

Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression

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The global epidemiology of coronavirus disease 2019 (COVID-19) suggests a wide spectrum of clinical severity, ranging from asymptomatic to fatal. Although the clinical and laboratory characteristics of COVID-19 patients have been well characterized, the pathophysiological mechanisms underlying disease severity and progression remain unclear. This review highlights key mechanisms that have been proposed to contribute to COVID-19 progression from viral entry to multisystem organ failure, as well as the central role of the immune response in successful viral clearance or progression to death.

coagulation; COVID-19; cytokine storm; multisystem organ failure; pathophysiology

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel beta-coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As of June 15, 2020, the number of global confirmed cases has surpassed 8 million, with over 400,000 reported mortalities. The unparalleled pathogenicity and global impact of this pandemic has rapidly engaged the scientific community in urgently needed research. Preliminary reports from the Chinese Center for Disease Control and Prevention have estimated that the large majority of confirmed SARS-CoV-2 cases are mild (81%), with ~14% progressing to severe pneumonia and 5% developing acute respiratory distress syndrome (ARDS), sepsis, and/or multisystem organ failure (MOF) (144). Although more data is urgently needed to elucidate the global epidemiology of COVID-19 (80), a wide spectrum of clinical severity is evident, with most patients able to mount a sufficient and appropriate immune response, ultimately leading to viral clearance and case resolution. However, a significant subset of patients present with severe clinical manifestations, requiring life-supporting treatment (51). The pathophysiological mechanisms behind key events in the progression from mild to severe disease remain unclear, warranting further investigation to inform therapeutic decisions. Here, we review the current literature and summarize key proposed mechanisms of COVID-19 pathophysiological progression (FIGURE 1).

Key Pathophysiological Mechanisms: Our Current Understanding

Viral Invasion

The first step in COVID-19 pathogenesis is viral invasion via its target host cell receptors. SARS-CoV-2 viral entry has been described in detail elsewhere (138). In brief, SARS-CoV-2 consists of four main structural glycoproteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The M, E, and N proteins are critical for viral particle assembly and release, whereas the S protein is responsible for viral binding and entry into host cells (33, 76, 89, 143, 148). Similar to SARS-CoV, several researchers have identified human angiotensin converting enzyme 2 (ACE2) as an entry receptor for SARS-CoV-2 (75, 99, 148, 156). SARS-CoV-2 is mostly transmissible through large respiratory droplets, directly infecting cells of the upper and lower respiratory tract, especially nasal ciliated and alveolar epithelial cells (161). In addition to the lungs, ACE2 is also expressed in various other human tissues, such as the small intestine, kidneys, heart, thyroid, testis, and adipose tissue, indicating the virus may directly infect cells of other organ systems when viremia is present (77). Interestingly, although the S proteins of SARS-CoV-2 and SARS-CoV share 72% homology in amino acid sequences, SARS-CoV-2 has been reported to have a higher affinity for the ACE2 receptor (18, 21, 143).

Following host cell binding, viral and cell membranes fuse, enabling the virus to enter into the cell (89). For many coronaviruses, including SARS-CoV, host cell binding alone is insufficient to facilitate

membrane fusion, requiring S-protein priming or cleavage by host cell proteases or transmembrane serine proteases (9, 10, 90, 94, 108). Indeed, Hoffman and colleagues demonstrated that S-protein priming by transmembrane serine protease 2 (TMPRSS2), which may be substituted by cathepsin B/L, is required to facilitate SARS-CoV-2 entry into host cells (58). In addition, unlike other coronaviruses, SARS-CoV-2 has been reported to possess a furin-like cleavage site in the S-protein domain, located between the S1 and S2 subunits (31, 138). Furin-like proteases are ubiquitously expressed, albeit at low levels, indicating that S-protein priming at this cleavage site may contribute to the widened cell tropism and enhanced transmissibility of SARS-CoV-2 (123). However, whether furin-like protease-mediated cleavage is required for SARS-CoV-2 host entry has yet to be determined. Blocking or inhibiting these processing enzymes may serve as a potential antiviral target (130). Interestingly, SARS-CoV-2 has developed a unique S1/S2 cleavage site in its S protein, characterized by a four-amino acid insertion, which seems to be absent in all other coronaviruses (4). This molecular mimicry has been identified as an efficient evolutionary adaptation that some viruses have acquired for exploiting the host cellular machinery.

Once the nucleocapsid is deposited into the cytoplasm of the host cell, the RNA genome is replicated and translated into structural and accessory proteins. Vesicles containing the newly formed viral particles are then transported to and fuse with the plasma membrane, releasing them to infect other host cells in the same fashion (33, 89, 105). Although much progress has been made in our understanding of the mechanisms underlying SARS-CoV-2 invasion, additional research is needed to delineate exactly how cleavage of the S proteins by TMPRSS2 confers viral particle entry as well as how S-protein cleavage by membrane proteases contributes to viral penetration.

Host Response

Initial Physiological Immune Response

A timely, localized, and well-coordinated immune response presents the first line of physiological defense against SARS-CoV-2 infection (FIGURE 2). Similar to other cytopathic viruses, SARS-CoV-2 infection induces cellular death and injury in airway epithelial cells through diverse processes such as pyroptosis (19, 153). Viral-mediated cell death causes release of various damage-associated molecular patterns (DAMPs) and pathogen-associated

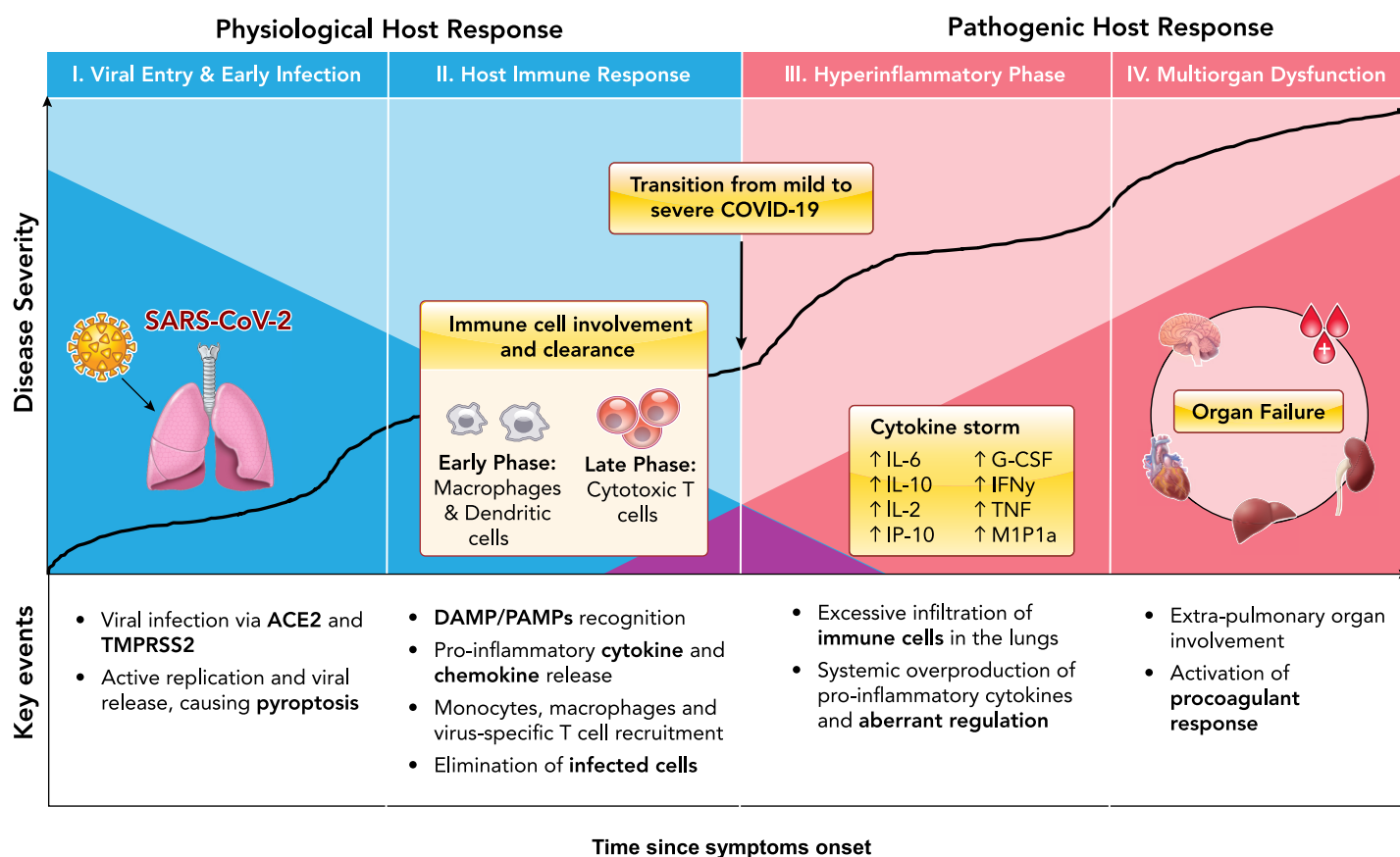


FIGURE 1. Characterization of key events in COVID-19 disease pathophysiological progression

The dark blue shading indicates physiological viral host response over time, and the dark red shading indicates pathogenic hyperinflammatory host response over time. Figure adapted from Ref. 124, with permission from the *Journal of Heart and Lung Transplantation*.

molecular patterns (PAMPs), which are believed to be recognized by pattern-recognition receptors on alveolar macrophages and endothelial cells. For example, Toll-like receptors (TLRs) recognize PAMPs in mostly the extracellular space, triggering induction of proinflammatory cytokine transcription factors such as NF- κ B, as well as activating interferon regulatory factors that mediate the type I interferon-dependent antiviral response (122, 125). In contrast, nucleotide-binding domain leucine-rich repeat (NLR) proteins recognize DAMPs expressed intracellularly, thus triggering activation of inflammasomes and conversion of proIL-1 β to active IL-1 β (122, 125). Circulating levels of IL-1 β in COVID-19 patients suggests local inflammasome activation with no systemic manifestations (61). In total, these processes foster an increased secretion of proinflammatory cytokines and chemokines, such as IL-6, type II interferon (IFN γ), monocyte chemoattractant protein 1 (MCP1), and interferon gamma-induced protein 10 (IP-10), as well as subsequent

pulmonary recruitment of immune cells, including macrophages and dendritic cells. Direct viral infection of macrophages and/or dendritic cells is estimated to propagate further cytokine and chemokine release, subsequently activating late-phase immune-cell recruitment of antigen-specific T cells to destroy virally infected alveolar cells (61, 130, 132, 149). In addition to cytokine release and immune cell recruitment, another potential mechanism that could contribute to successful viral clearance is antibody neutralization. Current literature suggests seroconversion in COVID-19 patients occurs ~7–14 days post symptom onset (12). However, antibody kinetics of different immunoglobulins have not been well characterized, and reported findings are conflicting (12). Although currently available commercial serological assays do not provide information on whether SARS-CoV-2 antibodies confer immune protection, recent reports using specialized laboratory-based neutralization assays have observed a marked correlation between the levels of SARS-CoV-2 spike/

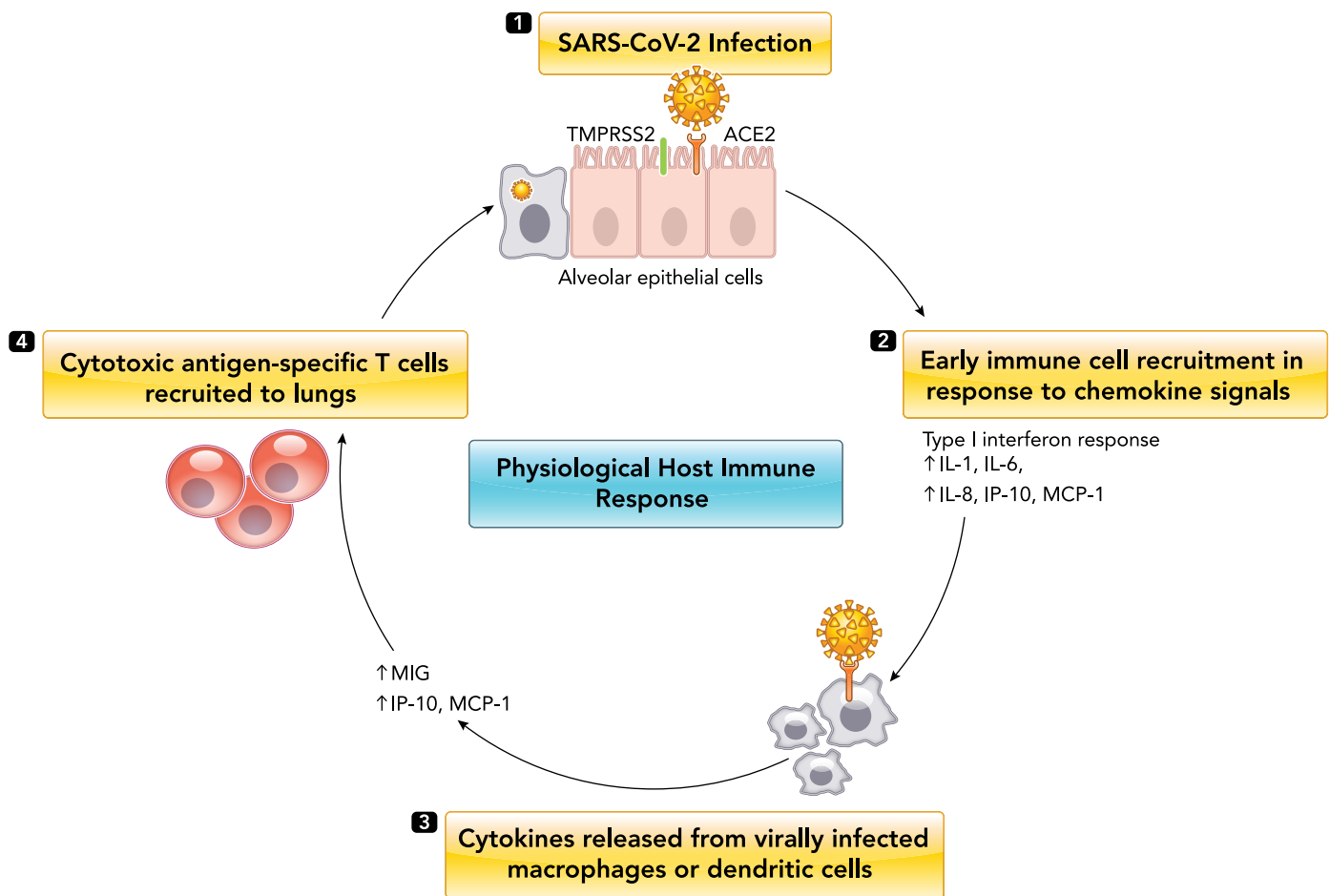


FIGURE 2. Physiological host immune response to SARS-CoV-2 infection

1: SARS-CoV-2 enters alveolar epithelial cells by binding to angiotensin converting enzyme 2 (ACE2) through surface spike (S) protein mediated by transmembrane serine protease 2 (TMPRSS2). 2: pulmonary recruitment of macrophages and dendritic cells in response to chemokine and cytokine release (early phase). 3: direct viral infection of pulmonary macrophages and dendritic cells causes expression of several proinflammatory cytokines and chemokines. 4: dendritic cells phagocytose virus in the lungs, migrate to secondary lymphoid organs, and activate antigen-specific T cells, which travel to the lungs and destroy virally infected alveolar cells.

receptor binding domain (RBD) antibodies and the neutralization capacity of patient sera, suggesting its potential beneficial role in clearance (3, 98, 103, 107, 160).

In most COVID-19 patients, the combined immune response of initial cytokine release and activation of antiviral interferon response followed by immune-cell recruitment should result in successful SARS-CoV-2 clearance from the lungs (FIGURE 2). However, as has been reported extensively, viral infection can progress to severe disease due to dysregulated immune response.

Induction of Marked and Pathogenic Proinflammatory Cytokine Storm

Several cohort studies have observed markedly elevated levels of circulating proinflammatory cytokines and chemokines, significantly correlating to disease severity and mortality. The main drivers of this response have been postulated and thoroughly reviewed elsewhere (125, 130, 151). Notably, increased levels of IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP1, IFN γ , macrophage inflammatory protein 1 α (MIP1 α), and tumor necrosis factor (TNF) have all been implicated in COVID-19 severity, suggesting a combined T-helper type 1 (Th1) and Th2 cell response (61, 130). In particular, IL-6 has emerged as a candidate treatment target due to its robust association with disease progression. A recent meta-analysis suggested serum IL-6 cut-offs of >55 pg/ml and >80 pg/ml to identify patients at high risk for severe COVID-19 and mortality, respectively (5). Prospective validation of these proposed cut-offs across different assay methodologies and patient populations are urgently awaited to establish clinical utility. Notably, the cytokine concentrations observed in hospitalized COVID-19 patients are rarely elevated to the same extent as in secondary hemophagocytic lymphohistiocytosis and cytokine release syndrome following CAR-T cell treatment (64).

In addition to the observed maladaptive cytokine release, elevations in more traditional biochemical markers of acute infection, including C-reactive protein (CRP) and ferritin (both positive acute phase reactants), as well as continual decreases in lymphocytes and significant elevations in neutrophils, are evident (43, 79). As such, the neutrophil-to-lymphocyte ratio appears to be a useful indicator of disease prognostication and management (83). The mechanisms behind progressive lymphopenia in severe COVID-19 remain unclear, although T-cell redistribution via pulmonary recruitment, exhaustion, as well as depletion through TNF- α -mediated apoptosis or even direct cytopathic injury have been suggested (35, 147). It is also important to note that immune-cell infiltration can lead to the excessive secretion of pro-

teases and reactive oxygen species, fostering further damage and hyperinflammation (130). In addition, direct viral infection of immune cells such as monocytes and macrophages have been proposed to contribute to dysregulated immune response, as has been observed in SARS (23, 52, 136). Nevertheless, the exact contribution of direct viral immune cell infection is unknown and highly debated (155). Finally, recent data also suggest SARS-CoV-2-specific antibody titers are elevated in patients with severe disease (98). It is unclear whether increased antibody prevalence in severe COVID-19 patients suggests potential antibody-dependent enhancement (ADE) or is simply a result of higher viral antigen exposure. Further studies are needed to evaluate the contribution of antibodies to both physiological and pathogenic host response (39, 160).

Prominent Changes in Hematology and Coagulation

Since a hyperinflammatory profile consistent with cytokine storm has been robustly associated with COVID-19 severity and suggested as the predominant cause of patient mortality, most initial literature has focused on the dysregulation of immune response in COVID-19 patients and the potential value of immune modulating treatments. However, evidence of alarming coagulation abnormalities and high incidence of thrombotic events in COVID-19 patients is prevalent (70). Early reports from Wuhan, China demonstrated prolonged activated partial thromboplastin time (aPTT) and prothrombin time, and elevated D-dimer as well as thrombocytopenia (20, 139, 155). In a more in-depth study of 183 patients by Tang et al., 71.4% of non-survivors and 0.6% of recovered cases met the criteria for disseminated intravascular coagulation during hospitalization (128). In addition to prolonged prothrombin time, studies in other cohorts have reported high prevalence of lupus anticoagulant in the circulation (13). Recent autopsy data from Italy also observed fibrin thrombi in pulmonary small arterial vessels in 87% of fatal cases examined, suggesting the contribution of coagulation in diffuse alveolar and endothelial damage (15). These data clearly suggest a state of hypercoagulability in severe COVID-19.

Although prominent changes in blood coagulation may be a contributing mechanism to COVID-19 mortality, its pathogenesis is estimated to be tightly linked to inflammation and cytokine release. Specifically, immunothrombosis is a phenomenon known to occur as a result of host defense against various pathogens, including viral infection (30). For example, the activation of complement pathways can lead to initiation of the coagulation cascade (30, 127). Complement-mediated pulmonary tissue damage

and microvascular injury have been observed in small cohorts with severe COVID-19 (85). Procoagulant response is also associated with the inflammatory effects of cytokines in the vascular endothelium, including increased vascular permeability and damage as a result of immune-cell infiltration (62). Given the correlation of IL-6 levels with increased fibrinogen and D-dimer in severe COVID-19 patients, it is likely that cytokine-mediated procoagulant changes are partially responsible for the specific thrombosis profile observed in critically ill patients (41, 110). Presence of neutrophil extracellular traps (NETs) are also possibly linked to COVID-19 thrombosis via activation of intrinsic coagulation (8, 50, 162). Overall, the predominant mechanism seems that encompassing SARS-CoV-2-induced endothelial damage fosters monocyte recruitment and activation, along with tissue factor exposure, which then activates blood coagulation. Recruitment of neutrophils by activated endothelial cells can also synthesize and release multiple cytokines into the circulation, further accelerating this process (93). In addition to the coagulopathy observed in COVID-19, severe bleeding in patients is rare in comparison to other RNA-type viruses with hemorrhagic manifestations (30). However, a recent

report in *Blood* characterized bleeding as a significant cause of morbidity in COVID-19 patients, emphasizing the need for randomized trials on the benefit of escalated prophylaxis (1). By taking these data into consideration, a close connection between the inflammatory and coagulation response of COVID-19 patients appears to exist, wherein treatment options for both contributing factors should be explored.

Extrapulmonary Involvement and Progression to Multisystem Organ Failure

One of the key hallmarks of COVID-19 severity is the progression to systemic disease characterized by multisystem organ damage or failure. Many groups have suggested extrapulmonary involvement in COVID-19 is a direct result of unrestrained inflammation. However, other contributing mechanisms have been proposed and are explored below (FIGURE 3).

Cardiovascular Complications

Significant cardiovascular damage has been observed in severe COVID-19 patients. Several studies have demonstrated significantly elevated levels







Extrapulmonary Involvement in COVID-19	
Laboratory/Clinical Profile	Key Potential Mechanisms
 <ul style="list-style-type: none"> • Headache, dizziness • Confusion, epilepsy • Ataxia, anosmia, ageusia etc. 	<ul style="list-style-type: none"> • Direct viral infection • Systemic inflammation and cerebral edema • Pulmonary hypoxia, metabolic acidosis
 <ul style="list-style-type: none"> • ↑ Cardiac troponins • ↑ NT-proBNP, BNP 	<ul style="list-style-type: none"> • Direct viral infection • Systemic inflammation • Myocarditis • Stress-induced cardiomyopathy
 <ul style="list-style-type: none"> • ↑ Serum creatinine • ↑ Urea • Proteinuria 	<ul style="list-style-type: none"> • Direct viral infection • Systemic inflammation
 <ul style="list-style-type: none"> • ↑ ALT & AST • ↑ Lipase, amylase • ↑ Albumin • Vomiting, nausea 	<ul style="list-style-type: none"> • Direct viral infection • Systemic inflammation, IL-6 pleiotropic effects • Drug-induced liver injury • Hypoxic-mediated dysfunction
 <ul style="list-style-type: none"> • ↑ Prothrombin time • ↑ D-dimer • ↑ Fibrinogen • ↑ aPTT 	<ul style="list-style-type: none"> • SARS-CoV-2-mediated endothelial dysfunction • Systemic inflammation (e.g. cytokine, complement pathways)
 <ul style="list-style-type: none"> • ↑ Ferritin • ↑ C-reactive protein • ↑ ESR • Lymphopenia, fever 	<ul style="list-style-type: none"> • Systemic inflammation

FIGURE 3. Laboratory/clinical profile and key potential mechanisms underlying extrapulmonary manifestations observed in severe COVID-19 patients

NT-proBNP, NH₂-terminal-proB-type natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ESR, erythrocyte sedimentation rate.

of classical markers of cardiac injury and failure [i.e., cardiac troponin and brain natriuretic peptides (BNP)] in patients with greater disease severity (53a, 78). Notably, increasing cardiac troponin levels have been correlated to other inflammatory markers, such as CRP, ferritin, and IL-6, suggesting inflammatory damage as opposed to primary myocardial injury (28). Maladaptive cytokine release is known to directly affect cardiomyocytes as well as to lead to endothelial cell reprogramming and dysfunction, supporting their causative role in COVID-19 cardiovascular manifestations (71, 131). However, it is important to note that a handful of studies have described patients presenting with primary cardiac symptoms, suggesting myocarditis and stress-related cardiomyopathy due to respiratory failure and hypoxemia (60, 63, 152). Currently, there is insufficient evidence to support direct viral infection of cardiomyocytes, although SARS-CoV-2 genomes have been effectively detected in endomyocardial biopsies, mostly involving immune cell infiltrates (40, 149). Previous data from the SARS epidemic suggests 35% of heart specimens showed presence of viral RNA in the myocardium. Given the homology between these viruses, such direct viral invasion should not be discounted (100, 106).

Renal Injury and Failure

In addition to cardiovascular damage, renal involvement is frequently observed in COVID-19, varying from mild proteinuria and minor serum creatinine elevations to acute kidney injury (AKI) and renal failure. Initial studies have reported varying incidences (3–15%) of AKI during illness (20, 22, 155). Now considered a valuable prognostic indicator for COVID-19 survival, AKI is estimated to affect 20–40% of critically ill patients in intensive care, necessitating renal replacement therapy and extracorporeal support therapies such as blood purification (112, 155). An understanding of the complex and likely multifactorial pathophysiological mechanisms behind kidney failure in COVID-19 is thus needed for early recognition and appropriate treatment selection. Direct renal infection and damage presents one potential contributing mechanism. ACE2 is expressed in the kidney, and although previous studies suggested absence of viral particles in postmortem renal specimens from SARS patients (27), electron microscopic examination of 26 postmortem COVID-19 patients demonstrated direct virulence in tubular epithelium and podocytes (126). Direct SARS-CoV-2 infection of the renal epithelium is estimated to result in mitochondrial dysfunction, acute tubular necrosis, and protein leakage (72, 118). In addition to direct infection, uncontrolled cytokine release, thrombo-

sis, and ischemia can also result in further kidney dysfunction, characterized by intrarenal inflammation, increased vascular permeability, and volume depletion (88). Cytokine-mediated inflammatory AKI has been described previously in the literature in other clinical contexts such as CAR-T-cell treatment in cancer patients (102, 104, 117).

Gastrointestinal, Hepatic, and Pancreatic Manifestations

The involvement of the gastrointestinal (GI) tract and hepatic system in COVID-19 disease progression is being increasingly reported. The most common GI manifestations reported in both adult and especially pediatric COVID-19 patients include diarrhea, nausea, vomiting, and abdominal pain (16, 133, 157). Similar to renal COVID-19 involvement, there is evidence of direct SARS-CoV-2 GI infection through isolation of viral RNA from GI epithelial cells (146). It is thus hypothesized that the GI manifestations observed in COVID-19 are a result of SARS-CoV-2 infection of intestinal enterocytes and subsequent dysfunction in the ileum and colon (16). The association of GI manifestations with disease severity is not well described, with many conflicting results reported (25, 139, 154).

In addition to GI manifestations, several studies have reported elevated liver enzymes and higher rates of liver injury in patients with severe COVID-19. Specifically, in a study of 417 COVID-19 patients, 76.3% had abnormal liver tests, and 21.5% had liver injury during hospitalization (14). Patients with abnormal liver function tests, particularly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), also had significantly higher risk of developing severe pneumonia (14). These findings have been observed in numerous studies, and several potential pathophysiological mechanisms have been proposed (11, 20, 42, 61, 74, 139, 141). First, there is potential for ACE2-mediated liver dysfunction. Although hepatocytes have not been shown to exhibit high ACE2 expression, previous studies have demonstrated a high level of ACE2 expression in cholangiocytes, suggesting direct bile duct infection/damage as a potential cause of abnormal liver enzymes (17). This, however, is unlikely since significant increases in circulating levels of common bile duct injury markers (e.g., serum bilirubin, gamma glutamyltransferase, and alkaline phosphatase) have not been extensively reported (7). Contrary to earlier studies, a recent study by Wang et al. observed abundant SARS-CoV-2 viral particles in hepatocytes of postmortem specimens, prompting further research on hepatic viral infection/clearance (141). Additional pathophysiological mechanisms underlying liver injury include drug-induced liver injury as well as

hypoxic hepatitis. However, the validity of these mechanisms have been debated, since abnormal liver enzymes have been reported at hospital admission before any drug treatment as well as in patients without the need for mechanical ventilation (7). A more plausible mechanism behind liver dysfunction in COVID-19 is the observed systemic inflammatory response, as described previously, leading to cytotoxic T-cell-mediated necrosis and MOF. The pleiotropic hepatic effects of IL-6 could play a particularly important role, inducing expression of serum amyloid A, fibrinogen, and CRP (121).

Pancreatic injury has also been reported in patients with COVID-19. Single-cell RNA sequencing suggests that ACE2 is expressed in both the exocrine and islet cells of the pancreas (81). In terms of exocrine-related damage, a study by Wang et al. reported that 17% of COVID-19 patients in their cohort ($n = 52$) had serologic evidence of exocrine pancreatic injury, defined as elevated amylase or lipase (140). In a more recent study, hyperlipasemia was reported in 12.1% of COVID-19 patients ($n = 71$) but was not associated with worse outcome (91). Due to the low specificity of lipase elevations, exocrine pancreatic injury and inflammation is challenging to confirm without abdominal imaging (32). Few case reports have observed acute pancreatitis in COVID-19 patients (2, 45, 54), although it is expected to be quite uncommon. Some authors have proposed this is due to direct exocrine damage, whereas others suggest it is likely resultant from the gastrointestinal symptoms observed in many COVID-19 patients (32). In addition to exocrine damage, there is much debate regarding the impact of COVID-19 on the endocrine pancreas and its subsequent effect on glucose regulation. Acute diabetes has been previously observed in SARS-CoV patients (150). Although direct damage of pancreatic β -cells has been proposed as a plausible mechanism behind this phenotype, immune destruction of β -cells has also been suggested in addition to bystander death due to exocrine infection (101). Importantly, COVID-19 appears to enhance complications in patients with diabetes, likely due to viral-induced pancreatic dysfunction as well as associated immune dysregulation, vasculopathy, and coagulopathy (29, 37).

Central Nervous System Involvement

The neurological manifestations of COVID-19 have not been of much focus in the literature, but a few published reports are concerning. In a case study series of 214 patients diagnosed with COVID-19, neurological symptoms were observed in 36.4% of

patients, and this percentage increased to 45.5% when examining patients with severe infection (86). The reported neurological manifestations of COVID-19 include headache, dizziness, confusion, epilepsy, ataxia (lack of voluntary muscle movement), altered sense of smell (hyposmia/anosmia), loss of taste (ageusia), and Guillain-Barré syndrome, among others (97, 115, 134). Altered sense of taste or smell can be present in up to 80% of patients with mild to moderate COVID-19 (73). The underlying pathophysiology of the loss of these olfactory and gustatory perceptions have been postulated to be related to direct damage of the supporting cells of the olfactory epithelium, olfactory bulb and altered function of the olfactory neurons, altered ACE2 signal transmission, and accelerated gustatory particle degradation by sialic acid (87, 137). Autopsy findings in SARS-CoV infections have shown strong evidence of neuro-invasion, with demonstrated viral presence in the cerebrospinal fluid (6, 95). The pathophysiological mechanisms behind the neurological manifestations of COVID-19 have not been well elucidated. Potential mechanisms include 1) viral entry via ACE2 receptors into the endothelia that line the blood capillaries and subsequent neuro-invasion, 2) neurological edema and brain stem compression as a result of breached blood-brain barrier, 3) neurological edema and hypercoagulability as a result of cytokine storm syndrome, and 4) propagation via mechanoreceptors and chemoreceptors in the lung and lower respiratory airways (65). Importantly, it is possible that the neurological manifestations of COVID-19 could be a result of hypoxia, respiratory, and/or metabolic acidosis at end-stage disease (6).

Pediatrics and Pregnancy: Special Considerations

The pathophysiological mechanisms proposed above primarily relate to observations in non-pregnant adult patients. Although the clinical picture of COVID-19 in pediatrics and pregnancy is less understood, their respective characteristics appear different when compared with non-pregnant adults.

Pediatrics

In a case study series of >2,000 children with suspected or confirmed COVID-19 in China, 5% of symptomatic children had dyspnea or hypoxemia, and only 0.6% progressed to ARDS or MOF (36). A multicenter European study of children with PCR-confirmed SARS-CoV-2 infection also reported that 8% of pediatric patients required ICU admission, 4% required mechanical ventilation, 3% required inotropic support, and <1% required extracorpo-

real membrane oxygenation (49). Although these reports indicate a milder COVID-19 profile in pediatric patients compared with adults (159), reports from China and the CDC indicate that the documented hospitalization and mortality rates in pediatric cases are concerning and emphasize the importance of comprehensive studies to examine the clinical picture of pediatric disease (15a, 36). Interestingly, current evidence suggests that the laboratory profile observed in pediatric COVID-19 patients is different from that of adults. A recent meta-analysis identified 24 studies, including a total of 624 pediatric cases with PCR-confirmed COVID-19, and reported common laboratory abnormalities in mild and severe disease. Their study demonstrated frequent elevations in CRP, procalcitonin, and LDH in severe pediatric COVID-19, similar to adult findings (56). However, no consistent trend in lymphocyte count was reported (56). This is surprising since lymphopenia has been estimated to be one of the most consistent laboratory abnormalities in adult patients with severe COVID-19 illness (57). It is important to note that the heterogeneous standards used to interpret laboratory tests in pediatrics could contribute to the variation observed in study findings. More comprehensive studies based on larger sample sizes are needed to better characterize the laboratory and clinical profile of mild versus severe pediatric COVID-19 and to help develop our understanding of immune pathogenesis.

Increasing evidence also suggests the emergence of an associated multisystem inflammatory condition with similar features to Kawasaki disease and toxic shock syndrome in a small subset of pediatric patients (24, 26, 34, 44, 67, 113). This condition appears to be associated with prevalent cutaneous manifestations as well as significant GI symptoms. Some cases of cutaneous manifestations in adult COVID-19 patients have been reported, although varying incidence among patients has been noted (68, 111, 120). The urgent need to appropriately identify these patients has led the World Health Organization (WHO) and other regulatory bodies to develop a preliminary case definition known as Multisystem Inflammatory Disorder in Children and adolescents (MIS-C) (142a). Interestingly, a recent study characterizing a small cohort of previously healthy children and adolescents who developed an inflammatory profile related to COVID-19 in New York City described a unique cytokine pattern characterized by elevated IL-6 and IL-10 production, as well as increased interferon signaling components. Increases in TNF- α were not observed in contrast to adult patients (24). A recent, large, multi-center U.S. study of 186 patients who met the broad CDC criteria for MIS-C reported 92% of patients had at least four laboratory

results indicating inflammation, including but not limited to elevated CRP and ferritin, lymphocytopenia, neutrophilia, hypoalbuminemia, thrombocytopenia, anemia, as well as elevated D-dimer and fibrinogen (44). Elevations in troponin and brain natriuretic peptide were also observed in the majority of patients (44). The pathophysiological mechanisms behind this novel disease are unknown. Some have suggested MIS-C is mainly resultant from post-infectious IgG-mediated enhancement, whereas others have proposed it is due to blockage of type I and III interferon responses, leading to uncontrolled viral replication and high viral load (119). Due to the paucity of data in this area, further research is required to elucidate what mechanisms confer protection from COVID-19 in most pediatric patients as well as what factors predispose children to progress to MIS-C.

Pregnancy

Evaluating the risk of severe outcomes of SARS-CoV-2 infection in pregnant women is imperative for both mother and child. Several original studies and systematic reviews have been completed, assessing clinical characteristics of pregnant women with COVID-19 (46, 69, 135). Interestingly, most studies report similar clinical characteristics and mortality rates in pregnant women with COVID-19 compared with nonpregnant women of reproductive age (48). This is in contrast to what has been observed in other respiratory viruses, including SARS-CoV (142). Some have suggested this is likely a result of the physiological immune adaptations that occur during pregnancy, preventing escalation to the hyperinflammatory phase of COVID-19 (48). However, despite evidence of mild COVID-19 in pregnant patients, a recent report by the CDC suggests pregnant women may be at higher risk for more severe outcomes, estimating a higher proportion of pregnant women with COVID-19 undergo hospitalization compared with nonpregnant women (38). This study, however, is limited by the lack of information regarding whether hospital admission was due to COVID-19 illness or pregnancy-related conditions, complicating interpretation (38). In addition to these reports, there is increasing evidence of higher rates of miscarriage and preeclampsia in pregnant women with SARS-CoV-2 infection, suggesting placental involvement (5a). Most studies have reported no evidence of detectable SARS-CoV-2 RNA in the placenta. However, a recent case report showed evidence of SARS-CoV-2 in the syncytiotrophoblast cells of a pregnant COVID-19 patient in the second trimester of gestation with preeclampsia (59). A unique correlation between the laboratory profile observed in pregnant patients with preeclampsia and COVID-19 also appears to exist, prompting questions

of shared disease pathways (116). Finally, it is important to note that current evidence suggests vertical transmission of SARS-CoV-2 is unlikely (55). However, as described above, there is potential for SARS-CoV-2 to significantly affect the placenta and thus negatively impact fetal development. Further research is urgently needed to better characterize the clinical picture of COVID-19 at each trimester of pregnancy.

Future Directions and Unanswered Questions

Most of our knowledge on COVID-19 pathophysiological progression has been observed through a laboratory lens, inferring potential causative mechanisms from observed biomarker trends across patients. Based on the current evidence, it is clear that, although direct SARS-CoV-2 infection of multiple organs as well as hypoxia and stress-related injury may contribute to COVID-19 pathophysiological progression, systemic inflammation and aberrant cytokine regulation is a hallmark of disease severity. Considering this, it is still unclear what factors influence the transition from normal physiological to pathogenic hyperinflammatory response. The nuances of age-related immune response appear to play a role, with increasing disease severity observed in older populations (82). Furthermore, limited available data in the pediatric population suggests a distinct and diverse spectrum of disease completely different from adults, further reinforcing the importance of age-related immune responses (84, 145). In addition to age, emerging clinical and epidemiological data suggest sex-specific differences in the clinical characteristics and case-to-fatality ratio of COVID-19, with worse prognosis observed in males (66, 92). This disproportionate clinical epidemiology may be explained by sex-specific regulation of ACE2, increased incidence of preexisting comorbidities in males (i.e., hypertension, diabetes, cardiovascular disease), as well as sex-specific differences in viral immune response, as described elsewhere (47, 109). Genetic predispositions have also been proposed, including polymorphisms in ACE2 and genetic variability in histocompatibility complex (MHC) class I genes (96). Finally, several comorbidities have been associated with poor outcomes, likely due to the fact that organ and immune function may already be compromised and in a state of sub-clinical inflammation (53, 158). Notably, in a case study series of 5,700 patients from New York City, the most commonly observed comorbidities were hypertension, obesity, and diabetes (112). These factors need to be observed more thoroughly to complete our clinical understand-

ing of COVID-19. In addition to understanding relevant risk factors, there is increasing suspicion of delayed but severe COVID-19 presentation, particularly in children, even after viral clearance (113). This not only suggests the importance of defining the timing of antibody response through serological testing in multiple age groups but also points toward the increasing complexity of COVID-19.

This review presents various potential pathophysiological mechanisms behind SARS-CoV-2 infection. The evidence behind these proposals are based on previous experience with similar coronaviruses, as well as clinical characteristics, laboratory testing, and postmortem pathological analysis of COVID-19 patients around the world. The exact contribution of risk factors to disease progression is still partially undefined. Additionally, further research is needed to examine the main drivers of COVID-19 and their molecular mechanisms of action in both pediatric and adult populations, since this should inform appropriate risk stratification and therapeutic strategies. From our preliminary understanding, immunomodulatory therapies are likely to be equally or more effective than solely targeting viral host cell entry. Furthermore, treatment approaches may be further tailored to the disease course of the patient by bolstering immune response earlier during disease progression to enhance an efficient antiviral response and blocking inflammation once severe disease develops.

To conclude, current evidence highlights that appropriate immune response is fundamental to COVID-19 pathogenesis, but much remains unknown regarding the key drivers of progression. As new therapeutic paradigms emerge, our understanding of disease pathophysiology will undoubtedly advance and not only inform current clinical practice for COVID-19 but fundamentally shape our understanding of immune involvement in systemic disease. ■

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