



## Immunopathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a concise update

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### ABSTRACT

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus which has been identified as the cause of the recently emerging coronavirus disease 2019 (COVID-19), a respiratory-related infectious disease, in late 2019. As of May 2020, SARS-CoV-2 has infected millions of people with almost 300.000 deaths worldwide only within few months since its first case was reported. While this infection mostly results in mild diseases, the increasing number of severe cases and deaths cannot be overlooked. Due to its novelty, many facets of SARS-CoV-2 pathogenesis are not well understood. This review presents updated knowledge on the key virus characteristics of SARS-CoV-2 and critical notes in the pathogenesis of this viral infection in human that is currently proposed to largely involve various aspects of the host immune responses. While the immediate impact of viral infection in the target cells contributes to the development of the disease, the ability of the virus to modify the host responses may result in the dysregulation of innate and adaptive immune responses, which commonly manifest in the severe spectrum of the disease. Having deep understanding on this complex process is central for tailoring appropriate management for the infected patients as well as for developing effective preventive measures, most importantly vaccine, which is hoped to occur in the near future.

### ABSTRAK

*Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) adalah suatu jenis virus corona baru penyebab *coronavirus disease 2019* (COVID-19), suatu penyakit infeksi pada saluran napas, yang muncul akhir tahun 2019. Hingga bulan Mei 2020, SARS-CoV-2 telah menginfeksi jutaan orang dan menyebabkan hampir 300.000 kematian di seluruh dunia, hanya dalam waktu beberapa bulan setelah kasus pertama dilaporkan. Walaupun infeksi ini sebagian besar menyebabkan gejala ringan, peningkatan jumlah kasus berat dan kematian tidak dapat diabaikan. Dikarenakan kebaruan virus ini, banyak aspek patogenesis SARS-CoV-2 yang belum diketahui dengan baik. Tinjauan ini membahas pengetahuan terkini tentang karakteristik penting virus SARS-CoV-2 serta aspek penting patogenesis infeksi virus ini pada manusia, yang melibatkan berbagai komponen respon imun inang. Walaupun efek langsung infeksi virus pada sel target berperan dalam perkembangan penyakit, kemampuan virus ini untuk memodifikasi respon inang dapat menyebabkan disregulasi respon imun bawaan dan adaptif, yang bermanifestasi menjadi penyakit yang berat. Pemahaman mendalam kompleksitas proses ini sangat diperlukan dalam penentuan manajemen yang tepat untuk pasien yang terinfeksi dan dalam upaya prevensi yang efektif, seperti vaksin, yang diharapkan dapat diwujudkan dalam waktu dekat.

### Keywords:

SARS-CoV-2;  
COVID-19;  
pathogenesis;  
ACE-2;  
immune response;

## INTRODUCTION

At the end of 2019, an outbreak of a new coronavirus (CoV) infection causing respiratory-related illness was reported in Wuhan, China. On 11 February 2020, the World Health Organization (WHO) officially named the disease as coronavirus disease 2019 (COVID-19).<sup>1,2</sup> COVID-19 is not the first severe respiratory disease outbreaks caused by the coronaviruses. In the past two decades, coronaviruses have caused three epidemic diseases, namely, COVID-19, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>3,4</sup> The new CoV as the causative agent of this respiratory disease was identified and its genome was fully sequenced. Based on the phylogeny and taxonomy and due to a close relationship to SARS-CoV which caused SARS, the International Committee on Taxonomy of Viruses (ICTV) named this novel CoV as SARS-CoV-2.<sup>5</sup>

Since its first reported case in late 2019, this viral infection has spread to almost all parts of the world, with variable transmission rates, mortality rates, and clinical manifestations were reported between countries. It may take years until we can fully comprehend the whole picture of the characteristics of the pathogen and its likely origin, clinical manifestations, and the host immune responses in controlling the infection. In this review, we provide understanding on how this novel disease develops in human and to serve as scientific basis on selecting and/or developing the best management, both preventive and curative, as an initial effort to control the infection globally. The characteristics of the virus and possible (immuno)-pathogenesis of the disease will be described based on the current updated reports.

## DISCUSSION

### Characteristics of SARS-CoV-2

#### *Virus origin*

SARS-CoV-2 belongs to the *Coronavirinae* subfamily in the *Coronaviridae* family. CoVs are large enveloped virus which contain a positive-sense single-stranded RNA as their genome. Based on their genomic structures, CoV subfamily can be classified into 4 genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Naturally, they are zoonotic, with alphacoronaviruses and betacoronaviruses have mammals as their hosts, while gammacoronaviruses and deltacoronaviruses mostly infect birds.<sup>6</sup>

There are currently seven CoVs that are known to be transmitted from animals to humans, including the newly emerged SARS-CoV-2.<sup>1,7</sup> Two (HCoV-NL63 and HCoV-229E) are of the *Alphacoronavirus* and five (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2) are of the *Betacoronavirus* genus. With the exception of SARS-CoV, MERS-CoV, and SARS-CoV-2, most of these human CoVs usually cause mild common cold-like illness in immunocompetent individuals. In contrast, viral pneumonia and severe respiratory distress have been shown to occur in response to the previously pandemics SARS-CoV (in 2002-2003) and MERS-CoV (in 2012), resulting in mortality rates of 10% and 37%, respectively.<sup>7</sup> Severe pneumonia has also been reported with SARS-CoV-2, and while mortality rate has not been able to be accurately measured, infection from this virus has resulted in 6.95% death globally as of the time of this writing.<sup>8</sup>

The three highly pathogenic viruses were suggested to emerge from bats as

their natural reservoirs. Recent study has shown that SARS-CoV-2 spike protein gene sequence is 93.1% identical to those of bat CoV RaTG13.<sup>9</sup> However, these three viruses were likely to undergo recombination which allow them to then infect human cells. In the case of SARS-CoV and MERS, civet and camel were thought to be the intermediary animals, while for SARS-CoV-2, pangolin may be the culprit as shown by the sequence similarity between pangolin CoVs and SARS-CoV-2.<sup>10</sup>

#### *Viral structure & entry into the host cells*

Genome-wide analysis indicated that SARS-CoV-2 genome sequence is 79.5% and 50% identical to those of SARS-CoV and MERS-CoV, resulting in various similarities between SARS-CoV-2 to the two latter viruses, particularly to SARS-CoV, in terms of viral characteristics and pathogenesis in human.<sup>10</sup> SARS-CoV-2 virus particle is around 60 - 100 nm in diameter with a round or slightly oval shape.<sup>11</sup> Similar to other betacoronaviruses, the structure of the virion consists of a single-stranded RNA genome associated with a nucleocapsid which is surrounded by a phospholipid bilayer envelope bearing multiple glycoprotein projections.

The genome is ~29.9 kb, and consists of at least ten open reading frames

(ORFs) of which 6 are conserved across betacoronaviruses (ORF1a, ORF1b, S, E, M, N).<sup>11,12</sup> The first two third of the RNA from the 5'-end comprises the overlapping ORF1a and ORF1b which are translated into two polypeptides and further processed into 15 non-structural proteins (nsp1-nsp16). These nsps form the viral replicase complex which function mainly in viral replication and/or transcription. A third of the genome toward the 3'-terminus possesses multiple ORFs encoding 4 major structural proteins: spike (S), envelope (N), membrane (M), and nucleocapsid (N); as well as accessory proteins (FIGURE 1).<sup>13,14</sup> S, E, and M proteins make up the viral envelope with M glycoprotein being the most abundant one. The M and E proteins are located among the spikes or S proteins and participate in the assembly of virus particles.<sup>11</sup> On the other hand, S glycoproteins which protrude on the outer surface of the virus are particularly important in promoting viral infection as it mediates the attachment of virion to the host cell receptor. The S protein consists of two functional subunits, with the S1 subunit being important in the recognition and binding to the cell receptor and the S2 subunit being involved in the virus-host membrane fusion, eventually allowing the delivery of viral genetic materials into the host cells.<sup>10</sup>

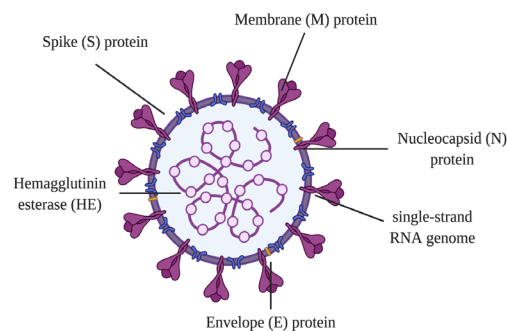


FIGURE 1. SARS-CoV-2 viral structure

Similar to SARS-CoV, a recent study has confirmed that SARS-CoV-2 uses ACE2 (angiotensin-converting enzyme 2) as the key receptor to enter the host cells, most likely via similar entry mechanism (FIGURE 2).<sup>15</sup> It has been suggested that mutations in the receptor binding domain (RBD) of the S1 subunit account for cross-species recognition of SARS-CoV-2 and evolution in this domain possibly contributes to 10-20 fold higher affinity of this virus to

human ACE2 compared to SARS-CoV.<sup>10,15</sup> The entry process also depends on the presence of type II transmembrane serine protease TMPRSS2, which cleaves the ACE2 receptor and activates the viral S protein upon binding, resulting in the entry of the virus. It has been indicated that SARS-CoV-2 requires both ACE2 and TMPRSS2 to enter cells, hence cells that possess both proteins have been suggested to be most susceptible to SARS-CoV-2 infection.<sup>7,16</sup>

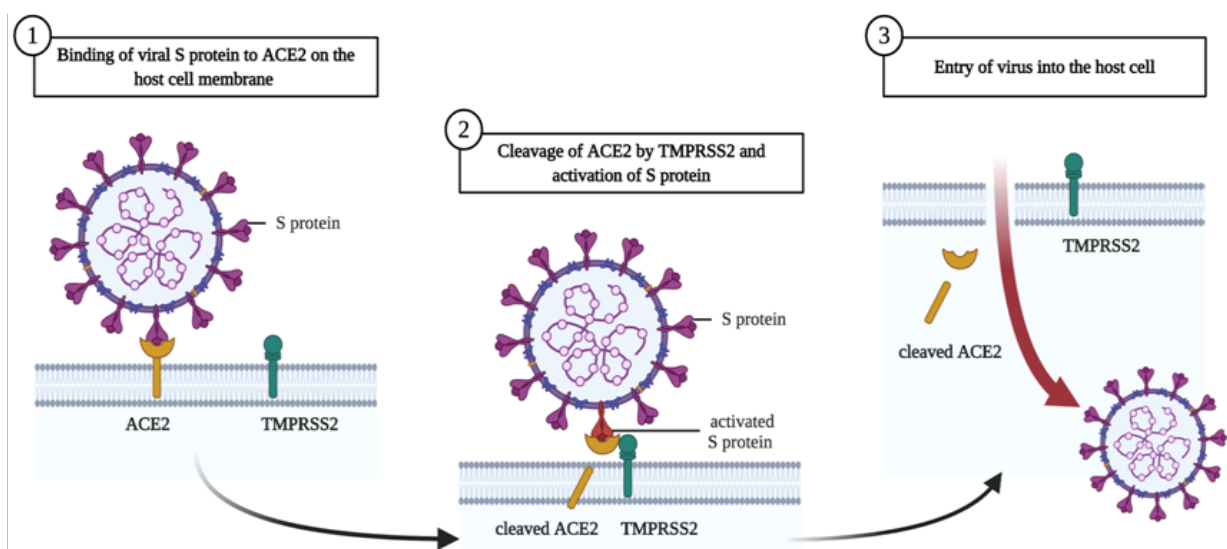


FIGURE 2. SARS-CoV-2 mechanism of cell entry [modified from<sup>7</sup>]

Human angiotensin-converting enzyme 2 (ACE2) functions mainly to cleave angiotensin (Ang) I to produce Ang-(1-7) and participates in the regulation of blood pressure.<sup>17</sup> It is a type I transmembrane glycoprotein that is expressed in almost all cells in various organs such as lung, heart, kidney, and intestine.<sup>10</sup> In the respiratory tract, the expression of ACE2 is widely distributed on the epithelial cells of trachea, bronchi, and alveoli, as well as on the alveolar macrophages and monocytes.<sup>18</sup> However, it has been reported that ACE2 is particularly enriched in the surfactant-producing alveolar type II cells (AECII) in the lung, as well as ciliated and goblet

cells in the airway, making these cells highly vulnerable to this viral infection and likely serve as the portal of entry in human.<sup>19,20</sup> ACE2 is also highly expressed on the intestinal epithelial cells and has diffuse expression on the endothelial cells of arteries and veins, epithelial cells of the kidney, cerebral neurons, and immune cells.<sup>18</sup>

### Transmission

The wide distribution of this viral receptor provides insights on the transmission routes, pathogenesis, and clinical manifestations of SARS-CoV-2 infection. The main source of human transmission is those that are infected,

and while severe patients are more contagious, asymptomatic infected patients were shown to also shed the virus.<sup>10</sup> SARS-CoV-2 has been suggested to be mainly transmitted through respiratory droplet, close contact, and aerosols.<sup>21</sup> One study has reported that SARS-CoV-2 persisted on plastic and stainless-steel surfaces for up to 72 hours and remained viable in the air for up to 3 hours.<sup>22</sup> Since high expression of ACE2 was also found in the intestine, faecal-oral transmission is also predicted with the intestine as the entry point.<sup>21</sup> Nevertheless, current studies highlighted respiratory tract as the main entry point, with primary viral replication occurring in the mucosal epithelium of upper respiratory tract and subsequent multiplication in the lower respiratory tract and intestinal mucosa.<sup>10</sup>

### **Immunopathogenesis**

Several outcomes have been observed following SARS-CoV-2 infection: asymptomatic (1.2%), mild to moderate cases (80.9%), severe cases (13.8%), critical cases (4.7%), and death (2.3%). This infection has been considered a self-limiting disease, and most people were recovered in 1-2 weeks. However, small proportion of patients, especially those who were elderly or had co-morbid conditions, experienced severe clinical manifestations and death due to acute respiratory distress syndrome (ARDS) and multi organs failure.<sup>10</sup> SARS-CoV-2 infection results in exaggerated and persistent lung inflammation. Since this virus uses the same cell receptor as SARS-CoV, several mechanisms that are similar to SARS-CoV are thought to underlie the pathogenesis of this infection.

#### *Innate immune responses against SARS-CoV-2*

After successfully entering the target cells such as pneumocytes or endothelial

cells, SARS-CoV-2 can initiate antiviral response either inside these infected target cells or in the uninfected tissue macrophages and dendritic cells that have taken up the lysed cells as a result of the infection. As with other RNA viruses, it is likely that SARS-CoV-2 uses viral RNA genome or its intermediates such as dsRNA as their pathogen-associated molecular patterns (PAMPs), which are recognized by the pattern recognition receptors (PRRs) on the host cells, in this case are either the endosomal RNA receptor, Toll-Like Receptor (TLR) 3 and TLR7, or the RNA sensor in the cytosol, Retinoic-acid Inducible Gene (RIG)-I/melanoma differentiation-associated protein (MDA)5. Additionally, various PRRs may also recognise endogenous damage-associated molecular patterns (DAMPs) originate from the host cells, such as nuclear and cytosolic proteins, that are released by injured tissues and dying cells as a result of the infection.<sup>23</sup> These recognitions lead to the activation of downstream signalling and eventually the expression of type I interferon (IFN) and other pro-inflammatory cytokines. The binding of type I IFN to its receptor on host cells result in the transcription of IFN-stimulated genes (ISG) which can suppress viral replication early in the infection. Indeed, main effector in innate immune response against various virus infections involves type I interferon response pathway which is vital not only for controlling viral replication but also for inducing adaptive immune response.<sup>24</sup>

In the severe cases of SARS-CoV and MERS-CoV, high influx of macrophages and neutrophils are regularly observed (FIGURE 3).<sup>24</sup> Tissue macrophages have been linked to epithelial damage that initiates ARDS. Macrophage activation leads to the production of type I and type III interferons, which stimulates antiviral states in the surrounding cells and limits early viral replication, as well as IL-6 and IL-1 $\beta$  that are important for the

initiation of inflammation by recruiting neutrophils and cytotoxic T cells. Activated neutrophils release reactive oxygen species and leukotrienes, and while they are important for neutrophil-mediated early virus control, they can

also directly damage pneumocytes and endothelial cells in the lung and cause acute lung injury. In fact, persistent neutrophil-mediated damage to the alveolar cells is commonly observed in severe or chronic viral infection.<sup>25</sup>

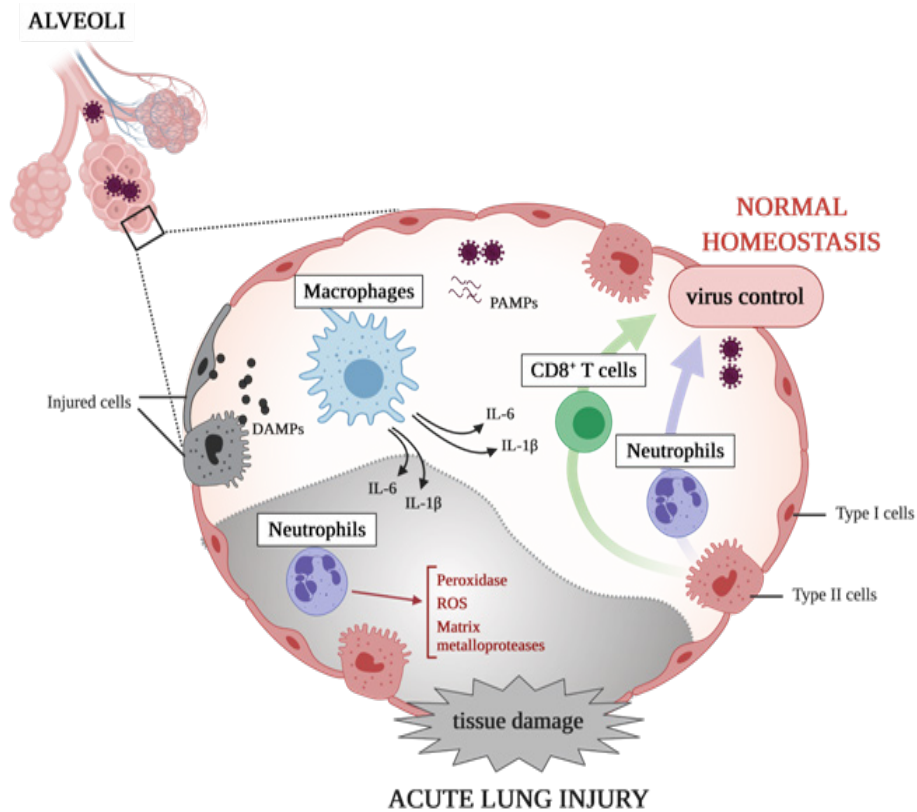


FIGURE 3. Contribution of innate immune responses to antiviral immunity and lung injury [modified from <sup>25</sup>]

Using a mouse model of SARS-CoV infection, it has been demonstrated that severe pneumonia was mainly caused by dysregulation of type 1 IFN response as well as inflammatory monocyte-macrophages.<sup>24</sup> Indeed, evidences have strongly suggested that alteration in the innate immune response correlates with clinical manifestations in COVID-19 infection. As with SARS-CoV and MERS-CoV, it is predicted that SARS-CoV-2 utilizes various mechanisms to dampen type I IFN response either by suppressing the production of type I IFN and/or the signalling downstream of its receptor in the target cells (FIGURE 4).

Similar to the two earlier pandemics, in SARS-CoV-2 infection,

there might be a delay in type 1 IFN response which impairs early virus control, resulting in the influx of large number of neutrophils and monocyte-macrophages.<sup>20,24,25</sup> Recent studies have also demonstrated that COVID-19 patients have an expanded population of circulating monocytes producing IL-6 and IL-1β.<sup>25</sup> The overproduction of pro-inflammatory cytokines by these cells, particularly IL-6, IL-1β, and TNFα, and chemokines leads to “cytokine storm”, which increases the risk of widespread vascular hyperpermeability, systemic inflammation, multiorgan failure, and eventually death if it is uncontrolled over time.<sup>26</sup> Via similar mechanism, SARS-CoV-2 targeting other ACE2-expressing

cells in various organs contributes to systemic sepsis which increases the risk of multiple organ damages and fatalities.<sup>10</sup>

SARS-CoV-2 may also cause pyroptosis of macrophages and lymphocytes, contributing to peripheral blood lymphopenia in vast majority of patients.<sup>27</sup> Studies have shown that patients in severe condition are characterized by increased total neutrophil, decreased lymphocytes, increased serum IL-6, and increased level of innate cytokines including IL-1 $\beta$ .

Indeed, neutrophilia, lymphopenia, and increased level of IL-6 have been shown to significantly correlate with severity of the disease.<sup>24,25</sup>

In addition to mechanisms mentioned above, SARS-CoV-2 infection in the lung is predicted to cause downregulation and promotion of ACE2 shedding, causing loss of pulmonary ACE2 function and renin-angiotensin-system dysfunction, which further increase vascular permeability, recruitment of neutrophils, and exacerbate inflammatory responses.<sup>10</sup>

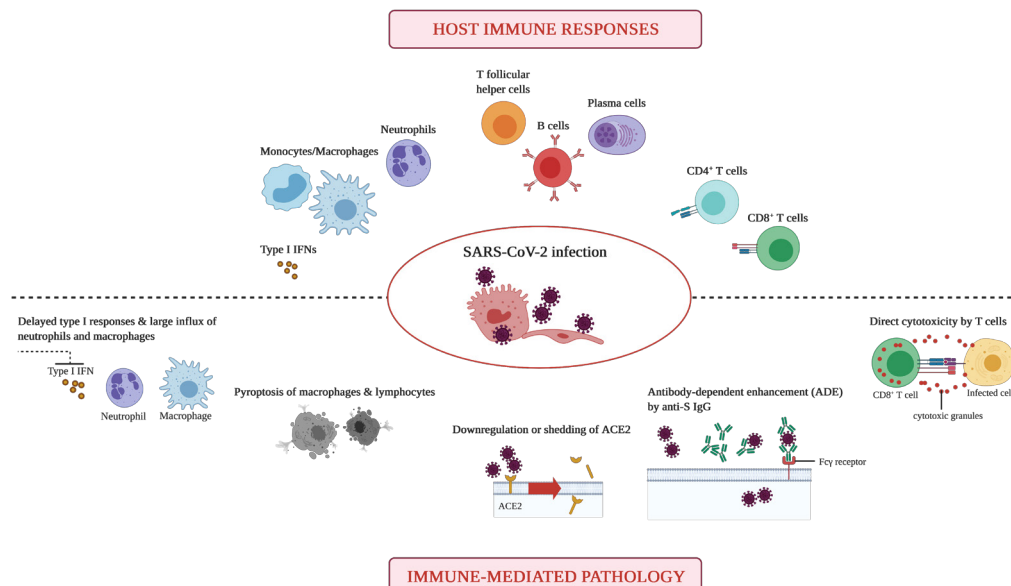


FIGURE 4. Proposed host immune responses and immunopathology during SARS-CoV-2 infection

#### *Adaptive immune responses against SARS-CoV-2*

The recognition of PAMPs and activation of innate immune responses lead to the induction of adaptive responses. T cells are particularly important in antiviral immunity, with CD4<sup>+</sup> Th1 cells being central in shaping the overall adaptive immune response and CD8<sup>+</sup> T cells being important in killing virally infected cells. On the other hand, neutralizing antibodies as part of the humoral response are important for limiting virus infection at later stages and prevent reinfection. A recent study has indicated that both cellular and

humoral immunity might be required for effective viral clearance following SARS-CoV-2 infection.<sup>28</sup>

Studies examining the humoral response to SARS-CoV-2 infection are limited. From currently available evidences, there seems to be a slight difference in terms of the kinetics of antibody generation in SARS-CoV-2 infection compared to the previous two pandemics. In SARS-CoV infection, IgM seroconversion is observed as early as day 4 after onset of the disease, while MERS-CoV infection results in a seroconversion on week 2-3 after onset. Following SARS-CoV-2 infection, one study reported a peak of anti-nucleocapsid (N) IgM

level on day 9 after disease onset and a switch to IgG by week 2.<sup>1</sup> Both anti-nucleocapsid (N)-specific and anti-spike (S)-specific IgM and IgG, mainly in IgG1 isotype, could be detected in recovered patients in a recent study, with S-specific IgG showing a neutralization activity.<sup>28</sup> Indeed, recently published study has observed strong correlation between levels of RBD-binding antibodies and SARS-CoV-2 neutralizing antibodies in PCR-confirmed COVID-19 patients.<sup>29</sup> The occurrence of antibody-producing cells and T follicular helper cells, which are important for antibody production, was reported to coincide with the start of viral clearance. These findings suggested that neutralizing antibodies correspond to the protective humoral immunity against SARS-CoV-2 infection.<sup>28,30</sup> Cross-reactivity with SARS-CoV was also seen in sera from 5 COVID-19-confirmed patients, although further studies using larger cohorts are required.<sup>1</sup>

It has been reported that early development of anti-spike (S) IgG, while providing some control to the infection, correlates with more severe conditions via a mechanism called antibody-dependent enhancement (ADE). This sub-optimal antibody response may create a complex with the virus which increases the cellular uptake and infection of the target cell, resulting in persistent viral replications.<sup>31</sup> This antibody-virus complex might also alter inflammatory responses and causes severe lung injury, by promoting macrophages accumulation, activating complement classical pathway, and potentially mediating antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism.<sup>20,27</sup>

Evidences have indicated the requirement of T cells in controlling SARS-CoV-2 infection particularly at the later stage. In non-severe recovered patients, an increase in peripheral blood CD4<sup>+</sup> and CD8<sup>+</sup> T cell frequency was observed at around day 7-8 after disease onset, preceding the resolution

of symptoms. The co-expression of CD38 and human leukocyte antigen (HLA)-DR in subsets of these cells suggests activated cells. A recent study has demonstrated that following mild SARS-CoV-2 infection, activated CD8<sup>+</sup> CD38<sup>+</sup>HLA-DR<sup>+</sup> T cells produced greater response than that of their CD4<sup>+</sup> T cells counterparts.<sup>30</sup> In contrast, consistent with lymphopenia previously reported in severe patients with ARDS, there was a reduced CD8<sup>+</sup> and CD4<sup>+</sup> T cell counts in the peripheral blood with signs of hyperactivation, and an increase in CD4:CD8 ratio which may indicate migration of CD8<sup>+</sup> T cells to the respiratory airway.<sup>32,33</sup> There was also increased proinflammatory Th17 phenotype in the CD4<sup>+</sup> T cells pool, as opposed to IFN $\gamma$ -producing Th1 cells that were identified in recovered patients.<sup>28,33</sup>

T cells reactive to nucleoprotein (N), main protease, and spike (S) could be detected in previously infected patients.<sup>28</sup> Interestingly, one study recently demonstrated that although with lower frequency, seronegative healthy individuals also contain a population of anti-spike (S) CD4<sup>+</sup> T cells. Whilst these CD4<sup>+</sup> T cells in COVID-19 patients recognized both RBD-containing S1 subunit and S2 subunit of S protein, cells from the healthy controls only recognized S2 subunit but not S1, suggesting that RBD-S1 is the major epitope for inducing CD4<sup>+</sup> T cell response.<sup>34</sup>

While T cell response are inarguably vital for successful viral clearance, T cell-dependent cytokine production and particularly CD8<sup>+</sup> T cell-mediated direct cytotoxicity, can potentially cause tissue injury and exacerbate inflammation if not cautiously controlled. Viral dissemination and uncontrolled infection are key drivers for severe SARS-CoV-2 infection. A dysregulation of innate responses undoubtedly plays a crucial role in the failure to control the virus at the early stage. However, it is likely that dysregulation in adaptive responses also contributes to immunopathology later



during infection. Uncontrolled CD8<sup>+</sup> T cell responses may directly contribute to lung pathology in ARDS, as evidenced by the presence of T cells in the lung section and high concentration of cytotoxic granules in CD8<sup>+</sup> T cells indicating high toxicity status of these cells.<sup>20,33</sup>

The prolonged subacute rather than acute clinical characteristics of COVID-19 infection could potentially lead to T cell exhaustion and depletion, which manifest as progressive lymphopenia and immunosuppression in severe patients (FIGURE 5). Indeed, one study has demonstrated that both CD4<sup>+</sup> and CD8<sup>+</sup> T cells in COVID-19 patients highly

expressed markers of T cell exhaustion, such as programmed cell death protein (PD)-1 and T-cell immunoglobulin mucin (Tim)-3.<sup>35</sup> In contrast, peripheral T cells from recovering patients display signs of effective adaptive immune response, including clonal expansion, T cell activation, and memory formation. Therefore, it is currently proposed that during early infection with SARS-CoV-2, as a result of rapid expansion, effector CD8<sup>+</sup> T cells contribute to lung inflammation, and later in the process, persistent viral infection may cause T cell exhaustion and depletion, leading to more severe conditions and fatality.<sup>25</sup>

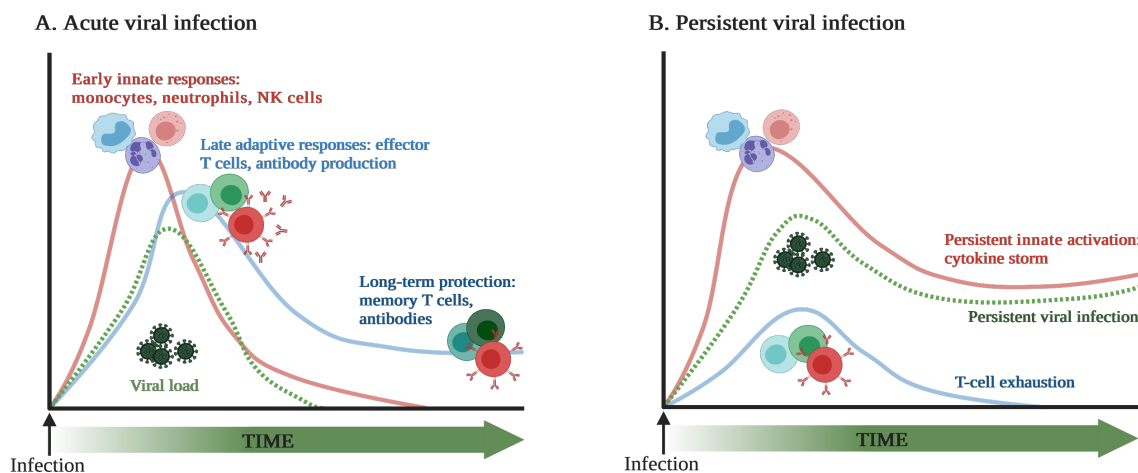


FIGURE 5. Immune responses in acute and uncontrolled viral infection [modified from <sup>25</sup>]

## CONCLUSION

COVID-19 is a serious respiratory disease caused by a novel betacoronavirus, SARS-CoV-2, which exhibits homologies with other coronaviruses causing previously pandemic SARS and MERS. Entry to the host cells depends on the interaction of viral spike protein with ACE2 receptor on the target cell surface. Disease transmission from infected to healthy individuals has been thought to occur via respiratory droplets (primarily), close contacts, aerosols, and possibly faecal-oral. While most infected individuals have mild disease and even asymptomatic, a proportion of patients

can develop severe disease and death due to ARDS and multi organ failure. The pathogenesis of COVID-19 has been thought to result not only from the direct impact of viral infection on tissue destruction but also from the complex interplay of the virus with the host immune responses. While innate and adaptive immune responses are inarguably important for controlling viral dissemination, an immune-induced pathology has been proposed as a consequence of the virus ability to modify the host responses through various mechanisms, resulting in the dysregulation of both the innate and adaptive responses and severe clinical manifestations in the susceptible infected

individuals. As currently available data on the pathogenesis of this novel virus infection are still limited, its complexity necessitates further studies both in the *in vitro* and *in vivo* settings to better elucidate this process.

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