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PATHOGENESIS OF COVID-19: NEW INSIGHTS

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Abstract

Coronavirus disease 2019 (COVID-19), the viral illness caused by the novel coronavirus SARS-CoV-2 has resulted in significant morbidity and mortality across the world since the first cases were identified in Wuhan China, in December 2019. Since then, scientists have been studying the effects of this virus on the human body and its consequences in patients with COVID-19.

Significant endothelial damage has been reported in COVID-19 and growing evidence supports the key pathophysiological role of this alteration in the onset and the progression of the disease. In particular, the impaired vascular homeostasis secondary to the structural and functional damage of the endothelium and its main component, the endothelial cells, contributes to the systemic proinflammatory state and the multiorgan involvement observed in COVID-19 patients.

This article summarizes the available data on pathogenesis of SARS-CoV-2 with an emphasis on molecular mechanisms and current information on post-COVID-19 syndrome.

Key words

post-COVID-19 syndrome, cytokine storm, angiopoietin 2, angiotensin-converting enzyme 2, NO, von Willebrand factor, factor VIII.

Introduction

Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a diameter ranging from 60 to 140 nm. Their surface is characterized by spike-like projections that form a crown-like appearance under electron microscopy, giving rise to their name [11].

Over the past two decades, three major coronavirus outbreaks have been documented:

1. SARS-CoV (2002-2003): A novel β-coronavirus of bat origin that crossed into humans via palm civets in Guangdong Province, China. This virus, designated as the severe acute respiratory syndrome coronavirus, infected 8,422

individuals primarily in China and Hong Kong, resulting in 916 deaths (case fatality rate: 11%) before containment [38].

2. MERS-CoV (2012): Another bat-origin coronavirus that emerged in Saudi Arabia, using dromedary camels as intermediate hosts. It caused 2,494 infections and 858 deaths (fatality rate: 34%) [38].

3. SARS-CoV-2 (2019-present): The causative agent of coronavirus disease 2019 (COVID-19), first identified in Wuhan, Hubei Province, China in December 2019. Phylogenetic analyses using molecular clock dating suggest initial cases likely emerged between October and November 2019 [34,1].

By January 2020, SARS-CoV-2 had spread to all 31 Chinese provinces and was reported in East/Southeast Asia, Europe, and the United States. Community transmission was subsequently documented across Asia, most of Europe, the Middle East, and the U.S. by February 2020. Global cases surpassed one million by April 2020 as countries implemented partial or nationwide lockdowns. The global death toll reached one million by September 25, 2020, and by December 22, 2020, cases had been reported on all seven continents, including Antarctica [40]. As of February 4, 2022, WHO reported 386,548,962 confirmed COVID-19 cases and 5,705,754 deaths worldwide [49].

Pathogenesis

Thousands of SARS-CoV-2 variants are currently circulating. The transmission dynamics of these variants are influenced not only by genetic differences but also by population behavior and the effectiveness of epidemiological surveillance policies. While international travel restrictions may limit global spread of certain variants, they also contribute to the emergence of dominant variants in individual countries [14].

The life cycle of SARS-associated coronaviruses (SARS-CoV and SARS-CoV-2) initiates with binding of the spike glycoprotein to its cognate receptor, angiotensin-converting enzyme 2 (ACE2). Subsequent host cell entry depends on: (I) cleavage of the S1/S2 site by the transmembrane serine protease 2 (TMPRSS2); and/or (II) endolysosomal cathepsin L, which mediates viral fusion with cellular membranes at either the cell surface or within endosomal compartments. Following entry, the RNA genome is released into the cytosol where it is translated into replicase polyproteins (open reading frame 1a/b: ORF1a/b). These polyproteins (pp1a and pp1ab) are processed by viral proteases into individual nonstructural proteins (nsps) of the replicase complex, including RNA-dependent RNA polymerase (RdRp). Replication occurs within virus-induced double-membrane vesicles derived from the endoplasmic reticulum, ultimately forming an intricate network of convoluted membranes. The positive-sense genomic RNA serves as template for

both full-length negative-sense RNA and subgenomic (sg) RNAs. Translation of sgRNAs yields structural and accessory proteins that are incorporated into the ER-Golgi intermediate compartment (ERGIC) for virion assembly. Finally, newly synthesized virions containing positive-sense RNA genomes are secreted via the plasma membrane [18].

Most SARS-CoV-2 infections are non-severe [51]. The incubation period ranges from 2 to 14 days [24], with respiratory symptoms typically appearing 3-7 days post-exposure [47]. Clinical manifestations include fever, dry cough, and fatigue, along with non-respiratory symptoms such as palpitations, diarrhea, or headache. Risk factors for severe pneumonia or fatal outcome include age ≥60 years, smoking, and comorbidities including diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, and malignancy. Transmission occurs via inhalation of respiratory droplets and/or aerosol particles, contact with fomites, and person-to-person contact. Larger droplets deposit in the upper respiratory tract, while smaller aerosol particles can reach and deposit in the alveoli of the lower respiratory tract. Smaller particles also remain airborne longer, increasing potential exposure time [48].

The effective human immune response against viruses involves secretion of proinflammatory cytokines and activation of T cell subsets, which are crucial for controlling viral replication, limiting viral spread, modulating inflammation, and clearing infected cells. In healthy individuals, the T cell response represents a precisely balanced system comprising populations of reactive T cells. Persistent antigen stimulation leads to CD8+ T cell exhaustion (Tex), characterized by reduced effector function and proliferative capacity. These exhausted cells exhibit overexpression of inhibitory receptors including CD279 (PD-1), a surface protein of the immunoglobulin superfamily of lymphoid cells, and members of the extended CD28/CTLA-4 family of T cell regulators that serve as checkpoints modulating apoptosis. The interaction between PD-1 and its ligands (PD-L1 or PD-L2 - both members of the B7 family of T cell co-receptors that includes CD28) represents critical negative immune checkpoints that attenuate cell-mediated immune responses, particularly CD8+ responses, while exacerbating developing pathologies. Additionally, exhaustion markers such as NKG2A are activated in NK cells and cytotoxic T lymphocytes in COVID-19 patients [2].

Accumulating evidence indicates that viral infection can trigger an exaggerated or hyperactive host immune response leading to a "cytokine storm" [22]. Massive immune system activation results in a severe complication termed cytokine storm or cytokine release syndrome (CRS), characterized by massive, uncontrolled release of proinflammatory cytokines and other inflammatory

mediators that drive excessive inflammation. The cytokine storm, arising from activation of multiple inflammatory signaling pathways, has been identified as a major cause of mortality in COVID-19 patients. Following pathogen encounter, immune cells (T cells, endothelial cells, dendritic cells, macrophages, monocytes, natural killer cells, and cytotoxic lymphocytes) become activated [10].

When exposed to viral antigens, both innate and adaptive immune cells participate synergistically in the antiviral response [2]. Early studies demonstrated involvement of various immune cell populations in COVID-19. One study of 41 patients associated severe disease requiring intensive care and mortality with neutrophilia and lymphopenia [2,50]. Another study reported significant lymphopenia (77.6%) and thrombocytopenia (41.2%) in a cohort of 85 fatal cases. A hallmark of severe SARS-CoV-2 infection is lymphopenia with markedly reduced numbers of CD4+ T cells, CD8+ T cells, B cells, and NK cells. Decreased percentages of monocytes, eosinophils, and basophils have also been reported [2,12]. Another feature observed in severe cases is increased neutrophil counts and neutrophil-to-lymphocyte ratio, which correlated with greater disease severity and worse clinical outcomes [6].

Notably, significant increases in neutrophil counts and neutrophil-to-lymphocyte ratio were not observed in mild cases. Marked lymphopenia, indicating immune system impairment, is characteristic of the most severe COVID-19 cases [2,35,52]. Thus, it can be concluded that in COVID-19, neutrophils and leukocytes, along with lymphocytes, contribute to and amplify the cytokine storm. Several studies have reported eosinopenia among hospitalized COVID-19 patients [2,45,25], with approximately 82% of fatal cases showing pronounced eosinopenia. However, eosinopenia was not detected in early stages or mild cases of the disease [2,26]. Furthermore, Lucas et al. demonstrated increased monocytes, low-density neutrophils, and eosinophils correlating with disease severity. Their study also established an association between elevated basophil and eosinophil levels and COVID-19 severity, with both cell types being among the most dynamically changing populations during severe disease, suggesting important contributions to both antiviral defense and immunopathology [2,27,41].

The primary cytokines involved in cytokine storm development are IL-1β, IL-6, and TNF-α, which correlate with disease severity. IL-1β, IL-2R, IL-6, and TNF-α are key mediators of the cytokine storm. Cytokines can act on different cells: those that secrete them (autocrine), nearby cells (paracrine), or distant cells (endocrine) [10]. The cytokine storm correlates with infection severity and often causes extensive tissue damage. Moreover, it is considered the primary cause of ARDS and multiple organ failure, which are closely associated with COVID-19 severity and

progression. Indeed, the cytokine storm and related complications represent the leading cause of death in COVID-19 patients [22].

Preliminary studies indicate that patients with cardiovascular risk factors and/or established cardiovascular disease have the highest risk of COVID-19 hospitalization and severe disease progression. These risk factors include advanced age (>65 years), hypertension, obesity, diabetes mellitus, chronic lung disease, coronary artery disease, and heart failure. Interestingly, endothelial dysfunction appears to be the common denominator among these cardiometabolic disorders. The endothelium plays a crucial role in maintaining vascular tone and homeostasis - its dysfunction is associated with vasoconstriction, inflammation, increased permeability, and coagulation abnormalities. These changes are linked to major risk factors including age, hypertension, diabetes, and obesity, as well as to the development and progression of cardiovascular diseases [31].

SARS-CoV-2 directly infects vascular endothelial cells, causing cellular damage and apoptosis, thereby reducing the antithrombotic activity of normal endothelium. Alveolar damage, vascular wall edema, hyaline thrombi, microhemorrhages, and diffuse thrombosis of peripheral small vessels have emerged as key features of COVID-19 contributing to respiratory failure [4].

The primary site of COVID-19 infection is the upper and lower respiratory tract. Here, SARS-CoV-2 infects goblet secretory cells of the nasal mucosa and type II alveolar pneumocytes by binding to membrane-bound angiotensin-converting enzyme 2 (ACE2) [54]. Following priming of the viral spike protein by the human protease TMPRSS2, the virus is internalized and replication begins. In severe COVID-19, progressive infection of alveolar pneumocytes with significant viral shedding leads to apoptosis and necrosis [29]. Interferon-mediated upregulation of ACE2 may facilitate infection of neighboring pneumocytes [54]. Subsequent immune responses lead to progressive interstitial and alveolar edema that impairs gas exchange and may ultimately result in acute respiratory distress syndrome (ARDS) [31].

SARS-CoV-2 induces acute inflammatory effects with hypercoagulability, platelet activation, and endothelial dysfunction [23]. A key feature of COVID-19-associated coagulopathy is microcirculatory endothelial injury in the pulmonary vasculature and other vascular beds. Since SARS-CoV-2 directly infects vascular endothelial cells, causing cellular damage and apoptosis, the antithrombotic activity of the luminal surface is markedly reduced.

SARS-CoV-2 enters endothelial cells via endocytosis mediated by interaction between angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS-2), which cleaves the spike protein to facilitate viral entry.

Infected endothelial cells lose their ability to maintain normal physiological functions. Subsequent endothelial injury leads to procoagulant changes in the vascular lumen, immunothrombosis formation, and organ hypoperfusion [20].

Healthy endothelial cells synthesize nitric oxide (NO) through conversion of L-arginine to L-citrulline by nitric oxide synthase. Endothelium-derived NO prevents leukocyte and platelet adhesion, inflammatory cell migration into the vascular wall, smooth muscle cell proliferation, while suppressing apoptosis and inflammation [20].

Although SARS-CoV-2 primarily infects bronchial ciliated epithelial cells and type II pneumocytes, electron microscopy has also detected residual viral particles in endothelial cells. This observation confirmed that SARS-CoV-2, like SARS-CoV-1 and MERS-CoV, can directly infect endothelial cells, leading to cellular apoptosis and reduced endothelial NO [43].

Furthermore, decreased NO production also occurs as viral infection progresses. SARS-CoV-2 enters host cells via binding of its surface spike glycoprotein to angiotensin-converting enzyme 2 (ACE2), subsequently downregulating ACE2 expression. ACE2 is known to convert angiotensin I (AngI) to the proinflammatory peptide angiotensin II (AngII), while also metabolizing AngII to generate angiotensin-(1-7); AngII-(1-7) promotes NO production by endothelial cells. Due to ACE2 downregulation, suppression of ACE and its downstream product AngII is reduced. ACE inhibits NO production and promotes reactive oxygen species (ROS) generation and inflammation. Additionally, as a proinflammatory peptide, AngII itself activates macrophages to produce proinflammatory cytokines and ROS, leading to excessive inflammatory responses and NO/ROS imbalance [17].

A unique feature of COVID-19-associated coagulopathy is increased von Willebrand factor (vWF) and factor VIII levels, believed to represent a vascular response to SARS-CoV-2 infection. vWF and factor VIII are stored in endothelial Weibel-Palade bodies and released in response to infectious stimuli. Elevated vWF suggests possible similarities with thrombotic thrombocytopenic purpura; however, in COVID-19, although ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) levels are reportedly decreased, they may not be as severely depleted as in thrombotic thrombocytopenic purpura. The 3-4 fold increases in vWF levels observed in COVID-19 patients may overwhelm ADAMTS13 activity, preventing cleavage of ultra-large vWF multimers [34].

Similar to factor VIII and vWF, angiopoietin-2, also stored in Weibel-Palade bodies, is released, and its circulating levels increase in COVID-19 [1].

Post-COVID Syndrome

More than a year after the declaration of the coronavirus disease 2019 (COVID-19) pandemic, the world continues to face its devastating impact not only on morbidity, mortality, and healthcare services but also its profound social and economic consequences globally. While the overwhelming focus of COVID-19 knowledge has been almost exclusively on acute illness, it has become apparent that long-term sequelae occur [28].

Post-COVID syndrome was first described in spring 2020 in the context of a patient-led citizen science study of prolonged COVID-19 symptoms. Shortly after the initial COVID-19 cases emerged, these researchers noted that some patients experienced persistent symptoms for weeks following acute infection [33].

Post-acute COVID-19 is a syndrome characterized by persistence of clinical symptoms beyond four weeks after onset of acute illness. The Centers for Disease Control (CDC) has defined "post-COVID conditions" to describe health problems that persist more than four weeks after COVID-19 infection. These include:

- Long COVID (encompassing a wide range of symptoms lasting weeks to months) or persistent post-COVID syndrome
- Multiorgan effects of COVID-19
- Effects of COVID-19 treatment/hospitalization

Typical clinical symptoms of "long COVID" include fatigue, dyspnea, brain fog, autonomic dysfunction, headache, persistent loss of smell or taste, cough, depression, low-grade fever, palpitations, dizziness, and musculoskeletal pain.

Multiorgan effects of COVID-19 involve clinical manifestations affecting the cardiovascular, pulmonary, renal, and neuropsychiatric systems, although the duration of these systemic effects remains unclear.

The long-term "effects of treatment or hospitalization for COVID-19" are similar to other severe infections. These include post-intensive care syndrome resulting in profound weakness and post-traumatic stress disorder. Many patients with these COVID-19-related complications improve over time. Post-COVID care clinics have been established at multiple medical centers across the U.S. to address these specific needs [8].

Based on the chronic course of post-COVID symptoms, Nalbandian et al. classify post-acute COVID-19 as follows:

- Subacute or persistent symptomatic COVID-19 (up to 12 weeks from initial acute episode)
- Chronic or post-COVID syndrome (symptoms beyond 12 weeks), which should not be attributable to alternative diagnoses [32].

Beyond these symptoms, more diverse and debilitating impairments affecting pulmonary, cardiovascular, dermatologic, musculoskeletal, and neuropsychiatric systems have been reported [16].

The most frequently reported symptom was dyspnea, followed by cough and loss of taste/smell in 32% of patients who reported persistent symptoms during 60-day follow-up of 488 patients hospitalized with acute COVID-19. This observational cohort study also showed 15% rehospitalization rate and 6.7% mortality [9].

Another study evaluating 110 COVID-19 patients for 90 days post-discharge found fatigue and dyspnea (39%) to be the most common symptoms, followed by sleep disturbances (24%), chest pain (12%), and cough (11%) [3].

The respiratory system is most frequently affected by SARS-CoV-2, with cough and dyspnea being the most common pulmonary complaints in long COVID subjects. However, the most concerning health issue is development of post-COVID interstitial lung disease in a small subset of patients [3].

A meta-analysis by Garg et al. showed that pulmonary fibrosis signs, manifested as persistent ground-glass opacities and consolidations, represent the most common CT findings in acute COVID-19 that were reported by several authors at discharge/follow-up [15,46]. Wang et al. reported resolution of lung abnormalities on CT in only 4/70 patients at discharge, with residual findings in 66/70 patients. Persistent ground-glass opacities were documented in 60% of patients [46,17].

It is well-established that COVID-19 affects the cardiovascular system, potentially leading to myocarditis, acute/decompensated heart failure, acute coronary syndrome, arrhythmias, and thromboembolic events in patients with or without pre-existing cardiovascular disease [21]. The predominant mechanism of cardiac injury in acute COVID-19 primarily involves indirect progressive systemic inflammation, endotheliitis, and type II myocardial infarction due to hypoxia [7,43,53].

Acute COVID-19-associated thromboembolism results from a hyperinflammatory and hypercoagulable state rather than consumptive coagulopathy as in disseminated intravascular coagulation. Hypoxia, endothelial injury, platelet activation, and proinflammatory cytokines contribute to disproportionately high thromboembolic rates in acute COVID-19. Both duration and severity of this hyperinflammatory state influence thrombotic complication risk in the post-COVID phase [8].

The international COVID-19 Dermatology Registry reported various cutaneous manifestations associated with COVID-19, including morbilliform rash,

urticaria, and papulosquamous lesions. While urticarial and morbilliform rashes were transient, pernio (6.8%) and livedo reticularis persisted beyond 60 days [30].

Neurological manifestations occur in half of hospitalized patients, with higher rates of complications reported in critically ill patients that often persist into post-rehabilitation phases. These range from mild symptoms (headache, myalgia, weakness, dizziness, chemosensory dysfunction) to severe complications (seizures, encephalopathy, stroke). "Brain fog" - a collective term describing cognitive impairments including confusion, short-term memory loss, dizziness, and inability to concentrate - is another common long COVID manifestation believed to result from SARS-CoV-2-induced hypoxia and mitochondrial dysfunction causing microstructural brain damage [16].

Cognitive, attentional, concentration, and sleep disturbances are the most frequent neuropsychiatric manifestations in post-COVID rehabilitation. The causes of post-COVID neuropsychiatric sequelae are multifactorial - consequences of encephalitis/cerebral hypoxia, medical interventions, physical isolation, psychosocial impact, and social stigmatization, among others [36].

One study found executive dysfunction (including inattention, poorly organized motor tasks, and disorientation) in one-third (15/45) of patients with severe COVID-19 pneumonia [19].

Viral damage, inflammatory, and immunological injuries contribute to post-acute endocrine manifestations of COVID-19. Isolated cases of diabetic ketoacidosis, subacute thyroiditis, and Hashimoto's thyroiditis have been reported weeks after resolution of acute COVID-19 symptoms [5,37]. Immobilization, steroid use, and vitamin D deficiency during acute and post-acute COVID-19 recovery may promote bone demineralization [8].

Conclusions

This review, based on current understanding of COVID-19 pathogenesis and post-COVID syndrome, provides clearer insight into the mechanisms underlying COVID-19 symptoms and syndromes. The information presented in this article demonstrates that COVID-19 manifestations are broad and unpredictable, ranging from asymptomatic or short-term illness to fatal multi-organ failure. This underscores the importance of understanding disease pathophysiology for characterizing, predicting, and treating patients at risk of severe disease.

The data summarized in this article indicate that endothelial cells are primary targets of SARS-CoV-2 and confirm the clinical significance of endothelial dysfunction in COVID-19 pathophysiology.

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