Review

COVID-19, the disease that changed the world

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INFECTIOUS DISEASES

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Abstract

Five years ago, the COVID-19 coronavirus emerged as an invisible threat that profoundly disrupted the world, becoming a public health challenge. The COVID-19 pandemic has shown us how important it is to have health systems that can quickly find and track new viruses as they spread and has ushered in a new era of genomic surveillance, allowing scientists to track the evolution of the coronavirus, providing public health strategies.

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), responsible for the COVID-19 pandemic, has been associated with very important global morbidity and mortality. The discovery of SARS-CoV-2 in bats and pangolins in South Asian countries indicates that SARS-CoV-2 likely originated from wildlife being the third highly pathogenic human coronavirus. The increased contagiousness of SARS-CoV-2 virus was due to the spike glycoprotein (S) that favors the attachment of the virus to the cell surface. SARS-CoV-2 infection triggers a damaging triad of oxidative stress, intense inflammation with cytokine storm, and endothelial dysfunction, leading to widespread cellular damage, blood clotting with thrombosis, and organ failure by overwhelming the body's antioxidant defenses, damaging blood vessel linings, and promoting hyper-inflammation, all crucial factors in severe COVID disease.

The purpose of the review is to make a synthesis of the data known so far about SARS-CoV-2 virus etiology, the complex interactions between the virus and the host, imbalanced immune response and cytokine storm, molecular mechanisms by which the spike protein drives endothelial dysfunction and, multisystemic pulmonary, cardiovascular, neurological, renal involvement.

Keywords: SARS-CoV-2 virus, COVID-19 pandemic, infectiousness, cytokine storm, oxidative stress, endothelial dysfunction

Introduction

Five years ago, COVID-19 emerged as an invisible threat that profoundly disrupted the world, becoming a public health challenge. The COVID-19 pandemic has shown us how important it is to have health systems that can quickly find and track new viruses as they spread, and has ushered in a new era of genomic surveillance, allowing scientists to track the evolution of the coronavirus, providing public health strategies.

SARS-CoV-2, responsible for the COVID-19 pandemic, has been associated with very significant global morbidity (95%UI:55.0–69.9 million) and mortality (95%UI:7.8–17.4 million) [1]. In the last 20 years, the World Health Organization (WHO) has reported three major outbreaks of coronavirus, a zoonotic virus that causes respiratory diseases, which have led to epidemics: SARS-CoV (Severe Acute Respiratory Syndrome), MERS-CoV (Middle East Respiratory Syndrome), and most recently, SARS-CoV-2. The last one, involved in COVID-19, was first reported in Wuhan, Hubei Province, China, in December 2019 and early spring of 2020, where attempts to contain it failed, allowing the virus to spread to other areas of China and subsequently around the world. The WHO declared the outbreak a public

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health emergency of international concern on January 30th 2020 and a pandemic, which has affected social and economic environments worldwide, on March 11th 2020. The emergence of the SARS-CoV-2 virus at the end of 2019 caused health systems in all countries of the world to face significant problems in combating and spreading the infection.

The COVID-19 pandemic has had devastating consequences in terms of patient morbidity and mortality, profoundly changing the world, disrupting almost every aspect of human life and society. The COVID-19 pandemic has led to a massive global recession, forced rapid technological change, exposed global health inequalities, and prompted significant changes in daily routines, the workplace, and education, accelerating scientific research and technological advances. Globally, as on January 27th 2023, the COVID-19 pandemic has recorded 752,517,552 confirmed cases, including 6,804,491 deaths, making it one of the highest mortality rates in human history [2]. The spread of the virus has been a major public health challenge.

The paper aims to review the characteristics of the SARS-CoV-2 virus, the complex interactions between the SARS-CoV-2 virus and the host, the mechanisms of disease transmission, the strategies to avoid antiviral immunity, as well as understanding the complex molecular and cellular mechanisms of the disease that underpin preventive and therapeutic measures.

Epidemiology

A group of coronaviruses related to SARS-CoV-2 have been identified in pangolins, but the infectivity and pathogenicity of these pangolin-origin coronaviruses (pCoVs) in humans have remained largely unknown [3]. The COVID-19 pandemic caused by SARS-CoV-2 has presented unprecedented challenges to global health. Although the first cases were linked to the Huanan seafood and animal market, the potential animal intermediate hosts involved in the transmission of SARS-CoV-2 to humans remained unknown. Pangolin-associated coronaviruses related to SARS-CoV-2 (Pangolin-CoV) have been identified from Malaysian pangolins, providing new insights into potential intermediate hosts.

The intermediate host for SARS-CoV-2 was studied by comparative analysis of the sequence of residues interacting with the receptor-binding domain of the spike glycoprotein in bat SARS-CoV-2 samples with host angiotensin convertase-2 (ACE-2), with the corresponding residues in pangolin-isolated CoVs collected from Guangdong Province and Guangxi Autonomous Regions in southern China. The results demonstrated that Guangdong pangolins are the intermediate hosts, which provided further evidence that the Guandong Pangolin-CoV receptor-binding domain (GD) has a stronger affinity for the ACE-2 receptor compared to SARS-CoV2 [4-6]. A study identified that a SARS-CoV-2-related virus (MpCoV-GX) from Malayan pangolins can infect human ACE- 2-expressing mice but causes only mild lung issues (slight inflammation), not severe disease, suggesting it has zoonotic potential but limited virulence, highlighting the need for continued surveillance of these wildlife viruses for more dangerous variants [7].

At least five genomes of the new coronavirus have been isolated, and as with SARS-CoV, it has been established that SARS-CoV-2 is a member of lineage B, Beta-CoV [8]. The receptor binding domain of Pangolin-CoV shows very high sequence similarity to SARS-CoV- 2, indicating a significant risk to human public health. However, the pathogenicity and transmissibility of Pangolin-CoV remain largely unknown [9]. Coronaviruses or Coronavirinae, abbreviated CoV, are a subfamily of viruses in the Coronaviridae family that includes four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. COVID-19 is caused by the SARS-CoV-2, a virus that belongs to the Coronaviridae family, subfamily Orthocoronaviridae, subgroup betacoronavirus B, which infects animals and humans, but also has the ability to be transmitted from animals to humans. The Omicron variant, an emerging variant, presented more than thirty mutations in the spike protein, which gave it increased contagiousness [10,11].

The successive waves of viral infections were caused by Omicron sublineages, with each viral variant of SARS-CoV-2 being completely novel, with unique combinations of mutations, novel antigenic properties, and variations in clinically relevant traits, including immune evasion, disease severity, and sensitivity to therapy (particularly monoclonal antibodies) [12,13]. Human and animal coronavirus infections cause mainly respiratory or digestive diseases. The International Committee on Virus Taxonomy has classified this new virus as SARS-CoV-2 based on practical standards of pathology, phylogeny, and taxonomy [14].

Etiology

Coronaviruses have a variable shape, spherical or ovoid, pleomorphic, 120-160 nm in diameter, with an external shell on which there are glycoprotein protrusions, called spicules (peplomers), very long (24 nm), pedunculated, with rounded, bulbous extremities. SARS-CoV-2 is a single-stranded positive-sense DNA virus with a diameter of 60-140 nanometers. The viral genome is between 29.8-29.9 kb and encodes four structural proteins and other accessory or non-structural proteins (nsp) including, the viral replicase pp1a- pp1ab, the 3C-like protease (3CLpro), the papain-like protease (PLpro) and the RNA polymerase RdRp [15,16]. Structural and nsp components of SARS-CoV-2 play an important role in infectivity, some of which are important in the pathogenesis of coagulation disorders, cardiovascular diseases, and neurodegenerative disorders. Studies based on the analogy and similarity of SARS-CoV

and SARS-CoV-2 viruses demonstrate that nsp10 causes mitochondrial damage, while nsp10 and nsp14 of SARS-CoV-2 are considered as potential drug targets [17,18].

Pathophysiology

The structure of the SARS-CoV-2 virus

The structural proteins of SARS-CoV-2 are:

• Spike protein (S) - forms large trimetric structures essential for host cell entry through receptor binding and membrane fusion. Spike proteins are the target of host neutralizing antibodies;

• Envelope (E) - present only in small amounts and forms ion channels. E proteins are not required for viral replication but are essential for infectivity and pathogenicity;

• Membrane (M) - the most abundant structural protein of the virus, responsible for the curvature of the viral envelope, especially through interaction with E proteins;

• Nucleocapsid (N) - binds to the viral ribonucleic acid (RNA) genome and ensures that the RNA is maintained in a "pearls on a string" conformation [19].

Attachment of the virus to the host cell surface is facilitated by the spike (S) glycoprotein. The structure of SARS-CoV-2 is shown in figure 1 [20].

Attachment and entry of the SARS-CoV2 virus into the host cell

The receptors for the virus are the ACE-2 receptors, while transmembrane serine protease 2 (TMPRSS2) plays an essential role in activating the virus's spike protein [21]. During the pandemic, new viral variants with a high rate of viral replication and several mutations in the SARS-CoV-2 Spike protein emerged [22]. Viral variants have increased viral transmission efficiency, cellular tropism and pathogenicity, evading host immune recognition. Most of the new viral variants have incorporated new mutations in the S1 domain of the spike protein, which led to increased interaction with ACE-2 and decreased efficacy of neutralizing antibodies (monoclonal antibodies, convalescent plasma and serum from vaccinated individuals) [23]. The high mutation rate of SARS-CoV-2 has led to the classification of the viral genome into lineages, groups or clades. The mutations incorporated into the genome of new viral variants have led organizations and online platforms such as: WHO, PANGO, GISAID and Nextstrain, to classify them into variants, clades or lineages, to identify their global spread and to assess the potential for the emergence of other new viral variants [24].

Before the emergence of the Omicron strain, each of the dominant SARS-CoV-2 variants (alpha-, beta-, delta-) had evolved from pre-CoV progenitors and not from one another. In contrast, successive waves of SARS-CoV-2 viral infections were caused by Omicron sublineages, with each SARS-CoV-2 viral variant being completely novel, with unique combinations of mutations, novel antigenic properties, and variations in clinically relevant traits, including immune evasion, disease severity, and sensitivity to therapy (particularly monoclonal antibodies). The Omicron variant, an emerging variant, displayed more than thirty mutations in the spike protein, which conferred greatly increased infectiousness [25,26].

Attachment of the virus to the host cell surface is facilitated by the spike (S) glycoprotein via ACE-2 receptors, a type I transmembrane monocarboxypeptidase of the Renin-Angiotensin System (RAS) and, leads to fusion of the viral membrane with the host cell plasma membrane to release the viral genome into the cell cytoplasm [27,28]. Although ACE-2-dependent entry of the virus has been explored as the primary model for SARS-CoV-2 entry into cells, ACE-2-independent models have also been suggested, such as those mediated by Fc gamma receptors (FcγRs) in monocytes [29,30].

Virus replication organelles are membranous structures of various shapes and sizes that form in the perinuclear region of the host cell. These structures are surrounded by a double membrane originating from the endoplasmic reticulum (ER) and contain the viral replication complexes, which they sequester from innate immune cellular molecules. Genomic ribonucleic acid (RNA) synthesized at the replication site and viral structural proteins are translocated to the ER-Golgi intermediate compartment (ERGIC), by a still unknown mechanism. Only four viral proteins are incorporated into the virion: the Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins [31].

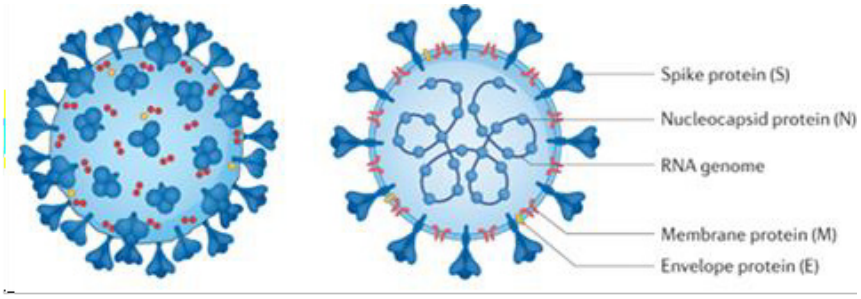

Figure 1. Structure of SARS-CoV-2.

Image taken from Lamers MM et al. SARS-CoV-2 pathogenesis. Nat Rev Microbiol. 2022;20:270-284. doi: 10.1038/s41579-022-00713-0

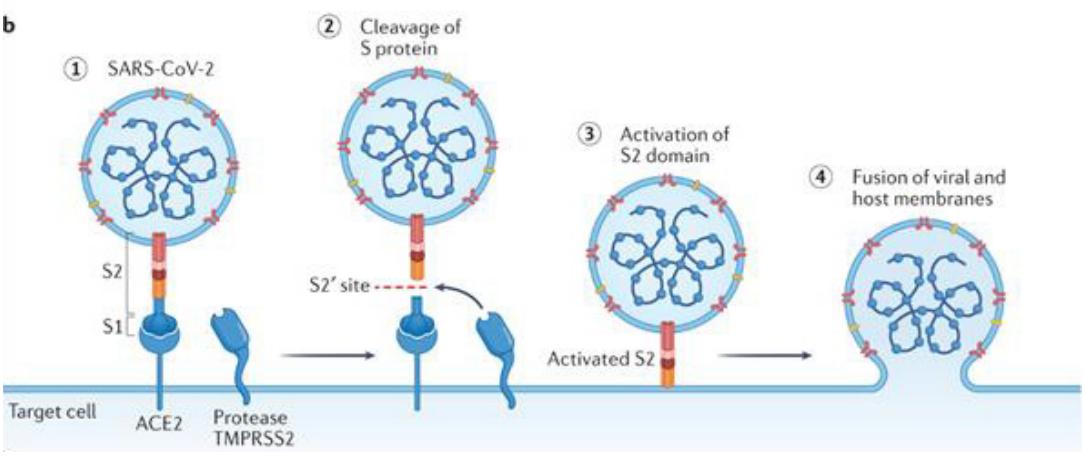

Figure 2. SARS-CoV-2 entry mechanism into the host cell.

Image taken from Lamers MM et al. SARS-CoV-2 pathogenesis. Nat Rev Microbiol. 2022;20:270-284. doi: 10.1038/s41579-022-00713-0

The S protein, assembled as a trimer, gives the appearance of a crown (corona) and is responsible for mediating the main steps of cell entry, including receptor binding and membrane fusion. During virus biosynthesis and maturation in the infected cell at the Golgi apparatus, the S protein is cleaved by a furin-like proprotein convertase into the S1 and S2 subunits, which remain associated and have different functions: in the new target cell, the S1 subunit binds the receptor, and the S2 subunit anchors the S protein to the virion membrane and mediates membrane fusion [32,33].

The E and M proteins contribute to virus assembly and budding through interactions with other viral proteins. The assembled viruses bud in the RE-ERGIC lumen and reach the plasma membrane via the secretory pathway, from where they are then released into the extracellular space after the virus-containing vesicles fuse with the plasma membrane [34]. The mechanism of entry of SARS-CoV-2 into the host cell is shown in figure 2 [35].

The life cycle of the SARS-CoV2 virus

Coronaviruses enter host cells via two pathways:

- the first involves fusion with the host cell plasma membrane, which allows direct delivery of the viral genome into the host cytosol, and
- the second involves receptor-mediated endocytosis. Receptor-mediated endocytosis is achieved through the interaction of the S protein with the ACE-2 receptor, a SARS-CoV-2-specific receptor [36,37].

The S protein binds to the host cell ACE-2 using the S1 domain (step 1), which allows TMPRSS2 to cleave the S protein (step 2) and activate the S2 domain for fusion (step 3) with the fusion of the viral and host lipid bilayers and the deposition of the positive-sense viral single-stranded RNA genome into the host cell (step 4). Studies have shown that TMPRSS2 cleaves the S protein of SARS-CoV-2 at multiple sites, including the S1/S2 cleavage site, providing the ground for drug development efforts to selectively inhibit TMPRSS2 [38,39]. Direct fusion between the virus and the host cell plasma membrane is facilitated by proteolytic cleavage mediated by host cell proteases at SARS-CoV-2 protein residues (position S2) [40]. Upon entry into the host cell, the viral RNA genome is cleaved into two sequences, leading to the assembly of viral progeny. Finally, budding occurs after transit of structural proteins through the endoplasmic reticulum (Golgi intermediate compartment) and interaction with the newly synthesized encapsulated RNA genome.

Several interferon (IFN)-stimulated gene products have been identified, important for SARS-CoV-2 replication, but only a few of them are involved in the steps of SARS-CoV-2 entry into the cell:

- interferon-induced transmembrane proteins (IFITM-IFITM1, IFITM2, IFITM3 and IFITM5), cellular antiviral proteins that prevent viruses from crossing the endosomal membrane to access the cellular cytoplasm (through a mechanism that is still unclear) and,
- Lymphocyte Antigen 6 Complex Locus E (LY6E), an antiviral protein, overexpressed through Glycosyl-Phosphatidyl-Inositol (GPI) biosynthesis that blocks viral replication (it is an innate antiviral defense mechanism) [41-44].

These pathways represent restrictions for virus replication that can be circumvented if SARS-CoV2 is directed to enter cells exclusively at the plasma membrane. Furthermore, the restriction by LY6E is amplified if SARS-CoV-2 removes the furin site and is compensated by overexpression of TMPRSS2, indicating that the membrane fusion site is crucial for the antiviral activity of IFITM proteins [45].

Viral replication creates double-stranded RNA (dsRNA) replication intermediates that can activate cytoplasmic innate immune sensing pathways by activating

melanoma-associated gene 5 (MDA5) or retinoic acid-inducible cytoplasmic helicase gene I (RIG-I), then initiating a signaling cascade through mitochondrial antiviral signaling protein (MAVS), a key protein in the host antiviral response that helps control viral replication, ultimately leading to the production of type I and type III IFN [46,47]. IFN I and III act in a paracrine and autocrine manner through plasma membrane receptors and a viral signaling cascade (JAK- STAT1/2), determining the host immune response to viral infection, through the production of interferon- stimulated genes that have direct and indirect antiviral functions.

Mechanisms that restrict viral entry such as Toll-like receptors (TLRs)

The mechanism restricting viral entry also involves cellular proteins such as Toll-like receptors (TLRs), which belong to the family of pathogen recognition receptors that detect host infection by reading pathogen- associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [48,49]. TLRs are crucial innate immune sensors that detect SARS-CoV-2, initiating protective interferon responses (beneficial role), but also driving the cytokine storm via excessive inflammation with severe lung damage, coagulopathy and multiorgan failure (harmful effects), depending on the stage of infection, the specific TLR involved and the intensity of the immune response. Most TLRs have mutations that could partially explain the susceptibility phenotypes to COVID-19 [50]. The six TLRs activated by PAMPs or DAMPs produced by SARS-CoV-2 infection bind to adaptor proteins and in turn initiate downstream signaling pathways with activation of Nuclear Factor Kappa enhancer of the light chain of activated B cells (NF-κB), resulting in the secretion of pro-inflammatory cytokines and/or type I IFNs [51-53].

In COVID-19, a key role is played by TLR7/8 (detect ssRNA) and TLR4 (recognizes spike protein/ DAMPs). Humans have 10 functional TLRs (TLR1-10). In addition, there are studies that suggest that although most TLRs play an important role in protecting most patients infected with SARS-16 CoV2, some TLRs are even responsible for the cytokine storm in patients with severe COVID-19 disease [54-56]. Activation of TLRs contributes both to viral clearance and disease resolution, and to the triggering of immune signaling, through the production of proinflammatory mediators, causing severe disease. A deeper understanding of the role of TLRs in the immunopathogenesis of COVID-19 disease could lead to the development of prognostic biomarkers and help develop new and effective therapies for COVID-19.

SARS-CoV-2 mechanisms of evading host immunity

In SARS-CoV-2 pathogenesis, one of the critical strategies to evade host immunity was Open Reading Frame (ORF), which are gene segments coding for non-structural or accessory proteins. In total, there are nine accessory ORF genes (ORF3a, 3b, 6, 7a, 7b, 8, 9a, 9b, and 10), which are not essential for viral replication but are critical in attenuating host-virus interactions [57].

SARS-CoV-2's ORF8 is a crucial accessory protein, due to its hypervariability, secretory properties, that significantly impacts viral replication, immune evasion, and disease severity by messing with cell pathways, causing ER stress, mimicking histones to affect DNA, antagonism of multiple immune signaling pathways, such as major histocompatibility complex (MHC-I), type I IFN, IL-17, modification of monocyte function and influencing Spike protein packaging, making it a key player in COVID-19 pathogenesis. ORF8 is the viral protein secreted at the highest rate among all accessory factors [58]. The important role of ORF8 in the SARS-CoV-2 gene is both in viral replication and immune evasion in patients who presented with a milder form of COVID-19, when infected with a 382 nucleotide deletion of ORF8. A better understanding of the interactions of ORF8 with host and viral factors may be essential in elucidating the mechanisms of SARS-CoV-2 infection, and may provide strategies for the development of new therapies for COVID-19 [59].

The accessory protein ORF8 can act through the pro-inflammatory cytokine receptors IL-17 (IL-17RA), TLR-3, TLR-7, TLR-8, TLR-9 or TLR-2, TLR-4, TLR-5. The IL17RA cascade involves IL-17 cytokines (like IL-17A, IL-17F) binding to the IL-17RA on cells, activating pathways like NF-κB, p38 MAPK, leading to inflammation, neutrophil recruitment and tissue damage, which plays a complex role in SARS-CoV-2 severity. ORF8 protein activates the host's IL-17RA receptor, which then triggers inflammation, leading to the activation of NF-κB and the release of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and IL-12, contributing to COVID- 19's cytokine storm [60].

A better understanding of the interactions of ORF8 with host and viral factors is essential in elucidating the mechanisms of SARS-CoV-2 infection, and may provide strategies for the development of novel therapies in COVID-19.

Cytokine storm

The invasion of SARS-CoV-2 can disrupt immune activation, leading to cytokine storm and eventually, ARDS, which has been identified as a key factor in COVID-19 mortality. In patients with severe COVID- 19, the molecular mechanisms of the cytokine storm are not fully understood. Transcriptomic studies on lung biopsies from COVID-19 patients showed a pattern of gene enrichment identical to that of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)-knockout. These studies demonstrated for the first time the involvement of the macrophage-PPARγ complex and their role in the monocyte/macrophage-mediated inflammatory storm in severe COVID-19 lung disease, as

well as the possibility of developing promising therapeutic approaches against the mechanisms of cytokine storm production in patients with severe COVID-19 [61,62].

In severe SARS-CoV-2 infection, the cytokine storm activates platelets that interact with neutrophils, leading to the formation of neutrophil extracellular traps (NETs). NETs stimulate thrombin production and fibrin deposition, leading to thrombosis (microvascular and macrovascular). During NET- osis, neutrophil DNA is shed outside the cell, releasing toxic enzymes such as elastase, which damage lung tissue [63]. In COVID-19, the beneficial importance of NET formation in the pathogen-fighting mechanism has been highlighted, although excessive NET formation can lead to the development of acute lung injury, thromboembolic complications, and ARDS by creating the NET-IL-1β loop [64]. In patients with severe COVID-19, aberrant NET activation can amplify the cytokine storm and macrophage activation syndrome. SARS-CoV-2 can affect ROS production, both through the NADPH oxidase and mitochondrial pathways.

NADPH oxidase is responsible for ROS production and linked to the activation of nuclear factor-κB (NF- κB), mediated by the converting enzyme ACE2 during SARS-CoV-2 invasion and replication. NF-κB activity leads to increased expression of proinflammatory cytokines, IL-6 and IL-1β, which in turn induce mitochondrial ROS production [65,66].

The ROS burst from SARS-CoV-2 infection has detrimental effects on endothelial cells, leading to decreased eNOS expression and NO bioavailability, as well as flow-mediated vasodilation in COVID-19 patients. Targeted anti-NET therapy from natural or synthetic sources could reduce the exaggerated immune response induced by SARS-CoV-2 infection, hyperinflammation, immuno-thrombosis, and other complications. These findings may inform the development of drugs with NET-regulating properties as potential therapeutic strategies for COVID-19 progression [67].

All cellular and molecular events in COVID-19 lead to endothelial dysfunction and extravasation of immune cells into the alveolar space, producing a ground-glass appearance on chest radiographs. In inflamed lung tissue, IL-8 has a chemotactic role in attracting neutrophils into the lung parenchyma to further exert various pathological effects. SARS-CoV-2 proteins, such as accessory proteins in the reading window (ORF7a, ORF3a), nsp1, nsp3a, and nsp7a, can directly reduce NF-κB signaling, thereby contributing to increased production of pro- inflammatory cytokines [68].

Molecular and cellular events from virus entry into the cell, replication and assembly of viral RNA, to the release of viral particles, are modulated by the ORF8 and include responses to ER stress, post-transcriptional histone modifications, and spicule expression [69]. The recruitment of chemokines to the site of infection plays a key role in the activation and early migration of immune cells, including B and T cells. B-cell activating factor (BAFF) and proliferation-inducing ligand (APRIL) are cytokines that are members of the TNF superfamily and play important roles in antibody production, B-cell activation, and cell differentiation. CXCL12 and CXCL13 are potent chemokines with chemoattractant effects on B cells, while CCL21 and CCL19 are T-cell chemokines [70-72].

These chemokines are mainly activated in secondary lymphoid tissues. SARS-CoV-2 has used numerous strategies to evade host immunity to efficiently infect, which may explain the high pathogenicity and rapid spread of SARS-CoV-2 during the pandemic.

Oxidative stress

COVID-19 may promote the excessive production of ROS and Reactive Nitrogen Species (RNS), through cytokine responses to viral components, disrupting the body's redox homeostasis, with inflammation, oxidative stress, and biological responses associated with disease progression [73,74]. ROS and RNS derived from the enzymes nicotinamide adenine dinucleotide phosphate (NOX) oxidase and oxidative stress are implicated in viral pathogenesis and could be at least one of the important pathways modifying COVID- 19 into a severe clinical form of disease [75,76].

The interaction of protein S with ACE-2 leads to increased levels of angiotensin II and activation of the nicotinamide adenine dinucleotide phosphate (NOX2) oxidase 2 pathway, resulting in the release of both ROS, RNS, and inflammatory molecules. SARS-CoV-2 infection causes neuroinflammation by activating the NOX2 pathway in microglia, which may explain the inflammation in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. SARS-CoV-2 can also activate NOX2 through TLR-7, leading to a decrease in the antiviral defense mechanism. SARS-CoV-2 uses NOX2 activation to restrict host immune responses and develop infection [77]. Oxidative stress, coupled with cytokine storm, has been suggested to contribute to COVID-19 pathogenesis through endothelial cell dysfunction and activation of the blood coagulation cascade, resulting in blood clotting and microvascular thrombosis.

SARS-CoV-2 forms a complex with ACE-2 and enters cells through receptors located in the cell membrane. The ubiquitous expression of ACE-2 in many cell types allows SARS-CoV-2 to infect various organs, including the nasopharynx, lungs, lymph nodes, small intestine, stomach, spleen, kidneys, and brain. The trimeric S protein of SARS-CoV-2 interacts with human ACE-2, allowing viral entry into host cells by fusing the viral membrane. This increased affinity is essential for the neuroinvasiveness of SARS-CoV-2 [78]. In SARS-COV2 infection, ACE-2 plays a dual role, both as a receptor and as a negative mediator for severe

symptoms of infection and lung injury. Studies have shown that binding of protein S to ACE2 causes a decrease in ACE with excessive production of profibrotic, proinflammatory and prooxidant agents, exacerbating lung injury with increased permeability of pulmonary vessels (″wet lung″). The lung represents a huge contact surface for the virus (approx. 100 m²). Type 2 epithelial cells in the pulmonary alveoli express high levels of ACE-2 and act as a viral reservoir in the human alveolar compartment. The affinity of SARS-CoV-2 for ACE-2 is approximately 20-fold higher than that of SARS-CoV, which partly explains its higher transmissibility. Therefore, the interference of SARS-CoV-2 on ACE-2 function may induce RAS deregulation at the expense of the alternative pathway, ACE-2/Ang-1-7/MasR, and in favor of its classical arm, ACE/Ang-II/AT1R, which could partly explain the pulmonary (fever, dyspnea, dry cough, myalgia, headache) and neurological (meningitis, ischemic stroke, cerebral thrombosis) clinical manifestations of COVID-19. In patients with COVID-19, additional quantification of RAS components in the blood and especially in the lung epithelium and vascular endothelium could provide additional information, but investigations are complex due to methodological challenges [79].

Patients with severe COVID-19 present characteristic signs of sepsis (fever, chills, shortness of breath, pain or discomfort, and confusion), explained by the exacerbation of macrophage activation, with excessive inflammation and the presence of acute phase reactants: D-dimers, fibrinogen, ferritin, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), etc., cytokine storm, overproduction of IL (IL-1β, IL-2, IL-6) and TNF-α, since the initial phase of the disease [80]. The cytokine complex induces the production of factors related to the coagulation cascade (factors I-XIII, von Willebrand factor, calcium and vitamin K) leading to the appearance of thrombi and associated disseminated intravascular coagulation. SARS-CoV-2 infection triggers both CD4+ (helper) and CD8+ (killer) T cells, crucial for adaptive immunity: CD4+ cells help coordinate the response by activating B cells (for antibodies) and CD8+ cells, while CD8+ cells directly kill infected cells, clearing the virus, with these responses often originating from pre-existing memory cells, like CMV-specific T cells, that get reactivated. The inflammatory response to SARS-CoV-2 in more than 80% of patients with a severe prognosis also causes lymphopenia with a more pronounced decrease in CD4+ T cells compared to CD8+ cells [81].

These events lead to imbalance of the innate/acquired immune response with delayed viral clearance and unusual increase in the number of hyperstimulated macrophages and neutrophils in the affected tissues. Activation of innate immunity in older adults and those at cardiovascular risk can lead to a hemophagocytic-like syndrome (macrophage activation syndrome), of excessive and ineffective immune response with uncontrolled amplification of cytokine production, endothelial dysfunction and multiorgan failure, the starting point of progression to serious and fatal complications of COVID-19.

Endothelial dysfunction

COVID-19 disease, initially characterized as a primary respiratory illness, is now recognized as a systemic vascular disease with profound endothelial involvement. Endothelial dysfunction is a consequence of Spike protein-mediated effects by disrupt endothelial homeostasis through ACE-2 dysregulation, contributing to vascular inflammation, barrier disruption, thrombosis, abnormal coagulation, hypoxemia and, multi-organ injury affecting the pulmonary, cardiovascular, cerebral, and renal systems.

The potential pathological mechanisms underlying endothelial dysfunction associated with COVID-19 proceed through both direct and indirect pathways. In patients with severe COVID-19, endothelial cell dysfunction occurs through multiple mechanisms:

- SARS-CoV-2 prevents ACE-2 from converting Ang II to Ang 1-7, leading to the formation of ROS and RNS;
- SARS-CoV-2 causes an increase in the number of neutrophils that produce ROS, RNS via key enzyme NADPH-oxidase pathway, leading to oxidative stress and tissue damage at the site of inflammation;
- SARS-CoV-2 Spike protein directly causes damage to endothelial cells in various organs with increased Ang II levels, decreased endothelial Nitric Oxide Synthetase (eNOS) activity and oxidative stress. eNOS is the enzyme responsible for the production of nitric oxide (NO) that inhibits SARS-CoV-2 replication [82]. In severe cases of COVID-19, activated macrophages contribute to the cytokine storm by releasing various cytokines (IL-6, TNFα). SARS-CoV-2 significantly activates NADPH oxidase, a key enzyme that produces ROS, leading to widespread oxidative stress, inflammation, and tissue damage in the lungs and other organs, with the viral Spike protein and subsequent inflammatory signals often triggering this enzyme's activity, contributing to severe disease.

Oxidative stress and cytokine storm induce endothelial cell dysfunction and inflammation and activation of the blood coagulation cascade, through factors V, VIII and von Willebrand factor (vWF). In addition, increased levels of CRP, D-dimers also promote hypercoagulability. SARS-CoV-2 infection affects both the pulmonary and extrapulmonary vascular systems, either directly (via viral infection) or indirectly (via cytokine storm), causing endothelial dysfunction (endotheliitis, endothelialitis and endotheliopathy) and multiorgan damage [83].

In SARS-CoV-2 infection, endothelial damage leads to decreased NO bioavailability, oxidative stress,

glycocalyx/barrier disruption, hyperpermeability, inflammation with leukocyte adhesion, hypercoagulability, thrombosis [84].

It has been suggested since the beginning of the pandemic that COVID-19 can be considered a microvascular and endothelial disease. The pulmonary capillary endothelium provides a fertile "soil" for viral entry and replication, facilitating viral penetration into the circulating blood. Thus, emerging therapies targeting endothelial dysfunction and endotheliopathy hold promise for ameliorating lung injury associated with COVID-19. COVID-19 also affects other organs, especially the heart. The increased mortality of COVID-19 patients was due to cardiovascular diseases, hypertension, and cardiovascular complications of endothelial dysfunction: arrhythmia, cardiac lesions (elevated Troponin I, creatine kinase, NT-proBNP), coagulation (elevated D-dimer levels), fulminant myocarditis, heart failure, and atherosclerosis. Patients with COVID-19 and heart failure who showed increased expression of the ACE-2 gene and protein were more susceptible to developing severe COVID-19 [85]. Figure 3 shows the mechanism of endothelial dysfunction in COVID-19 disease [86].

Furthermore, COVID-19 was also an important risk factor for the development of acute myocardial infarction, although some data from a study cohort showed that the majority of patients with acute myocardial infarction developed symptoms after COVID-19 vaccination [87]. During the pandemic, it was suggested that in patients with COVID-19 and endothelial dysfunction, the cause of coronary artery disease was atherosclerosis with an increased risk of cardiovascular events, but the mechanism remained unclear. A study published in 2025 evaluated the impact of SARS-CoV-2 infection on coronary inflammation and plaques using coronary CT angiography on the impact of clinical outcomes. SARS-CoV-2 infection was associated with faster progression of lesional plaque volume and an increased incidence of becoming a high- risk plaque [88].

COVID-19 disease is also associated with liver injury. Recent studies have suggested that cytokine storm causes increased IL-6 and dysfunction of sinusoidal endothelial cells in the liver, leading to endotheliopathy and liver injury [89-92]. SARS-CoV-2 infection can also cause acute kidney injury, through the mechanism of mitochondrial dysfunction, inflammation, necroptosis, capillary congestion and endothelial injury. ACE-2 is also expressed at high levels in renal tissues, the injury of which leads to proteinuria, hematuria and abnormal renal radiography. In COVID-19, acute kidney injury occurs through both direct and indirect mechanisms, including endotheliitis, thrombosis, and disturbances in carbohydrate and lipid metabolism [93,94]. Histopathological studies support direct viral infection of endothelial cells in lung, kidney, or liver tissues in patients with COVID-19.

These findings suggest that the interaction of S proteins with lung, kidney, and liver endothelial cells leads to inflammation, thrombosis, and the severity of COVID-19, and may provide new insights into the development of targeted therapies [95]. Increased endothelial inflammation, evidenced by increased expression of various cytokines/adhesion molecules, is a classic example of endothelial dysfunction. A retrospective study in patients with

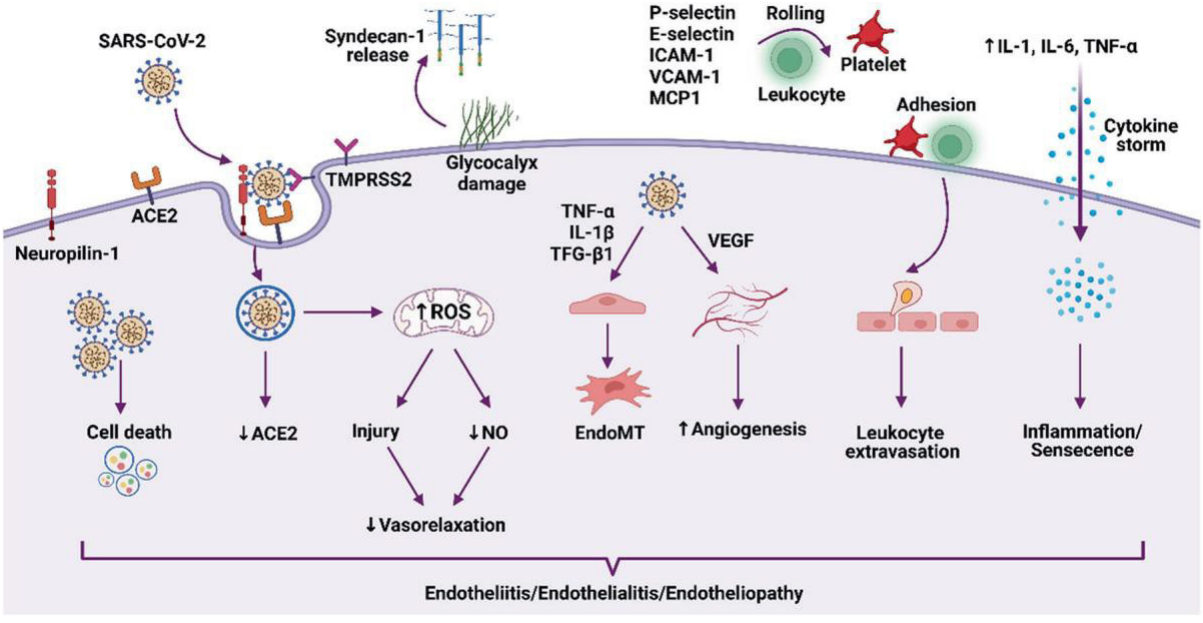

Figure 3. Mechanisms of endothelial dysfunction in COVID-19.

Image taken from Xu SW et al. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacologica Sinica. 2023;44:695-709. doi:10.1038/s41401-022-00998-0.

COVID-19 found that levels of soluble Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM- 1), Vascular Adhesion Protein-1 (VAP-1), von Willebrand factor, P-selectin, E-selectin, and angiopoietin-2 (Ang-2) were elevated, changed during disease progression and regression, and can be considered markers of endothelial inflammation and dysfunction [96,97].

Studies have shown that endothelial dysfunction is present in both COVID-19 and long-COVID. In patients at high risk of severe COVID-19, measurement of vascular endothelial function has been suggested. There are studies in patients with COVID-19 that have shown that the fragmented vascular endothelial glycocalyx (the network covering endothelial cells), essential for maintaining vascular homeostasis, is increased and can be used as a prognostic indicator of the development of severe complications [98]. However, endothelial ACE-2 levels are insufficient to allow replicative infection in many organs, including the heart. Therefore, it is possible that SARS-CoV-2 circulates in the bloodstream without entering cardiac tissues by crossing the endothelium due to the relatively low level of ACE-2 expression in endothelial cells of coronary capillaries. Therefore, direct infection and activation of endothelial cells by SARS-CoV-2 may also be mediated by mechanisms independent of ACE-2.

Studies have shown that, in addition to ACE-2, there are several cell surface receptors, such as neuropilin-1, scavenger receptor B type I (SR-B1) (major receptor for high-density lipoproteins), TLR-2, and TLR-4, that either facilitate viral entry into endothelial cells or activate endothelial cells after SARS-CoV-2 infection [99]. Furthermore, some cellular components have even been identified as attachment factors for SARS-CoV-2 on human endothelial cells, such as the intermediate filament protein vimentin, suggesting that direct entry of the virus into endothelial cells could also occur through other mechanisms. Furthermore, it is possible that ACE-2 mediates viral entry into endothelial cells through increased endothelial ACE-2 levels induced by SARS-CoV-2 infection. The SARS-CoV-2 Spike protein interacts with Vascular Endothelial Growth Factor-A (VEGF-A) via the receptor Neuropilin-1, which may affect nociceptor activity and contribute to the pain manifested in COVID-19 [100]. This type of interaction is a mechanism by which the virus can hijack host cellular pathways, leading to some of the systemic effects of infection, including the potential for increased VEGF expression in a specific context of COVID-19.

Protein S also stimulates VEGF production in duodenal enterocytes, leading to increased vascular permeability and intestinal inflammation. The paracrine component of VEGF secreted by infected enterocytes is the trigger for endothelial cell activation [101,102]. Viral particles have been identified in various organs such as the lung, heart, liver, small intestine, kidney, and may also be present in endothelial cells in the central nervous system and retina. Severe acute respiratory syndrome caused by SARS-CoV-2 also caused gastrointestinal manifestations due to intestinal inflammation. Plasma VEGF levels were particularly high in patients with gastrointestinal symptoms and significantly correlated with intestinal edema and disease progression [103]. Animal models of SARS-CoV-2 Spike protein-stimulated intestinal inflammation have shown that VEGF is overproduced in the duodenum by activating the Ras-Raf-MEK-ERK signaling cascade in enterocytes, inducing permeability and inflammation, before increasing in the circulation [104].

Thrombosis in COVID-19 was a typical manifestation of endothelial injury caused by SARS-CoV-2, including thromboembolism, vascular microembolism, and arterial thrombotic events. Some studies have shown that the prevalence of thromboembolic events such as deep vein thrombosis and pulmonary embolism in hospitalized patients with COVID-19 was 30% [105-107]. Vascular microembolism also explain the skin and kidney lesions present in some patients with COVID-19. The incidence of myocardial infarction and ischemic stroke was very high in the first week after the diagnosis of COVID-19. Different variants of SARS-CoV-2 contributed to a different degree to viral transmissibility, disease severity and vaccine efficacy, which demonstrated that there was heterogeneity in endothelial dysfunction. Among the SARS-CoV-2 variants, Alpha, Beta, Gamma, and Delta, patients infected with Delta were more prone to endothelial dysfunction and had the highest risk of intensive care unit admission and mortality.

Lymphopenia, a decrease in absolute lymphocyte count, was one of the most common laboratory abnormalities observed in patients with COVID-19. This specific finding is closely related to the inflammatory cytokine storm, characterized by increased proinflammatory cytokines, TNFα and IL-6, T-cell exhaustion, and direct SARS-CoV-2 infection of T cells [108]. Lymphopenia influenced the prognosis of COVID-19 patients, as it was a systemic manifestation of ACE2 overexpression on the surface of lymphocytes and T cells [109,110]. T cells themselves are a vital component of the adaptive immune response to viral infections. CD8+ T cells are important due to their specific cytotoxicity against infected cells, while CD4+ T cells are essential because they support the activation of CD8+ and B cells, while regulating cytokine production. These molecular mediators help recruit immune cells, such as macrophages, to the site of infection.

Furthermore, eosinophilia has been proposed to be beneficial in COVID-2019 disease due to its antiviral effect, as previously demonstrated in other viral infections such as influenza, while eosinopenia has been associated with a higher mortality rate [111,112]. COVID-19 infection causes alterations in arginine metabolism with lower

levels of eNOS and upregulated arginase, effects that are ascribable to the inflammatory mediators released by macrophages. Macrophages and dendritic cells, known as APCs, stimulate T cells for cytokine synthesis [113,114]. Emerging data from COVID-2019 pandemic showed increased risk of adverse cardiovascular events up to at least 12 months, helping to understand the mechanism of endothelial dysfunction COVID-2019 disease.

COVID-19 disease, initially characterized as a primary respiratory illness, is now recognized as a systemic vascular disease with profound endothelial involvement. Endothelial dysfunction is a consequence of Spike protein-mediated effects by disrupt endothelial homeostasis through ACE-2 dysregulation, contributing to vascular inflammation, barrier disruption, thrombosis, abnormal coagulation, hypoxemia and, multi-organ injury affecting the pulmonary, cardiovascular, cerebral, and renal systems.

Long COVID

The vast majority of COVID-19 disease survivors are left with variable degrees of health sequelae including pulmonary, cardiovascular, neurological and renal complications. Long COVID, or post-acute sequelae of SARS-CoV-2 infection, refers to a range of new, returning, or ongoing health problems three or more weeks after first being infected with the virus that causes COVID-19 disease [115,116]. Long COVID is largely driven by persistent endothelial dysfunction, where damage to the blood vessel endothelium by persistent viral presence causes chronic inflammation, oxidative stress, and immune system dysregulation [117,118].

Long COVID is a complex, multi-system condition characterized by a wide range of symptoms that can persist for months or years and is associated with over 100 potential biological markers. The mechanisms of long COVID are still unclear. The hypotheses under discussion are the persistence of residual viral components driving chronic inflammation, endothelial dysfunction, microembolization, alteration of the immune system and dysbiosis of microbiota [119-121].

Post-COVID-19 pulmonary fibrosis is one of the main concerns that has emerged after the recovery from this pandemic. There are clinical, biological, and radiological risk factors for post-COVID-19 pulmonary fibrosis. Clinical risk factors including age, male sex, smoking history, and comorbidities have been identified. The pathogenesis of early and late pulmonary fibrosis complicating COVID-19 disease has not been elucidated but it can be linked to the direct stimulation of the profibrotic cascade by SARS-CoV-2 and/or the immunological effects of the virus on alveolar epithelial cells. SARS-CoV-2 can also induce lung fibrosis in patients with either genetic predisposition or pre-existing subclinical interstitial lung abnormalities [122]. High-resolution Computed Tomography provides diagnostic utility to diagnose pulmonary fibrosis as it provides more details regarding the pattern and the extent of pulmonary fibrosis. Since the clinical and biological risk factors for post-COVID-19 pulmonary fibrosis match the clinical and biological profile of interstitial pulmonary fibrosis patients, there are concerns about the burden of pulmonary fibrosis complicating the COVID-19 course in the survivors and the severity of the fibrosis, fibrotic pattern, appropriate treatment options to treat/prevent post-COVID-19 pulmonary fibrosis, and the timing to starts treatment early or late in the course of the disease [123,124].

Key findings indicate that diagnosis relies on clinical evaluation, function tests and CT imaging, with management focusing on antifibrotic therapies and pulmonary rehabilitation. The Center of Disease Control (CDC) emphasizes strategies to preventing severe outcomes from COVID-19 illness that helps prevent also Long COVID, including vaccination.

Conclusions

Coronavirus-2019 disease, caused by the novel coronavirus SARS-CoV-2, was the most severe emerging infectious disease in the current century with an enormous impact on global health and economies.

Five years after the start of the COVID-19 pandemic, the exact pathophysiological mechanism of the disease is still unknown even though it is now recognized that it is a disease with three overlapping stages of viral replication in the upper respiratory tract with direct invasion into the alveolar epithelium and common symptoms of fever, fatigue, cough, and sore throat, hyperinflammatory cytokine storm with low oxygen levels, shortness of breath, and acute lung damage (COVID-19 pneumonia), and hypercoagulability or thrombosis which can lead to severe respiratory failure and multi-organ damage.

The prognosis of COVID-19 patients remains a multidisciplinary challenge, with evolutionary arguments that often depend on the patient comorbidities, the type of dysfunction determined or accentuated within COVID, and the severity of respiratory impairment.

The technical level and degree of multidisciplinary ad dress of these patients can also significantly influence morbidity and mortality indicators in affected population.

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