

# Hypercytokinemia and Pathogen–Host Interaction in COVID-19

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**Abstract:** Severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 (SARS-CoV-2) is a novel coronavirus identified as the cause of coronavirus disease-2019 (COVID-19) that began in Wuhan, China in late 2019 and spread now in 210 countries and territories around the world. Many people are asymptomatic or with mild symptoms. However, in some cases (usually the elderly and those with comorbidities) the disease may progress to pneumonia, acute respiratory distress syndrome and multi-organ dysfunction that can lead to death. Such wide interindividual differences in response to SARS-CoV-2 infection may relate to several pathogen- and host-related factors. These include the different levels of the ubiquitously present human angiotensin I converting enzyme 2 (ACE2) receptors gene expression and its variant alleles, the different binding affinities of ACE2 to the virus spike (S) protein given its L- and S-subtypes and the subsequent extent of innate immunity-related hypercytokinemia. The extensive synthesis of cytokines and chemokines in coronavirus diseases was suggested as a major factor in exacerbating lung damage and other fatal complications. The polymorphisms in genes coding for pro-inflammatory cytokines and chemokines have been associated with mediating the response and susceptibility to a wide range of infections and their severe outcomes. Understanding the nature of pathogen–host interaction in COVID-19 symptomatology together with the role of hypercytokinemia in disease severity may permit developing new avenues of approach for prevention and treatment and can delineate public health measures to control the spread of the disease.

**Keywords:** SARS-CoV, MERS-CoV, SARS-CoV-2, COVID-19, hypercytokinemia

## Introduction

Over the past two decades, the world has experienced three acute lower respiratory tract outbreaks caused by coronaviruses. Those were the epidemic severe acute respiratory syndrome (SARS) coronavirus (CoV), the epidemic Middle East respiratory syndrome (MERS-CoV) and – presently – the pandemic coronavirus infection disease (COVID-19 or SARS-CoV-2), initially known as the 2019-novel (n)-CoV. Mainly prevalent in China and Hong Kong, between 2002 and 2003, SARS-CoV infection resulted in 8100 cases and more than 770 deaths with a case fatality rate (CFR) of about 10%.<sup>1–3</sup> The intermediate host was shown to be the civets.<sup>4</sup> MERS-CoV infection, on the other hand, was predominantly prevalent in the Middle East (2012–2014) and caused over 850 cases resulting in approximately 350 deaths, with a CFR of about 38%.<sup>5</sup> The intermediate host of MERS-CoV was identified to be dromedary.<sup>6</sup> In December 2019, SARS-CoV-2 infection began to spread from Wuhan, Hubei, China and by March 11, WHO declared COVID-19 a pandemic when the number of cases was increased 13 times (outside China) than the initial number of

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cases, reporting more than 118,000 infections and triple the number of countries primarily involved (114 countries) with over 4000 deaths.<sup>7</sup> As of June 16, 2020, there were approximately 7.9 million confirmed cases reported from 210 countries and territories around the world, claiming over 450,000 lives.<sup>7</sup> On that date, almost one third of the world confirmed cases and death toll were reported in USA alone.<sup>7</sup> So far, the crude CFR is around 6.5%, lower than that of the other two coronavirus pandemics.<sup>7</sup> Although yet to be fully realized, the intermediate host of SARS-CoV-2 is thought to be pangolin.<sup>8</sup> It is speculated that, like SARS-CoV and MERS-CoV, the natural host is bats.<sup>9</sup>

The Chinese Center for Disease Control and Prevention (CDC) divided the clinical manifestations of the disease severity into mild (non- or mild-pneumonia; occurred in 81% of the cases); severe (dyspnea,  $\geq 30$ /min respiratory frequency,  $\leq 93\%$  blood oxygen saturation, and/or more than 50% lung infiltrates within 1–2 days; in 14% of the cases) and critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure; in 5% of the cases).<sup>10</sup> In addition to the common systemic symptoms (eg, fever and fatigue), COVID-19 manifest in respiratory symptoms that range from mild (dry cough, difficulty in breathing, hypoxemia) to severe (acute respiratory distress syndrome – ARDS, and acute respiratory or multiple organ failure) (Table 1). COVID-19 can also cause severe pneumonia (with clinical manifestations), biomarker profile and lung imaging similar to that observed in SARS-CoV.<sup>1–3</sup> Some severe cases experience acute myocardial injury,

sepsis and/or fungal infection.<sup>11,12</sup> Severe clinical symptoms may eventually lead to death.

This article explores our current knowledge of the common and different characteristics of the coronavirus epidemic (SARS-CoV and MERS-Cov) and pandemic (SARS-CoV-2) infections emerged over the past two decades. Special emphasis is directed to understanding the pathogen–host interaction in disease symptomatology and severity, the development of innate immunity-related hypercytokinemia and the influence of the subsequent inflammation on disease outcome. Our current understanding of COVID-19 together with the knowledge gained from SARS-CoV and MERS-CoV infections would permit developing new avenues of approach for disease prevention and treatment and can define effective public health measures to control the spread of COVID-19 and other coronavirus-related diseases.

## Pathogen-Host Interaction: An Overview

SARS-CoV, MERS-CoV and SARS-CoV-2 are all enveloped positive-sense RNA viruses belonging to the *Coronaviridae* family, *Orthocoronavirinae* subfamily,  $\beta$  genus that mainly cause lower respiratory tract infections in humans.<sup>13–15</sup> SARS-CoV-2 genome is in 80% homology with SARS-CoV and 50% with MERS-CoV but it is 96% homologous with coronavirus isolated from the giant bats in Yunnan.<sup>9</sup> Typically, the coronavirus genome is 26–32 kilobases in length with a highly conservative basic structure. SARS-CoV-2 genome was reported to be 29,829 ribonucleotides in length.<sup>16</sup> In general, the coronavirus genome utilizes approximately 67% of the sequence to encode RNA polymerase that plays a role in viral protein processing, unwinding and replication and blocking host cell protein synthesis.<sup>9,13,17</sup> The remaining genome, however, encodes other structural and accessory proteins.<sup>4,14</sup> SARS-CoV-2 has evolved two subtypes, a more infectious L-type and the primary S-type.<sup>18</sup> The different virus subtypes may have a critical role in disease spread and can influence vaccine development and disease therapy.

In humans, coronavirus pathogenesis and infectivity are related to a specific binding between the virus spike (S)-protein, a glycoprotein that exists as a trimer on the surface of the envelope lipid layer, and a protease receptor on the human cell surface.<sup>19</sup> In SARS-CoV and MERS-CoV, the human cells receptors, respectively, are angiotensin I converting enzyme 2 (ACE2)<sup>20,21</sup> and dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing

**Table 1** Coronavirus Stages of Severity.<sup>10</sup>

Case Severity	Clinical Symptoms <sup>1</sup>	Frequency (%) <sup>2</sup>
Mild	Patients without pneumonia or cases of mild pneumonia	81
Severe	Patients suffer from shortness of breath, respiratory frequency $\geq 30$ /minute, blood oxygen saturation $\leq 93\%$ , P/F Ratio $< 300$ , and/or lung infiltrates $> 50\%$ within 24–48 hours.	14
Critical	Patients suffer from respiratory failure, septic shock, and/or multiple organ dysfunction/failure	5

**Notes:** <sup>1</sup>P/F Ratio: PaO<sub>2</sub>/FiO<sub>2</sub>; the ratio of arterial oxygen partial pressure (PaO<sub>2</sub> in mmHg) to fractional inspired oxygen (FiO<sub>2</sub> expressed as a fraction). <sup>2</sup>The reported estimates are based on symptoms reported in 44,415 confirmed Chinese patients suffered from COVID-19 from the early periods of the epidemic up to February 11, 2020. Published estimates suggest that only around 5% of cases in China have been diagnosed and recorded.

protein 2 or cluster of differentiation 26 (CD26).<sup>22</sup> ACE2 is also identified as the cell surface receptor for SARS-CoV-2 S-protein.<sup>17</sup> DPP4, the receptor for MERS-CoV, is expressed ubiquitously in many tissues – endothelia and epithelia – including but not limited to kidney, liver, lung, intestine and, interestingly, also on immune cells (eg, T cells, activated natural killer (NK) cells and myeloid cells).<sup>23</sup> DPP4 is known to play a major role in glucose metabolism which may explain the high prevalence of diabetes observed in severe MERS-CoV cases.<sup>24,25</sup> ACE2, the receptor for SARS-CoV and SARS-CoV-2, although ubiquitously present in many tissues, it is primarily expressed in the epithelial cells of the tracheobronchial tree and respiratory system, kidneys, digestive tract, cardiovascular system and skin.<sup>26</sup> ACE2 is a membrane protein with protease activity that plays a critical role in the regulation of blood pressure by catalyzing the cleavage of the vasoconstrictor angiotensin II into the vasodilator angiotensin (1–7) to antagonize the potentiating function of ACE1.<sup>27</sup> Attenuation of pulmonary ACE2 activity was found to impair bradykinin and facilitate lipopolysaccharide (LPS)-induced neutrophil infiltration.<sup>28</sup> Such a process has long been known to be sufficient to induce respiratory symptoms (eg, airflow obstruction and increased airway hyperreactivity) and inflammation (eg, expression and secretion of pro-inflammatory cytokines).<sup>29</sup> It is apparent, therefore, that the elevated ACE2 expression in lung tissue plays a significant role in the pathogenesis of the acute outcome of infection caused by SARS-CoV and SARS-CoV-2. Indeed, since ACE2 is the same receptor for both viral conditions, they may share the same target organs, pathogenic mechanisms, clinical manifestations, and – possibly – treatment options.

Following the binding of viral S-protein to human cell receptor, the viral membrane fuses with the human cell membrane, permitting entry of the viral genome to human cells. The receptor-binding domain (RBD) of S-protein determines its binding affinity to the human cell surface receptor, an observation that can be employed in vaccine development. In the determined effort to develop a SARS-CoV-2 vaccine, the molecular structure of its S-protein has been mapped.<sup>30</sup> It was found that the predominant state of the trimer has one of the RBDs rotated up in a receptor-accessible conformation and binds ACE2 with higher affinity (10- to 20-fold) than does SARS-CoV S-protein.<sup>16</sup> Such higher affinity between the S-protein and ACE2 in SARS-CoV-2 (compared to SARS-CoV) may help explain the elevated infectivity and rapid person-to-person spread of SARS-CoV-2 relative to SARS-CoV.

A comparative and systematic genetic analysis of *ACE2* gene in different populations was conducted recently.<sup>31</sup> The coding-region variants in *ACE2* may affect the expression of ACE2 receptors. This study indicated no evidence of coronavirus S-protein binding-resistant *ACE2* mutants in different populations. However, the data of variant distribution and allele frequencies were thought to contribute to the role of ACE2 in acute lung injury and lung function.<sup>31</sup> The study also concluded that East Asian populations have much higher allele frequency in the expression quantitative trait loci (eQTLs, the genomic loci that explain variation in mRNA expression levels) variants associated with higher ACE2 expression in tissues. This was suggested to influence different levels of susceptibility (or response) to SARS-CoV-2 in different populations under similar conditions. This observation warrants the need for further population-based genetic epidemiological studies on the potential effect of variants in the functional coding region of *ACE2* among different populations to characterize its role in the spread of COVID-19, disease severity, and response to treatment.

## Hypercytokinemia and Inflammation in Coronavirus Infection

Coronavirus infections were shown to induce massive synthesis and release of cytokines and chemokines, and lead to non-specific activation of mononuclear macrophages that – in a positive feedback loop – further release high levels of cytokines (see below). Such an excessive synthesis of pro-inflammatory cytokines in response to infections (and also a number of chronic diseases) results in a state of hypercytokinemia (also known as cytokine storm)<sup>32</sup> and can lead to severe outcome, eg, multiple organ failure.<sup>33</sup> Pneumonia cases from SARS-CoV and MERS-CoV were invariably accompanied by extensive inflammatory cell infiltration and hypercytokinemia leading to acute lung injury, ARDS and death.<sup>34</sup> Current evidence suggests that severe COVID-19 cases have significantly elevated levels of cytokines – compared to non-severe cases – similar to that observed in SARS-CoV and MERS-CoV. Interleukins (such as IL-2, IL-7, IL-10), granulocyte-colony stimulating factor (G-CSF), C-X-C motif chemokine 10 (CXCL10; also known as Interferon gamma-induced protein 10; IP-10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) were particularly and significantly elevated in

severe COVID-19 cases.<sup>35</sup> Other inflammatory factors such as IL-1 $\beta$ , IL-1RA, IL-7, IL-8, IL-9, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon  $\gamma$  (IFN $\gamma$ ), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) were also increased.<sup>35</sup> Several studies reported elevated levels of IL-6 in non-survival or critically-ill cases compared to survivals or those with a mild outcome.<sup>11,36,37</sup> Furthermore, severe COVID-19 cases with ARDS and hypercoagulation (leading to thrombosis, thrombocytopenia, and gangrene) had persistent very high levels of erythematous sedimentation rate (ESR) and C-reactive protein (CRP) accompanied by elevated levels of IL-6, TNF $\alpha$ , IL-1 $\beta$ , IL-8, and IL2R.<sup>38</sup>

The extensive synthesis of cytokines is known to stimulate massive proliferation of monocyte-macrophages and induce excessive apoptosis of lymphocytes, disrupting the immune system to develop a status of immunodeficiency that can lead to secondary infections.<sup>34,39</sup> Indeed, early stages of COVID-19 were shown to be characterized by a decrease in the absolute number of peripheral blood lymphocytes that progressively decline as the disease develops into a severe outcome.<sup>35</sup> Similar findings – with comparable lung lesions – were also reported in the severe SARS-CoV<sup>39,40</sup> and MERS-CoV.<sup>41</sup> Hypercytokinemia has been also noted in SARS-CoV<sup>39</sup> and MERS-CoV<sup>41</sup> and was suggested to result in inflammatory lesions in the lungs and extensive inflammatory reactions and necrosis in the spleen, lymph nodes and blood vessels. Such a profile of hypercytokinemia was further suggested to be a major causative factor in exacerbating lung damage and other fatal complications.<sup>38</sup> The profile of pro-inflammatory cytokines in coronavirus diseases may, therefore, be a common pathophysiological basis in pneumonias resulting from these infections.<sup>34,42</sup> Direct evidence for the role of proinflammatory cytokines and chemokines in the pathophysiology of coronavirus infections was noted, however, from SARS-CoV cases<sup>39,40</sup> where ACE2-positive cells were shown to express significantly higher levels of pro-inflammatory cytokines such as MCP1, transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1), TNF $\alpha$ , IL-1 $\beta$  and IL-6 than ACE2-negative or non-infected cells.<sup>40</sup>

Upon infection, the innate immunity-mediated synthesis of proinflammatory cytokines by target cells recruits and activates immune cells including monocytes-macrophages, lymphocytes, and neutrophils into the site of infection.<sup>43</sup> Based on our understanding of the coronavirus-induced

pneumonia, the accumulation of these cells in the lung and blood vessel walls mediate inflammatory reactions to clear the infection and further synthesize cytokines to stimulate immunity, leading to a state of hypercytokinemia.<sup>39–41</sup> Such a local reaction aggravates the lung and vascular tissue injury and may lead to lung exudate, pulmonary edema, hyaline membrane formation, and mucus cell activation to block the airway, ultimately manifesting in ARDS.<sup>16</sup> Early stage of this process is accompanied by extensive lymphocyte apoptotic cell death that attenuates cellular immune system leading to a state of immunodeficiency.<sup>39–41</sup> This complication may culminate to respiratory failure, systemic hypoxia, multiple organ failure and death. Such a proposed range of clinical events may permit identifying a set of biomarkers along the innate immunity pathway related to the synthesis of pro-inflammatory cytokines for early prediction of the severe outcome of infection. It may also delineate effective avenues for the treatment of early disease stages as well as in critically-ill patients. However, much is yet to be learned – particularly in the case of SARS-CoV-2 – to introduce such a proposition into clinical practices.

Innate immunity-related inflammatory response has long been characterized to play a critical role in the body's response to infection.<sup>33</sup> Several studies have demonstrated that hypercytokinemia is the principal immunopathological mechanism that contributes to severe clinical presentation in patients with infectious diseases.<sup>44–47</sup> The genes that code for pro-inflammatory cytokines and chemokines responsible for hypercytokinemia include TNF $\alpha$ , IFN $\gamma$ , IL-1, IL-6, IL-8, IL-9, IL-12, IL-15, and IL-17.<sup>44</sup> These genes are polymorphic and certain alleles have been associated with susceptibility to a wide range of infectious conditions as well as their severe outcome.<sup>45,46</sup> Although these mediators are principally related to immune reactions, they can also influence functions of epithelial and endothelial cells, smooth muscle, and adipose tissue and play a role in sepsis, shock, ARDS, and responses to toxic medication.<sup>47,48</sup> In general, clinical signs and symptoms associated with hypercytokinemia include headaches, muscle pain, nausea, diarrhea, vasodilatation, and hypotension.<sup>47</sup>

Several variants in the genes encoding for cytokines, eg, TNF (rs1800750 G/A), IL1B (rs16944 G/A), CCL (rs2282691 A/T) and IFITM3 (rs12252 T/C), have been associated with risk of an array of clinical manifestations in infectious diseases.<sup>32,49</sup> Furthermore, elevated levels of the resultant pro-inflammatory cytokines and chemokines were found in the plasma of patients with ARDS in response to

infection.<sup>16,50</sup> Previous studies examining the relationship between infectious diseases and cytokine markers suggest that host genetic factors may indeed influence these biomarkers and the subsequent disease severity.<sup>50–54</sup> This relationship may shed some light on the interindividual differences in response to SARS-CoV-2 infection and other coronavirus diseases and warrants analysis of the genetic variants in cytokine genes in coronavirus patients. Linking these genetic polymorphisms to the extent of hypercytokinemia and the individual's response to infection may identify novel approaches related to the risk of disease severity as well as effective measures of prevention and control. In this context, single nucleotide polymorphisms (SNPs) in cytokine genes can be employed to determine whether the patient's innate immune status is prone to hypercytokinemia in SARS-CoV-2 virus infection as proposed in other infectious diseases.<sup>32,44–47</sup> Attenuating the effect of these genes, ie, their role in extensive cytokine synthesis, can provide an approach for early intervention in subjects prone to hypercytokinemia upon infection. For example, we<sup>32,55,56</sup> and others<sup>57</sup> have proposed a utility of some nutritional factors to impact the expression of cytokine genes as in the early prevention of a number of infectious and chronic diseases. Furthermore, the use of IL-6 pathways blockers and other biologic drugs currently prescribed for rheumatology was suggested to be employed in targeting inflammation in patients prone to hypercytokinemia.<sup>58</sup>

## Conclusion

The systemic nature of coronavirus infection outcomes is perhaps due to the ubiquitous expression of the virus receptors (ACE2 in SARS-CoV and SARS-CoV-2 and DPP4 in MERS-CoV). Such an expression may further relate to the common hypercytokinemic responses in the lungs and vasculature characterized in these infections. The pathophysiological mechanism of COVID-19 (and other coronavirus diseases) may then relate to this state of hypercytokinemia that both exacerbates the inflammatory lesions in the target tissues and induces massive T cell apoptotic death and a subsequent vulnerability to immune deficiency. Furthermore, the notable higher affinity of SARS-CoV-2 S-protein to ACE2 (compared to SARS-CoV),<sup>16</sup> where a relatively lesser level of the virus can result in disease manifestation, may have influenced the extensive worldwide spread of COVID-19. Within this context, it is important to note that although respiratory transmission was considered as the principal route in the disease spread,<sup>59</sup> the ubiquitous expression of ACE2

receptors in many human tissues and organs suggests that new transmission routes (eg, aerosols and direct contact) should be also taken into consideration.

The interindividual differences in response to COVID-19 infection may relate to the genetic polymorphisms in genes regulating the virus S-protein binding receptor (*ACE2* gene) and those modulating the synthesis of pro-inflammatory cytokines and chemokines (eg, *TNF $\alpha$* , *IFN $\gamma$* , *IL-1*, *IL-6*, *IL-8*, *IL-9*, *IL-12*, *IL-15*, and *IL-17* genes). These genes influence both target organ function and injury<sup>31</sup> as well as host immune response to infection.<sup>45,46</sup> Various combinations of these genes can emerge to differentially determine the infection outcome in different individuals, populations and sub-populations. This observation underlines the necessity to conduct more systematic population-based genetic epidemiological studies to elucidate the influence of sequence variation in this array of genes on the response to (and treatment of) viral infection. Factors that modulate the expression and activity of these markers, eg, AT1 receptor blockers (ARBs) or mineralocorticoid receptor antagonists (MRAs) for ACE2<sup>60,61</sup> or anti-inflammatory factors for cytokines,<sup>62</sup> may need to be further considered in studies with a systematic population-based approach.

Overall, extensive research is warranted in many areas related to coronavirus diseases, particularly COVID-19. Work needs to be developed in areas related to the transmission route, pathological mechanism, natural history and prognosis of the disease, approaches for effective therapy and vaccine development. Ultimately, the establishment of effective public health measures for disease prevention and control is critical both regionally and globally. In this respect – and given the varying rates of disease prevalence among the different world regions, there is a need to characterize the effect of health inequities and inequalities within and between countries on public health and health-care response to COVID-19. The rapid and vast spread of the disease substantiate an urgency to develop a global policy coherence and complementation between public health authorities around the world that takes into consideration the well-known influence of socioeconomic status and inter-population differences on health.

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## Disclosure

The author declares no conflicts of interest.

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