

## Systematic Review

# A systematic review of immune pathogenesis of SARS-COV-2 infection

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**Received:** 21 April 2021

**Revised:** 29 May 2021

**Accepted:** 31 May 2021

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### ABSTRACT

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the world health organization on March 11, 2020. The host immune response to SARS-CoV-2 appears to play a critical role in disease pathogenesis and clinical manifestations. SARS-CoV-2 causes direct activation of anti-viral immune responses and leads to the release of uncontrolled inflammatory mediators. These SARS-CoV-2-induced immune responses may lead to various other abnormalities like lymphopenia, thrombocytopenia and granulocyte and monocyte dysfunction, making the patient more prone to secondary infections by microorganisms, which may result in further further serious complications like septic shock, severe multiple organ dysfunction and eventually death. Therefore, mechanisms underlying immune abnormalities in patients with COVID-19 disease must be elucidated to guide clinical management of the disease. Rational management in combating the disease includes enhancing anti-viral immunity and inhibiting systemic inflammation, which is key to successful treatment.

**Keywords:** SARS-CoV-2, Immune response, Pathogenesis

### INTRODUCTION

The rapid global spread of the coronavirus disease 2019 (COVID-19) poses a remarkable health crisis by affecting millions of people worldwide. It has caused a sudden significant increase in hospitalizations for pneumonia with multiorgan disease. Originated in the Wuhan province of China, the outbreak was reported to the World Health Organization (WHO) on December 31, 2019. Soon after, the causative pathogen was identified as a beta coronavirus belonging to the Coronaviridae family. It was also closely related to severe acute respiratory syndrome virus 1 (retrospectively named SARS-CoV-1) and Middle Eastern respiratory syndrome (MERS) coronavirus that caused zoonotic epidemic and local outbreaks in 2003 and 2012, respectively. Thus, SARS CoV 2 is the third coronavirus that has caused severe disease in humans in the past 2 decades.<sup>1</sup>

Many infected people of SARS-CoV-2 infection are asymptomatic or experience mild symptoms and recover without much medical intervention.<sup>2,3</sup> However, older people and those with comorbidities like hypertension, diabetes, obesity, and heart disease are susceptible to the progression of the disease to a life-threatening illness.<sup>4,5</sup> Severe cases of COVID-19 are not a consequence of viral burden and/or failure of the adaptive immune response to subdue the pathogen, rather it is a sequelae of immunopathology, resulting from imbalanced innate immune response, which may not be linked to pathogen burden at all.<sup>6</sup> This review will thematically focus on the innate and adaptive immune responses to SARS-CoV-2 to provide a deeper insight into the disease pathogenesis that likely contributes to disease severity and death and look over the extrapulmonary manifestations of COVID-19.

## METHODS

### *Protocol*

The study protocol was in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.

### *Search strategy*

A systematic search was done in databases like PubMed, Google scholar, Medline, American medical association, JAMA internal medicine, British medical journal, WHO, Elsevier, journal of the association of physicians of India, AJP, ISSN, Frontier's media, NIHR, IDSA, Cochrane, MDPI, Lancet, NICE, PLoS, Science Direct, PNAS, The new England journal of medicine, science translational medicine, ISCoS, medRxiv and Nature medicine. The following search terms were used: 'immune responses,' 'pathogenesis,' 'virus entry,' 'viral replication,' 'host defense,' 'inflammatory changes,' 'pulmonary manifestations,' 'extrapulmonary manifestations,' 'MIS.' The references of identified articles were also manually searched for additional studies meeting the study criteria.

### *Inclusion criteria*

Inclusion criteria for current study were; articles with abstract, original data and case reports, articles from March 2020 to November 2020, regarding immune responses and pathogenesis of COVID-19, articles with keywords in their title and abstract with their full text and articles published in English.

### *Exclusion criteria*

Exclusion criteria for current study were; articles that were only about SARS and MERS without any discussion on SARS-CoV-2, articles with the only abstract that had no full text, articles where original data were not reported (eg. review articles), articles related to treatment and vaccines, surveys, guidelines and cover letters were excluded.

### *Study selection*

A total of 110 articles were identified from initial database searches. 25 articles that addressed the treatment of SARS-CoV-2, 10 articles regarding the diagnosis of SARS-CoV-2 and 5 articles that addressed post COVID pathologies were excluded. 5 articles were also excluded as their full texts were not accessible. Therefore, a total of 65 potentially eligible articles were included in the final analysis. The titles and abstracts of all the studies were reviewed. Full texts of the citations were collected for further screening.

## RESULTS

From the review of studies, the initial immune response attracts T lymphocytes to the site of infection and the infected cells are eliminated even before the virus spreads, leading to recovery in majority of the population. In the small proportion of people who develop severe disease, an aberrant host immune response is elicited. Upregulation of chemokines and influx of neutrophils and monocytes into the airway has been observed, disrupting the air-blood barrier in the alveoli by causing damage to both the airway epithelial cells and vascular endothelial cells while increasing cytokine production. Ironically, enhanced immune activation is the prime cause of the severity of the disease.

## DISCUSSION

Coronaviruses, of order Nidovirales, have the largest genome of all RNA viruses. SARS-CoV-2 is the seventh virus to be identified among the beta-coronaviruses. It is an enveloped, positive-sense single-stranded RNA virus with protein spikes on its surface. The virus has 4 essential structural proteins, namely; spike envelope protein, nucleocapsid protein, matrix protein, and glycoprotein. The Spike proteins play a key role in the life cycle of the virus and host defense response.<sup>7</sup> Epidemiologic and virologic studies suggest that virus transmission mainly occurs by close contact with infected people through respiratory droplets. Studies demonstrate that SARS-CoV-2 is shed highest in the first 3 days from the onset of symptoms, in the early course of the disease. The incubation period for COVID-19 can be up to 14 days, the average is 5 to 6 days. Infected persons can be transmitting the disease even during this pre-symptomatic period.<sup>8</sup> Contact surface spread is another possible mode of transmission. However, the number of viruses detected on surfaces decay within 48 to 72 hours.<sup>9</sup> Experimental data also has suggested that SARS-CoV-2 may also be transmitted by aerosols (smaller droplets that remain suspended in air), so-called airborne transmission.<sup>10</sup>

A hypothesis states that blood group O individuals confer relative protection to SARS-CoV-2 infection. In vitro studies indicated that the virus particles could be glycosylated by the A and B variants of the ABO glycosyl transferases. This allows the anti-A and anti-B antibodies present on mucosal surfaces of some individuals to neutralize the virus, thus supporting the statement.<sup>11</sup> During viral infection, the spike protein is cleaved into S1 and S2 subunits. The Receptor Binding Domain in the S1 subunit binds directly to the peptidase part of the ACE2 receptor, while S2 is responsible for the fusion of the membrane.<sup>12</sup> During this binding, the complex is processed proteolytically by type 2 transmembrane protease TMPRSS2, leading to ACE-2 cleavage and spike protein activation, thus facilitating the entry of the virus into the target cell.<sup>13</sup> Furthermore, SARS-CoV-2 uses the host enzyme 'furin,' which is abundant in the respiratory tract, to cleave the viral spike

protein. The key determinant of transmissibility is the efficiency with which the virus binds to the ACE2 receptor.<sup>14</sup> Once the genetic material of the SARS-CoV-2 virus gets inside the cell, the virus assumes control over the kinase family of enzymes, particularly the p38/MAPK pathway, that through the process of phosphorylation, is also known to trigger the production of pro-inflammatory cytokines. This finding is remarkable in the pathogenesis of COVID-19.<sup>15</sup>

After the entry of the virus into the host cell, the initial immune response attracts T lymphocytes to the site of infection. The infected cells are eliminated even before the virus spreads, leading to recovery in most of the population. In the small portion of people who develop severe disease, an aberrant host immune response is elicited.<sup>16</sup> Recognition of SARS-CoV-2 by the innate immune system triggers the secretion of interferons (IFN) and an entire cascade of events is activated. The release of pro-inflammatory cytokines signals the endothelial cells, enables chemokines to spread throughout the bloodstream and causes recruitment of the immune cells at the site of infection. These cells interact with the activated endothelium and migrate to the site of infection, where they release reactive oxygen species (ROS) and perform effector functions, thereby killing the infected cells directly and activating an adaptive immune response that is pathogen-specific.<sup>17</sup> There is a significant rise in neutrophil levels in circulation and bronchoalveolar lavage fluid (BALF) in severe cases of COVID-19, in addition to the upregulation of chemokines that act as chemoattractants for neutrophils and monocytes.<sup>18</sup> The influx of these cell types into the airway disrupts the air-blood barrier in the alveoli, causing damage to both the alveolar epithelial cells and the vascular endothelial cells.<sup>19</sup> The most consistent finding in COVID-19 is lymphopenia with drastically reduced CD4+ and CD8+ T-cells. The underlying mechanisms for lymphopenia could plausibly include: as lymphocytes express ACE2 receptors, they are potential targets of the virus leading to lymphocyte death. Infiltration of T cells and subsequent trapping in the lower respiratory tract as well as immune cell death. Inhibition of lymphocytes by metabolic disorders, such as lactic acidosis. Patients with severe COVID-19 have increased blood lactic acid levels, which may affect the lymphocytes proliferation. Viral infection is a stressful condition to the body and leads to the activation of the hypothalamic-pituitary-adrenal axis. This results in the upregulation of endogenous corticosteroids, which might interfere with the immunopathogenic mechanisms of lymphopenia in COVID-19.<sup>20</sup>

Early in the course of infection, there is robust memory B cell and plasmablast expansion, along with the secretion of antibodies in the serum. IgM antibodies are released from day 5 to 7 and IgG antibodies are released from day 7 to 10 from the onset of symptoms. After the acute phase of infection, the antibody levels always decline as the plasmablasts secreted in the first week are short-lived.

Effector CD8+ T-cell responses also follow a similar pattern. The smaller number of long-lived plasma cells that reside in the bone marrow then maintains the serological memory and constitutively secretes antibodies even in the absence of the virus.<sup>21</sup> Studies have also shown that this cellular immunity persists at least for six months. Macrophage-activation syndrome (MAS), a life-threatening clinical entity, is associated with the pro-inflammatory responses induced by SARS CoV 2.<sup>22</sup> The pathogenesis of MAS is postulated as the impaired cytolytic activity of natural killer cells and specific CD8+ T-cell subpopulations, whose primary work is to lyse the infected host cells and prevent the prolonged secretion of inflammatory cytokines by the infected cells.<sup>23</sup> This defect in cell-mediated lysis is driven by elevated levels of IL-6, establishing a vicious cycle of cytokine-driven pro-inflammatory cytokine secretion. Therefore, raised IL-6 levels and their association with the severity of the disease are found to reflect an over-exuberant inflammatory response that lacks proper regulation and resolution, a condition called 'Cytokine storm.'<sup>24</sup> The inflammatory nature of the injury is confirmed by the post-mortem histology of lung tissues of patients who died of covid-19. The features are interstitial mononuclear inflammatory infiltrates, bilateral diffuse alveolar damage, formation of hyaline membrane, and desquamation suggestive of acute respiratory distress syndrome (ARDS).<sup>25</sup> The presence of mucus plugs with fibrinous exudate in the airway is a unique feature of COVID-19. This is potentially caused by the accumulation of massive amounts of pro-inflammatory cytokines, eventually leading to lung parenchyma damage.<sup>26</sup> Direct viral injury in the lungs results in the hypoxic injury of the vasculature, leading to activation of the coagulation cascade.<sup>27</sup> The result of the hypercoagulable state is excess thrombin generation and fibrinolysis shutdown. High levels of D-dimer and fibrinogen indicate it. At this stage, patients are more prone to stroke, pulmonary embolism, deep vein thrombosis and disseminated intravascular coagulation.<sup>28</sup>

There are also other mechanisms for activating endothelial cells and vasculitis, even in the absence of the virus itself for example, neutrophil extracellular traps (NETs) and hypoxia.<sup>29</sup> The ability of neutrophils to form NETs is highly beneficial in host defense against pathogens, but sustained NET formation can also lead to damaging inflammatory reactions. Increased NET-specific markers like myeloperoxidase DNA and citrullinated histone H3 were seen in the sera of COVID-19 patients.<sup>30</sup> The etiology put forward for Thrombocytopenia in COVID-19 patients are: the SARS-CoV-2 virus binds to bone marrow cells through the CD13 receptor, leading to the apoptosis of platelets in the bone marrow.<sup>31</sup> There is a hypothesis that by forming autoantibodies, COVID-19 causes increased platelet destruction. Viral epitopes circulating in the blood would mimic antigens present on the surface of platelets and lead to the formation of antibodies. These platelet

antibody complexes are then destroyed through a complement-independent immune-mediated response.<sup>32</sup>

Coronaviruses also infect the gastrointestinal tract due to the high expression of ACE2 receptors and TMPRSS2. The viral infection causes an alteration in the intestinal permeability resulting in enterocyte malabsorption, thus diarrhea being the frequent presenting symptom. Another possible explanation for diarrhea is the alteration of gut microbiota due to the antibiotics and anti-virals used in the treatment of COVID-19. The disappearance of symptoms after anti-viral therapy (oral lopinavir and ritonavir) supports the link between the symptom and COVID-19 disease.<sup>33</sup> The usual form of liver injury due to COVID 19 is raised transaminases rather than cholestasis. This suggests that the liver injury is likely to be mediated by the cytokines rather than direct effects of the virus in the hepatocytes, a phenomenon referred to as 'by-stander hepatitis.'<sup>34</sup> Hepatic side effects of some of the drugs used in the treatment of COVID-19 mandates caution while using in patients with cirrhosis. Remdesvir is known to cause elevated transaminases and bilirubin, even in patients without underlying liver disease.<sup>35</sup> Tocilizumab should not be given to patients with decompensated cirrhosis and should be used cautiously while treating patients with hepatitis B due to the risk of flare.<sup>36</sup>

The numerous contributory mechanisms for cardiac manifestations in COVID-19 patients include direct myocardial damage by the virus, hyperinflammatory state, downregulation of ACE2-receptor, hypoxia, hypotension and endogenous catecholamine adrenergic status.<sup>37</sup> Relative bradycardia, where there is the dissociation between pulse and temperature, is observed in COVID-19 patients. Direct pathogenic effect on the myocardium, release of inflammatory cytokines and increased vagal tone are the few possible reasons.<sup>38</sup> In the nasal cavity, coronavirus affects the sustentacular cells that provide structural support for all the nearby nerve cells. The immune system reacts by generating inflammatory cells, which can damage these nerve cells. Normally, signals are transmitted through the olfactory bulb to the brain, where the smell is identified. Damage to either of these structures can cause loss of perception of smell. Damaged olfactory nerves do not always regenerate properly. This results in a distorted sense of smell and makes the patients detect odd odors, a condition called 'parosmia.'<sup>39</sup> The ophthalmic manifestation commonly reported following the SARS-CoV-2 virus is conjunctivitis, bilateral, mild, and of the follicular type, without corneal involvement. Usage of high doses of chloroquine and hydroxychloroquine over a short period of time in the treatment of COVID-19 has risks of developing irreversible maculopathy.<sup>40</sup> The staggering diversity of neurological manifestations in COVID-19 ranges from mild olfactory and gustatory perception abnormalities to necrotizing encephalopathy and stroke. The mechanism postulated for SARS-CoV-2 induced neurogenic acute respiratory failure is that the

virus may affect the medullary respiratory centers, thereby playing a possible role.<sup>41</sup>

SARS-CoV-2 is likely to traverse in a retrograde fashion from peripheral nerves into the central nervous system. It is supported by the fact that in the majority of patients, SARS-CoV-2 first infects the gut. The enteric nervous system then becomes a portal of entry with retrograde migration of the virus through the vagal and sympathetic afferents.<sup>42</sup> Following SARS-CoV-2 infection, the rapid development of parkinsonism has been found in some patients. The three potential mechanisms postulated are: in severe COVID-19, in conjunction with a hypercoagulable state, vascular insults have been reported to develop in multiple sites, including the brain. This could damage the nigrostriatal system directly, akin to what is seen in vascular parkinsonism. Neuroinflammation and demise of nigral dopamine neurons could be triggered by the marked systemic inflammation caused by COVID-19, the most susceptible parts being the midbrain dopaminergic neurons.<sup>43</sup> Detection of viral RNA in post-mortem brains of some patients with COVID-19 suggests that SARS-CoV-2 may be a neurotropic virus.<sup>44</sup> COVID-19 has also been known to cause renal manifestations through multiple mechanisms. Some of them include direct viral invasion, systemic inflammation, hemodynamic disturbances, volume depletion effects and rhabdomyolysis. The inability of the lungs to oxygenate blood and offload carbon dioxide sufficiently has led to chemical and acid-base anomalies, causing harm to the renal regulatory systems. Hypoxemia itself can reduce renal blood flow. Retention of carbon dioxide causes acidification of blood, forcing the kidney to reabsorb bicarbonate and maintain physiologic pH, which in turn increases the oxygen requirement of the kidney, leading to hypoxic damage.<sup>45</sup> One dermatological manifestation that was found to be associated with COVID-19, possibly due to the anti-viral medications given, is exanthematous drug eruption. Though not very symptomatic, some patients have painful erythematous macules or papules. These lesions were discovered to be mainly located on the toes, soles, heels, fingers and extremities and are commonly referred to as 'COVID toes.'<sup>46</sup> A multisystem inflammatory illness has rarely been observed following acute SARS-CoV-2 infection. This has been termed multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A). Apart from early inflammation resulting from viral multiplication and cell death, a dysregulated host immune response, 2 to 5 weeks after onset of SARS-CoV-2 infection, can lead to hyperinflammation in organ systems other than those affected during COVID-19.<sup>47</sup> Patients with MIS are found to be almost universally antibody positive.<sup>48</sup>

### **Limitations**

There are three major limitations in this study that could be addressed in future research. All studies included in this review were short-term studies. Many studies

included were not randomized control trials. The study population taken in the reviews was too small to extrapolate the observations to the world population, especially in the midst of racial, ethnic, and geographical differences.

## CONCLUSION

Although the detection of the virus on surfaces reinforces the potential for transmission, droplet spread via person-to-person contact remains the primary mode of transmission. The host immune system mainly influences the severity of the disease. Therefore, the immune system needs to be targeted and modulated alongside the therapeutic interventions aimed at the virus to prevent the progression of the disease. More long-term studies encompassing a greater number of participants from diverse study populations are necessary to understand the disease further and evolve treatment and prevention strategies for the welfare of the global community.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Srikumar S, Perumal S. A systematic review of immune pathogenesis of SARS-COV-2 infection. *Int J Adv Med* 2021;8:978-83.