in the non-severe group (Long et al., 2020; Zhao et al., 2020a). Some studies have shown that an increased amount of antibody against S-protein and N-protein is correlated positively with the severity of the disease, especially in the elderly patients (Jiang et al., 2020; Tan et al., 2020).

While some of the analysis suggest nonexistence of antibody-dependent enhancement (ADE) at population level for the disease pathology of SARS-CoV-2 infection (Gan et al., 2022). ADE could be one of the contributing factors in patients who becomes quite severe and succumb to death as ADE in monocytes and macrophages can cause hyper inflammation and disease severity in a fraction of patients (Junqueira et al., 2022). A recent study identified the potential of certain neutralizing antibodies that have been approved for COVID-19 treatment, to cause ADE (Mu et al., 2022). Thus, future studies are required to constantly reevaluate the potential of ADE, especially in the context of new strains of SARS-CoV-2, such as Omicron. There could be many reasons for a potential ADE to occur in the case of current and future sub strains of SARS-CoV-2: first, anti-SARS-CoV-2 non-neutralizing antibodies may activate immune cells through Fc receptor-mediated signaling and start producing pro-inflammatory cytokine (Iwasaki and Yang, 2020) causing severe symptoms as shown by Junquira et al., 2022. Second, due to the epitope mimicry, SARS-CoV-2, similar to other coronaviruses (SARS-CoV), can induce the formation of non-specific or autoantibodies which may exacerbate the disease progression by promoting tissue damage, cytokine storm, and aberrant complement activation (Chang et al., 2021; Lin et al., 2005; Thurman and Yapa, 2019). This phenomenon is now well documented in severely ill patients and many studies have identified autoantibodies targeting diverse self-antigens such as angiotensin II (AngII), that regulate blood pressure (Briquez et al., 2022), interferons (Manry et al., 2022) and nuclear antigens (Son et al., 2022). In fact, the presence of autoimmunity is now considered as a hallmark of post covid symptoms including prolonged inflammation, fatigue, and persistence of respiratory symptoms (Rojas et al., 2022). The mechanism explained above and beyond might work synergistically to worsen disease outcome. Future studies are required to understand the range of specificity of antibodies and ASCs to SARS-CoV-2 and their potential pathological function in severe patients and patients reporting delayed COVID-19 associated symptoms.

4.3. T cells function in SARS-CoV-2 infected people

$CD4^+$ T cells primarily regulate adaptive immune response whereas $CD8^+$ T (cytotoxic T cells) cells directly impart cytotoxicity to the virus-infected cells by producing cell death-inducing molecules such as granzyme, perforin, IFNγ (Schmidt and Varga, 2018). SARS-CoV-2 reactive T cells were found in recovered COVID-19 patients and a small proportion of seronegative healthy donors, suggesting cross-reactive $CD4^+$ T cell response to SARS-CoV-2 and common cold coronaviruses, which may account for no or mild symptoms of SARS-CoV-2 infection (Braun et al., 2020; Grifoni et al., 2020). Kinetic analysis of immune cells and disease states in a 47-year-old patient who recovered from the mild COVID-19 symptoms showed a positive correlation of activated T cells generation and clinical outcome (Thevarajan et al., 2020). In this study, the frequency of activated $CD4^+$ and $CD8^+$ T cells peaked at the time of viral clearance and then decreased, but the frequency remained higher as compared to healthy control. Interestingly, activated $CD8^+$ T cells were produced at a higher frequency as compared to activated $CD4^+$ T cells in severe patients (Thevarajan et al., 2020). In contrast, another clinical study has shown that the frequency of IFNγ producing activated $CD4^+$ and $CD8^+$ T cells remains comparable in both severe and non-severe COVID-19 patients (Qin et al., 2020). However, recent reports collectively suggest that activated T cell response may have a more protective role than previously imagined. For example, SARS-CoV-2-specific T cell response is seen in the exposed family members and healthcare workers who were at high-risk and heavily exposed but remained seronegative for antigen (da Silva Antunes et al., 2021; Sekine et al., 2020), suggesting that T cell response may prevent the establishment of the infection. This is also seen in patients with impaired B cell response, such as cancer patients undergoing B-cell depleting anti-CD20 therapy, where the higher numbers of $CD8^+$ T cell were found to associated with improved survival (Bange et al., 2021). More direct evidence came from the primate model of SARS-CoV-2 infection where the depletion of $CD8^+$ T cells led to breakthrough SARS-CoV-2 infection, suggesting that $CD8^+$ T cells protect against reinfection when antibody titers are suboptimal and waning (McMahan et al., 2020). Moreover, SARS-CoV-2-specific CD8 + T-cells were found to respond towards multiple nucleocapsid protein domains (Le Bert et al., 2020) and are reported in recovered COVID patients (Le Bert et al., 2020). The longitudinal studies have suggested the long-term circulation of these T cells contributes to the post-infection immunity (Nelde et al., 2020; Peng et al., 2020; Sekine et al., 2020). SARS-CoV-2 induced alterations in the epigenetic landscape may also play a pivotal role in determining T cell fate and needs further investigation (Bhat et al., 2022; Rha and Shin, 2021). Considering the kinetic data and other patient-specific scenarios, we may incline to think that the activated $CD8^+$ T cells that appeared before the clearance of symptoms are directly involved in the killing of the virus-infected cells through the production of granzymes and perforin (Thevarajan et al., 2020).

The T cell functions are impaired in severe patients. The cellular mechanism of impaired T cells function in severe disease could be due to the following reasons. First, the proportion of activated T cells is comparable in severe and non-severe patients suggesting the involvement of other immune components with the severity of the disease (Qin et al., 2020; Xu et al., 2020d). One of the T cells types is the regulatory T cell (Treg), which can restrain other activated T cells' function (Sakaguchi et al., 2009). Severe patients may have significantly reduced Treg cells. In concordance, Qin et al. showed fewer Treg (specifically, induced Treg) in severe patients, thereby failing to restrain other T cell-mediated inflammation and positively contributing to cytokine storm and exacerbation of the disease (Qin et al., 2020). Second, the number of T cells or the level of T cell exhaustion may underlie the outcome in the patients. For example, a recent clinical report shows that the numbers of both CD4 + and CD8 + cells were significantly reduced in severely ill patients (Braun et al., 2020; Diao et al., 2020b), while the recent single cell sequencing data from 39 patients suggests that $CD8^+$ T cells remains

less exhausted in severely ill patients which can cause more cytotoxicity and worsen the outcome (Kusnadi et al., 2021). However, some reports also suggest decreased CD8 + T cell number, aberrant activation (Song et al., 2020), senescence, and exhaustion in severe COVID patients (De Biasi et al., 2020; Rha and Shin, 2021), suggesting a complex interplay of T cells in response to SARS-CoV-2 infection. Besides, possibly, T cells that are not specific to the virus are hyperactivated, which can cause disease exacerbation (Qin et al., 2020; Xu et al., 2020d). Fig. 3 presents an analysis of lymphocyte counts vs disease severity. Future studies may shed further light on the role of T cells in the non-severe and severe COVID-19 patients.

4.4. Memory lymphocyte generation and function in SARS-CoV-2 infected people

It seems that most of the people who recovered after SARS-CoV-2 infection develop an immune memory. However, the emergence of mutant variants has led to reinfection despite prior infection and vaccination. A large proportion of SARS-CoV-2 infected people harbor long-term memory B and T cells (Cohen et al., 2021). Despite memory response, a proportion of prior infected people can get reinfected by the same or a variant of SARS-CoV-2 within a few weeks after recovery (An et al., 2020; Lan et al., 2020; Xing et al., 2020a, 2020b). Plausible reinfection would mean an inadequate establishment of immune memory in patients, as a successful establishment of memory would provide long-term protective immunity against viral reinfection. During reinfection, pre-existing protective antibody provides the first line of defense, whereas faster reactivation of pathogen-specific memory lymphocytes provides the second line of defense.

The retrospective analysis shows that reinfected/ relapsed patients were characterized by early RNA negative-conversion in the first infection compared to non-reinfected/ relapsed patients (An et al., 2020). It might be possible that short exposure to SARS-CoV-2 (due to a quicker recovery by innate immune response) may not generate an adequate memory in COVID-19. However, the generation of inadequate memory can be much more complicated than just short exposure time, as a significant portion of reinfected/ relapsed patients were young and had non-severe symptoms (An et al., 2020; Lan et al., 2020; Xing et al., 2020b). It is now understood that the primary cause of reinfection was the emergence of newer variants of SARS-CoV-2 (cdc.gov). In the controlled experimental setup, a longitudinal study in the rhesus macaques model showed no recurrence of COVID-19 when the recovered monkeys were re-exposed to SARS-CoV-2 within 28 days of the first infection (Bao et al., 2020). This certainly proves the memory response, however, elevated levels of IFN-I and proinflammatory cytokines may also be contributing factors as reinfection is too soon. The duration of memory response for SARS-CoV-2 is determined in a few studies to last beyond 9 months (Cohen et al., 2021). Over the past few years, we have learned that the effective memory response wanes over time but still provides protection from the severity of the disease.

A longitudinal (6 years post-infection) study of 23 COVID-recovered patients has shown that all the 23 patients lack SARS-CoV-specific B cells, and 21 of them have undetectable SARS-CoV-specific antibodies. Interestingly, SARS-CoV antigen-specific memory T cell was identified in 60.9% of recovered SARS patients (Tang et al., 2011). This study suggests that SARS-CoV infection likely generates a long-term cellular memory but fails to generate a long-standing humoral memory. Another long-term study (up to 11 years) of SARS-CoV-recovered patients showed persistent memory T cells; however, the frequency of T cells varied widely (3.9–0.2%) after in-vitro expansion (Ng et al., 2016). Similarly, Libraty et al. have shown that the frequency of memory T cells significantly declines in SARS-CoV-recovered patients at 12 months post-infection (Libraty et al., 2007). Thus, the establishment and frequency of memory T cells significantly varied within the recovered patients' population and may depend on the severity of the disease. It appears that long-term memory $CD4^+$ and $CD8^+$ T cells against SARS-Cov-2 will follow a similar trend as SARS-CoV (Cohen et al., 2021). We will continue to learn the duration of adaptive memory in COVID-19-recovered patients when long-term follow-up studies start to pour in (Fig. 3). Hopefully, upcoming long-term longitudinal studies will help understand the quality and quantity of immune memory generated in COVID-19-recovered patients.

5. Immune response to SARS-CoV-2 in people with underlying conditions and genetic predisposition

Although the immune response to SARS-CoV-2 may vary among the normal healthy individuals, that may be a determinant for mild and severe symptoms. It is apparent that people with underlying medical conditions and genetic predispositions may cause a dysregulated immune response and are likely to experience severe and life-threatening symptoms. Some pre-existing conditions include age, hypertension, cardiovascular diseases, pulmonary disease, cancer, and obesity, which have been linked to developing severe conditions due to SARS-CoV-2 infection that may lead to more extended hospitalization and death (Santesmasses et al., 2020). It is now beginning to unravel how the existence of these comorbidities affects the overall response of the immune system against SARS-CoV-2 infection (Bajaj et al., 2021). Among many, age emerged as the most significant risk factor for both contracting the SARS-CoV-2 and worsening of the symptoms (Santesmasses et al., 2020). Aging causes changes in the host immune response and decreases the ability to mount an effective immune response to clear infections (Bajaj et al., 2021). Recent studies also report the higher expression of ACE-2 in the lungs of aged individuals (Jin et al., 2022), which may facilitate a higher propensity to catch an infection. Cancer patients undergoing chemo or radio-therapy may have dysfunctional cytotoxic CD8 + T cells and other immune components (Shaked, 2019), which may make them susceptible to infection and exacerbation of the disease progression. Chronic lung illnesses, such as Asthma, Bronchiectasis, Chronic obstructive pulmonary disease, Interstitial lung disease, Pulmonary embolism, and Pulmonary hypertension, are linked with an increased risk of morbidity due to COVID-19 (Schultze et al., 2020). Similarly, hypertension can induce CD8 +T cell exhaustion (Alexander et al., 2023), reducing the effector immune cells' function to control SARS-CoV-2 infection (Alexander et al., 2023). COVID-19 comorbidity may also be affected by genetic predisposition, which may aid in determining patient susceptibility and disease severity. A recent in silico study identified several genes, including AGT, FXIIIB, PV92 (Yamamoto et al., 2021), LZTFL1, MHC, DPP9, IFNAR2 (Horowitz et al., 2022), TLR4, NLRP3, MBL2, IL6, IL1RN, IL1B, CX3CR1, CCR5, and ACE, as possible predictors of disease severity (Feng et al., 2022). A more detailed synthesis of the data related to various comorbidities and their association with the COVID-19 outcome has been extensively covered elsewhere (Bigdelou et al., 2022; Honardoost et al., 2021; Zhang et al., 2022).

6. Therapeutic options

As the COVID-19 pandemic is ongoing, the effective treatments are also changing rapidly depending on the currently available information on the new SARS-CoV-2 strains and the success of clinical trials. Currently, multiple lines of treatments are available that can prevent the chances of hospitalization and severity of the disease. These therapeutic strategies can be primarily classified into two groups: first, targeting the SARS-CoV-2 directly using antiviral treatments, and second, targeting the host cells. In the United States, the Food and Drug Administration (FDA) authorized many different antiviral compounds (Nirmatrelevir, Remdesivir, Molnupiravir) that target different parts of the virus and prevent its multiplication in the cells. Another potential and much-hyped experimental antiviral agent Hydroxychloroquine was found to be ineffective in randomized clinical trials with significant side-effects (Boulware et al., 2020; Hennekens et al., 2022). Here, we focus on the

strategies to target the host cells, especially the host immune components. The immune systems can be targeted by two approaches, therapeutic and prophylactic. In the therapeutic approach, the drug is introduced in individual's post-infection to restore the immune system during the course of the disease. Pre-infection prophylaxis relies on activating the healthy host-immune systems before infection and onset of the disease. In this review, we will discuss a handful of molecules that were drawing significant attention in treating COVID-19 and the status of whether these molecules eventually pronounced effective in treating COVID-19. The therapeutic molecules encompases IFN-I, JAK/STAT, TNF, IL-1, IL6, GM-CSF, complement, and convalescent serum. The prophylactic molecules to be described here are the vaccine against SARS-CoV-2 antigens and the BCG.

6.1. IFN-I therapies (IFNα, IFNβ) and JAK-STAT inhibitors

The anti-viral IFN-I innate immune response is associated with the disease stage, and an early impaired IFN-I response is a critical factor contributing to the progression of COVID-19 pathogenesis. A significant IFN-I response is associated with late cytokine storm in severe COVID-19 patients (discussed in 3.1.1) (Siddiqi and Mehra, 2020). Therefore, a therapeutic-staging strategy to activate (Interferon therapy) or inhibit (JAK/ STAT inhibitor) the IFN-I response is warranted. Preclinical and clinical studies suggest an early-stage use of IFN-I treatment, particularly in combination with other antiviral drugs (Sallard et al., 2020). The effectiveness of early IFN-I therapy for COVID-19 is supported by an in vitro study showing that, unlike SARS-CoV, SARS-CoV-2 lacks some of the mechanisms to antagonize the IFN-I response (Lokugamage et al., 2020; Sallard et al., 2020). In concordance, two groups have shown that early IFN-Iα/β treatment suppresses SARS-CoV-2 replication in the cell lines (Lokugamage et al., 2020; Mantlo et al., 2020). In the early stages of the pandemic, a JAK-STAT pathway inhibitor- baricitinib, in combination with the antiviral Remdesivir, was proposed to treat severely ill COVID-19 patients (Kalil et al., 2021; Richardson et al., 2020). On July, 2021, the FDA approved Baricitinib as a standalone treatment for the severe COVID-19 cases. The updated information of FDA recommended interferon treatments and guidelines can be found on- https://www.covid19treatmentguidelines.nih.gov/.

6.2. Anti-Tumor necrosis factor-alpha therapy

COVID-19 patients have higher TNF-α as compared to healthy controls and are positively correlated with the severity of the disease (Gong et al., 2020; Zhou et al., 2020a). TNF-α is a proinflammatory cytokine that can amplify inflammation and is associated with viral pathogenesis (Feldmann et al., 2020). Anti-TNF therapy shows beneficial effects in a mouse model of respiratory infection and is clinically useful in many inflammatory diseases (Feldmann et al., 2020). Thus, the use of a TNF-α inhibitor can potentially reduce the inflammation to prevent the severity of COVID-19. The result of many recent clinical trials suggests that anti-TNF- α treatment has a protective effect on the progression of COVID-19, especially in preventing severe illness (Guo et al., 2022). However, due to the potential dampening of the host immune system, anti-TNF- α treatment may result in increased susceptibility to viral and secondary bacterial infections or autoimmune disorders (Minozzi et al., 2016), thus the treatment may be most effective for patients with a bleak prognosis. Clinical studies related to different TNF- α inhibitors are listed in Table 1.

6.3. Interleukin 1-β therapy

COVID-19 patients have a higher level of IL-1β as compared to healthy control and are an important mediator of the inflammatory response (Zhou et al., 2020a). Higher IL-1β level is associated with autoinflammatory diseases, and the use of an anti-IL-1β receptor blocker (anakinara) or a drug that blocks IL-1 signaling (mAb Canakinumab) are shown to be beneficial in managing COVID-19 (Dinarello et al., 2012). Thus, the use of an IL-1β inhibitor can potentially reduce the inflammation and severity of COVID-19. On November 8, 2022, the FDA approved the use of anakinara in selected severely ill COVID-19 patients (under emergency use authorization). More information related to the updated status of IL-1 targeting therapies can be found at https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-1-inhibitors/. Some of

Table 1
Representative list of some relevant Clinical Trials pertaining to some of the different approaches for the prevention and treatment of COVID-19.

Sl. No.	Study Title	Interventions	Sponsor/ Collaborators	NCT Number	Study duration, Phase (P)
Interferon therapy (IFNα, IFNβ) and JAK-STAT inhibitors					
1	A Study of Baricitinib (LY3009104) in Participants With COVID-19	Baricitinib	Eli Lilly and Company	04421027	Jun 2020 – Jun 2021, P3
2	Adaptive COVID-19 Treatment Trial 3 (ACTT-3)	Interferon Beta 1a, Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	04492475	Aug 2020 – Dec 2020, P3
3	TOGETHER trial: Effect of Peginterferon Lambda for the Treatment of COVID-19	Peginterferon Lambda-1A	University Health Network, Toronto	04967430	Aug 2021 – Jun 2022, P3
Interleukin 1-β therapy					
1	SAVE-MORE trial: suPAR-Guided Anakinra Treatment for Management of Severe Respiratory Failure by COVID-19	Anakinra; blocks IL-1α and IL-1β	Hellenic Institute for the Study of Sepsis	04680949	Dec 2020 – Feb 2022, P3
2	Treatment of COVID-19 Patients With Anti-interleukin Drugs	Anakinra, Siltuximab, and Tocilizumab	University Hospital, Ghent Belgium Health Care Knowledge Centre	04330638	Apr 2020 – Apr 2021, P3
3	CAN-COVID trial. Treatment of COVID-19 Patients With Anti-interleukin Drugs	Canakinumab	Novartis Pharmaceuticals	04362813	Apr 2020 - Dec 2020, P3
Anti-Tumor necrosis factor-alpha therapy					
1	Clinical Trial to Evaluate CERC-002 in Adults With COVID-19 Pneumonia and Acute Lung Injury	XPro1595	Inmune Bio, Inc.	04370236	Jun 2020 – Jan 2021, P2
IL-6 inhibitor					
1	Use of the IL-6 Inhibitor Clazakizumab in Patients With Life-threatening COVID-19 Infection	Clazakizumab	NYU Langone Health	04343989	Mar 2020 – Mar 2021, P2
2	EMPACTA trial: Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	Tocilizumab (anti- IL-6 receptor Ab)	Hoffmann-La Roche	04320615	Apr 2020 – Jul 2020
3	Assessing the Efficacy of Sirolimus in Patients With COVID-19 Pneumonia for Prevention of Post-COVID Fibrosis	Sirolimus	University of Chicago	04948203	Jul 2021 - Jul 2024, P3
4	Sarilumab COVID-19	Sarilumab	Sanofi Regeneron Pharmaceuticals	04327388	Mar 2020 – Sept 2020, P3

the notable current trials are shown in Table 1. Caution must be practiced in choosing the patients as the use of an IL-1β inhibitor can dampen the host's immunity to fight some other types of infections.

6.4. Complement proteins Inhibitors

Activated complement proteins are present at elevated levels in severe patients; inhibiting these activated complement proteins may reduce the innate immune-mediated consequences. A combination strategy may include a complement inhibitor combined with anti-viral therapeutics. In the past, complement inhibition has provided favorable outcomes in SARS-CoV and MERS-CoV murine models (Jiang et al., 2018; Sun et al., 2013). The success of anti-C5a therapy in mouse models of influenza virus and MERS-CoV have led to the development of humanized monoclonal antibodies against the human C5a protein by at least two pharmaceutical companies (US-based Alexion and Germany-based InflaRx). Various clinical trials for evaluating complement system therapies are underway, and it is still early to conclude how effective the complement-targeting therapies would be for severely ill COVID-19 patients (Afzali et al., 2021).

6.5. IL-6 inhibitor

IL6 is one of the major constituents of the cytokine storm in severe COVID-19 patients, and therefore, it is proposed that blockade of IL-6 in COVID-19 patients may ameliorate the COVID-19 associated symptoms (Qin et al., 2020). Initial clinical trials using IL-6 inhibitors in the treatment of COVID-19 have been promising. Although the precise mechanism by which IL6 inhibitor may control COVID-19 progression is not well understood, inhibition of IL-6 may likely reduce the IL-6-mediated inflammatory response, including reduced production of Th17 cells and restoration of lymphopoiesis and myelopoiesis balance (Xu et al., 2020d); (Pedersen and Ho, 2020; Qin et al., 2020). Some of the interesting clinical trials assessing the use of IL-6 inhibitors are mentioned in Table 1. Promising clinical benefits with reduced mortality, decreased requirement for assisted breathing, and minimized hospitalization have been observed using an IL-6 receptor inhibitor in severe COVID-19 patients (REMAP-CAP and RECOVERY trials). These promising findings resulted in the FDA approval (Dec 2022) of IL-6 targeting therapies that use human monoclonal antibodies against IL-6 receptors (Tocilizumab). This approval is for the use of intravenous (IV) tocilizumab for the treatment of COVID-19 hospitalized adults receiving systemic corticosteroids and need supplemental oxygen, noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). On the other hand, some trials showed some advantages but did not yield statistically relevant positive results with IL-6 inhibitors for survivability (COVACTA and EMPACTA trials) (Rubin et al., 2021). Tocilizumab's usage in conjunction with other therapies, such as corticosteroids and Remdesevir, is also studied. The recent REMDACTA trial attempted the combined use of Tocilizumab and Remdesevir but did not yield a significant survival advantage compared to Remdesevir alone. The CORIMUNO-19 study group conducted a clinical trial with Dexamethasone and Tocilizumab compared to Dexamethasone alone, but did not find advantages with ventilation support and mortality (Hermine et al., 2022). Several studies corroborate the potential effects of IL-6 inhibitors, however, some studies also present tricky concerns, making their optimal use challenging and demanding further examination. More information regarding IL-6 inhibitors can be found at https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/.

6.6. Granulocyte macrophage colony-stimulating factor (GM-CSF) inhibitor

It has been shown that severe COVID-19 patients generate GM-CSF producing $CD4^+$ T cells (Zhou et al., 2020a). GM-CSF plays a key role in hematopoiesis and is essential for the generation of inflammatory ($CD14^+CD16^+$) monocytes that are associated with COVID-19 disease severity. Thus, the use of a GM-CSF inhibitor can potentially reduce the generation of inflammatory monocytes to prevent the severity of COVID-19. Multiple antibodies targeting GM-CSF are currently under clinical trial (e.g., NCT04341116, NCT04351152, NCT04376684) (Perricone et al., 2020). Lenzilumab reduces immune hyperstimulation and improves clinical outcomes in high-risk COVID-19 patients. GM-CSFα antagonist Mavrilimumab improves clinical outcomes in COVID-19 patients with severe pneumonia (Kohler and Conway Morris, 2023). The trial (NCT04351243) using the Mab Gimsilumab for targeting COVID-19 pneumonia did not yield convincing results (Criner et al., 2022). In the OSCAR study, the anti–GM-CSF monoclonal antibody Otilimab was evaluated (NCT04376684). Otilimab is related to clinical improvements and slower progression, although there is no meaningful difference at Day 28 in the percentage of patients who are alive and devoid of respiratory distress (Patel et al., 2023). Thus, divergent data have emerged for or against using GM-CSF inhibitors for COVID-19. In addition, the precise mechanism of this niche-specific and temporal influence on the incidence of COVID pathology is unclear, as is whether it plays a bystander function. The potential benefit could be the restoration of anti-viral immunity and prevention of secondary infection in very severe ARDS COVID-19 cases, but at the same time, well-planned randomized, double-blind, placebo-controlled trials are needed.

6.7. Convalescent Plasma

Convalescent plasma (CP) as passive immune therapy has been used for more than a century to prevent and treat infectious diseases. CP from recovered COVID-19 patients can provide SARS-CoV-2-specific neutralizing antibodies as a therapeutic intervention to new SARS-CoV-2 infected patients or as prophylactic for individuals with a high risk of contracting COVID-19 (Casadevall and Pirofski, 2020). The use of CP in severe COVID-19 patients has shown significant improvements in clinical outcomes in several independent studies (Arnold Egloff et al., 2021; Duan et al., 2020; Libster et al., 2021; Salazar et al., 2020). Many clinical trials with larger cohorts have tested prophylaxis and therapeutic protocols against COVID-19 in randomized clinical trials and found contradictory outcomes. Nevertheless, other investigations comparing CP with neutralizing anti-SARS-CoV-2 antibodies to placebo revealed no benefit in COVID-19 hospitalized patients (Cho et al., 2021; Simonovich et al., 2021; Song et al., 2022). A group of companies has joined hands to develop a polyclonal antibody product: hyperimmune globulin (H-Ig) purified from the pooled plasma of COVID-19-recovered patients. SAb Biotherapeutics and the US Biomedical Advanced Research and Development Authority are collaborating to capture the entire human antibody repertoire against SARS-CoV-2 using a recombinant platform (Sheridan, 2020). At the initial stages of COVID-19 CP became a popular choice due to the inherent benefits, as CP was readily available, needed no significant research time to initiate trials, is polyclonal, inexpensive, accessible even in resource-limited nations, and recovering COVID convalescing survivors were available. CP also suffered from several critical pitfalls in the large-scale clinical applications of CP, including source, handling, determination of neutralizing antibodies titer, screening for transmissible pathogens and effectiveness of pathogen neutralization. Considering the conflicting data from different trails, FDA updated the guidelines for using only CPs with high-titer of anti-SARS-CoV-2 antibodies for immunosuppressant patients. The updated information on CP-based therapy can be found on the following website: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/covid-19-convalescent-plasma/.

6.8. SARS-CoV-2 specific vaccine

Within three years after SARS-CoV-2 was first identified in Wuhan,

many effective vaccines got developed through public-private partnerships in many countries. We now have many effective vaccines with proven efficacy. Globally, a massive vaccination drive has helped curb the infection, disease severity, and death rate due to SARS-Cov-2. As per WHO, 13,168,935,724 vaccines have been administered worldwide. The identification of the genetic sequence of SARS-CoV-2 has led to vaccine designs using traditional and new approaches to combat the disease. SARS-CoV-2 has a total of 11 structural and non-structural proteins (Jin et al., 2020). Spike protein was identified as the most appropriate vaccine antigen, which formed the backbone for most popular mRNA-based vaccine developed independently by "Moderna", and "Bio-Ntech & Pfizer". The race to develop effective vaccines started when a study showed that the inactivated SARS-CoV-2 virus provides protective immunity in monkeys (Gao et al., 2020a). The current vaccine development landscape now offers several technology platforms, including SARS-CoV-2 nucleic acid-based (DNA-ZyCoV-D, and RNA-Moderna, BioNTech/Pfizer), virus-spike protein subunit vaccine (Novavax), a replication-incompetent viral carrying the viral gene (AstraZeneca, Sputnik V, Janssen), live whole attenuated virus (COVI-VAC, under trails) (Chen et al., 2022; Liu et al., 2022) and inactivated whole virus (Valneva-VLA2001, under trails) (Lazarus et al., 2022). More detailed information on the currently approved/ under trial COVID-19 vaccines is available at the link (https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_12January2023.pdf). In addition to the antigen, various antigen delivery strategies are also being used for generating a better SARS-CoV-2 vaccine response. These methods include microneedle patches to deliver pieces of the spike protein via the skin (Kim et al., 2020), intramuscular injections (most vaccines), and nasal sprays (Waltz, 2022). Both Moderna and Pfizer mRNA vaccines use lipid nanoparticles for the delivery of mRNAs for the SARS-CoV-2 spike protein.

It appears that a multi-epitope vaccine designed using immunoinformatic and molecular modeling approaches for epitopes from multiple proteins could be a useful vaccine development strategy in the future (Martin and Cheng, 2021; Robson, 2020; Srivastava et al., 2020; ul Qamar et al., 2020). A multi-epitope vaccine increases the diversity of the immune repertoire and might be effective in providing protective immunity against genetically different variants of SARS-CoV-2. However, antibodies generated against these epitopes have a risk of mounting an ADE that needs to be appropriately evaluated (Peeples, 2020). With the emergence of new strains of SARS-CoV-2, next-generation of bivalent vaccines have been rolled out that are available in the form of "boosters" at specific intervals. These booster vaccines contain components of the original virus strain and the recently identified omicron variant to ensure widespread protection against diverse SARS-CoV-2 strains in circulation. The Moderna and Pfizer-BioNTech bivalent COVID-19 vaccines are FDA-approved to be administered as a solitary booster dose. On December 2022, Pfizer-BioNTech released COVID-19 vaccination for children aged 6 months - 4 years, thus covering almost the entire population range. These boosters activate the memory B cells that had been formed since the first vaccine dose and boost antibody production, thus extending the immunity against SARS-CoV-2 (Muecksch et al., 2022). More information on the status of boosters is available at https://www.cds.gov. The continuous process of complex viral evolution emphasizes the need to update the vaccine pipeline to improve vaccine effectiveness, followed by rigorous tracking and careful study design to better understand the preventive role of vaccine-derived immunity versus immunogenic protection from prior infection, and "hybrid" immunity.

6.9. BCG Vaccine

Many epidemiological studies have found a very good correlation between childhood Bacillus Calmette-Guérin (BCG) vaccination and a lower incidence and death rate from COVID-19 (Miller, 2020). It can be speculated that the BCG vaccine activates metabolic and epigenetic alterations to stimulate the innate immune response that can protect from subsequent infections by viruses, including SARS-CoV-2, via a process termed as "trained immunity" (Curtis et al., 2020; Netea et al., 2020). Antigen-independent bystander B and T cell activation may also confer protection (Goodridge et al., 2016). Several clinical trials are testing the power of trained immunity via the use of the BCG vaccine against COVID-19 (e.g., NCT04328441, NCT04327206, NCT04348370, NCT04369794, NCT04328441); (Curtis et al., 2020). However, it should be noted that many recent reports show that BCG vaccination offers no advantage against SARS-CoV-2 infection (Hamiel et al., 2020; Upton et al., 2022). The BCG vaccine-mediated non-specific heterologous protection may temporarily bring hope, especially when no preventive tools are available (Gonzalez-Perez et al., 2021) (Redelman-Sidi, 2020). Another aspect is whether BCG vaccination can protect people with underlying conditions. A recent trial (NCT02081326) demonstrated that multi-dose BCG immunizations could provide platform protection to susceptible type 1 diabetes patients against COVID-19 and other infections (Faustman et al., 2022). However, until confounding results are published and evaluated, careful monitoring should be practiced as the upregulation of immunity may activate COVID symptoms in some patients.

7. Conclusion

In this review, we have attempted to capture the heterogeneity and complexity of the hosts' immune responses in SARS-CoV-2-infected people. We have presented a proposed kinetics of disease severity, major symptoms, and immune response in mild/ moderate vs. severe (survivors and nonsurvivors) (Fig. 3). We have discussed the potential mechanisms pertaining to the protective and pathogenic immune responses in "mild/ moderate" and "severe" symptomatic COVID-19 patients, respectively. Furthermore, we discuss potential therapeutic options to target the immune components for the treatment of severe COVID-19 patients. The dysregulation of the immune system during severe COVID-19 disease involves (1) impaired early IFN-I production, (2) excess cytokine production, (3) uncontrolled activation of complement systems, (4) increased neutrophils, and reduced lymphocytes number, (5) production of pathogenic antibody in a few severe patients, (6) reduced Treg number, (7) impaired memory lymphocytes formation. So far, current data suggest that individuals with weak immune systems (older adults and people with chronic medical illnesses) have a higher propensity to develop a severe form of the disease. On the contrary, severely ill patients show a cytokine storm, which might be an indication of hyperactivated immune systems. Future time course studies are required to understand the progression of the immune response in severe conditions. Detailed studies in suitable model systems have helped decipher some of the cellular and molecular mechanisms of the immune responses that could be happening during the spectrum of COVID-19. Future studies will be important to understand the mechanism underlying the severe and non-severe COVID-19 conditions.

Data Availability

No data was used for the research described in the article.

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