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Severe Acute Respiratory Syndrome–Associated Coronavirus 2 Infection and Organ Dysfunction in the ICU: Opportunities for Translational Research

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OBJECTIVES: Since the beginning of the coronavirus disease 2019 pandemic, hundreds of thousands of patients have been treated in ICUs across the globe. The severe acute respiratory syndrome–associated coronavirus 2 virus enters cells via the angiotensin-converting enzyme 2 receptor and activates several distinct inflammatory pathways, resulting in hematologic abnormalities and dysfunction in respiratory, cardiac, gastrointestinal renal, endocrine, dermatologic, and neurologic systems. This review summarizes the current state of research in coronavirus disease 2019 pathophysiology within the context of potential organ-based disease mechanisms and opportunities for translational research.

DATA SOURCES: Investigators from the Research Section of the Society of Critical Care Medicine were selected based on expertise in specific organ systems and research focus. Data were obtained from searches conducted in Medline via the PubMed portal, Directory of Open Access Journals, Excerpta Medica database, Latin American and Caribbean Health Sciences Literature, and Web of Science from an initial search from December 2019 to October 15, 2020, with a revised search to February 3, 2021. The medRxiv, Research Square, and clinical trial registries preprint servers also were searched to limit publication bias.

STUDY SELECTION: Content experts selected studies that included mechanism-based relevance to the severe acute respiratory syndrome–associated coronavirus 2 virus or coronavirus disease 2019 disease.

DATA EXTRACTION: Not applicable.

DATA SYNTHESIS: Not applicable.

CONCLUSIONS: Efforts to improve the care of critically ill coronavirus disease 2019 patients should be centered on understanding how severe acute respiratory syndrome–associated coronavirus 2 infection affects organ function. This review articulates specific targets for further research.

KEY WORDS: angiotensin-converting enzyme 2 receptor; coronavirus disease 2019; critical illness; pandemic; severe acute respiratory syndrome–associated coronavirus 2

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The coronavirus disease 2019 (COVID-19) pandemic caused by the beta-coronavirus severe acute respiratory syndrome–associated coronavirus (SARS-CoV) 2 virus has resulted in more than 106 million cases and more than 2.32 million deaths (as of February 7, 2021) since

emerging in December 2019 (1–3). Approximately, 20% of patients require hospitalization, and 25% of those require ICU admission due to refractory hypoxemia, shock, or multiple organ failure (MOF) (4–7). Numerous descriptive studies of COVID-19 pathophysiology, mechanism, signaling, and potential immunologic consequences have been published, but many reports lack integration and context. COVID-19 victims do not succumb from the SARS-CoV-2 infection per se; rather, mortality occurs due to pneumonia, renal failure, thrombosis, and MOF that reflect the innate immune signaling response to the infection. The international community has been much less focused on the ramifications of innate immune signaling activation in COVID-19 (8).

In addition, analysis of COVID-19 outcomes further exposes existing health disparities: Black and Hispanic Americans are disproportionately impacted in terms of morbidity and mortality. Additionally, males have demonstrated lower survival rates (9–13). Although these differences clearly indicate the need for evaluation of social determinants of health in COVID-19, they may also reveal previously unrecognized mechanistic and signaling pathways that could be targeted for potential therapeutics. This review summarizes the current mechanisms and reported pathophysiology of COVID-19 disease to characterize and understand the illness and treatment. Since many patients present with single organ disruption and/or current level of evidence has been explored in specific organs, we present the known data in this fashion. We also explore why organ disruption in the setting of COVID-19 (e.g., pneumonia, acute respiratory distress syndrome [ARDS], renal failure) and the response to COVID-19 therapy appear to frequently differ from classical forms of these pathologies.

OVERVIEW OF DISEASE TRANSMISSION AND CLINICAL FEATURES

SARS-CoV-2 is predominantly transmitted via respiratory droplets released by coughing or sneezing (14). Similar to its predecessor SARS-CoV-1 (2003 SARS outbreak), SARS-CoV-2 binds to the angiotensin-converting enzyme (ACE) 2 receptor via the virus Spike protein (15). Host organs expressing the ACE2 receptor that are targets for the virus Spike protein are presented in **Figure 1**. After binding, the furin domain of the Spike protein is cleaved by host proteases (e.g., serine protease transmembrane protease, serine [TMPRSS]2), which enables viral and cellular membrane fusion and subsequent internalization and release of the viral RNA (15). The ACE2 protein is widely expressed on respiratory epithelium, which is the presumed entry point, although ACE2 protein expression has been detected in many different organs (16).

Infected individuals may remain asymptomatic or may develop a wide range of symptoms including fever, malaise, anosmia, hypogeusia, sore throat, headache, cough, shortness of breath, chest pain, nausea, abdominal pain, diarrhea, or cognitive changes. COVID-19 patients often present with lymphopenia, elevated nonspecific inflammatory markers (C-reactive protein, lactic acid dehydrogenase [LDH], D-dimer, ferritin, aspartate aminotransferase [AST]), and patchy/bilateral infiltrates on chest radiography. Patients who proceed to critical illness typically develop shortness of breath and hypoxemia within 5–8 days after symptom onset and are more likely to be older, blood type A, and have multiple comorbidities (7, 17–19). Critically ill COVID-19 patients often require prolonged respiratory support and have high risk for MOF, thrombotic coagulopathies, acute kidney injury (AKI), sudden myocardial dysfunction, and prolonged hospitalization (20, 21).

REPORTED HOST IMMUNE RESPONSES IN COVID-19

There are likely several SARS-CoV-2–induced inflammatory responses depending on host-pathogen interaction and disease evolution (summarized in **Fig. 2**). Similar to other viral infections, viral replication and cellular damage directly activate the host immune response, which contribute to the initial inflammatory response (22). Viral replication induces host cell death and the release of multiple danger-associated molecular patterns (DAMPs), which increase localized and systemic inflammation via proinflammatory cytokine and chemokine secretion (23). SARS-CoV-1 causes pyroptosis and activates the nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing-3 inflammasome, further activating a proinflammatory cytokine cascade (24). Thus, inflammasome activation may be one mechanism by which SARS-CoV-2 recruits host immune cells to the infection site, causing capillary leak, inflammatory

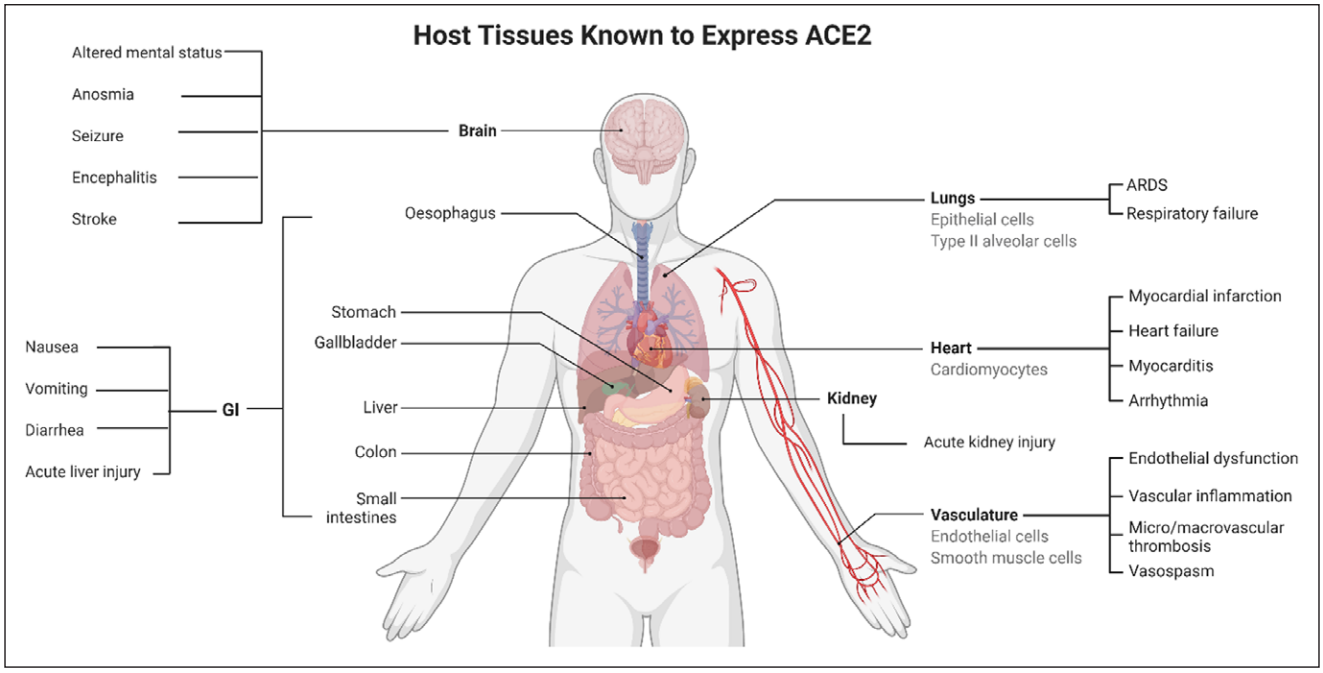

Figure 1. Tissues expressing angiotensin-2 receptor (angiotensin-converting enzyme [ACE] 2) and related COVID-19 symptoms. ARDS = acute respiratory distress syndrome, GI = gastrointestinal.

infiltrates, and pulmonary edema. Recent studies also implicated neutrophil extracellular traps (NETs) in disease progression, although their impact as a driver of downstream inflammation remains unclear (25–27).

Consensus is lacking on how to characterize the severity and nature of the inflammatory response. Several early case studies in COVID-19 reported markedly elevated levels of interleukin (IL)–1β, IL-6, IL-10, tumor necrosis factor (TNF)–α, and other mediators, leading many to characterize it as a "cytokine storm." However, not every perturbation in a disease setting is maladaptive, and response severity measured at indiscriminate time points does not necessarily correlate with pathogenicity. Distinguishing between appropriate and dysregulated inflammatory responses in critically ill patients remains challenging. Most cytokines induce pleiotropic downstream effects with interdependent biological activities, and interactions among these mediators are neither linear nor uniform. The term "cytokine storm" implies that the elevated cytokine levels are necessarily injurious to host cells, and widespread acceptance of this term fueled the repurposing of many immunotherapy drugs to suppress various inflammatory pathways. One approach to understanding these responses has been to use the first 72 hours of temperature data from hospitalized COVID-19 patients as a surrogate for the inflammatory response, thereby allowing subphenotyping of patients (28, 29). Perhaps not surprisingly, a subset of COVID-19 patients manifests a dysfunctional "hyperinflammatory" response with persistent fevers and elevated inflammatory markers, whereas a separate subset manifests a dysfunctional "hypoinflammatory" response, with an absence of fevers and worse MOF (29). Thus, any discussion of the immune response in COVID-19 must consider that although some patients mount an appropriate response and resolve the infection, others develop variably different dysfunctional responses which manifest as different COVID-19 subphenotypes.

Consistent with a hypoinflammatory subphenotype, a significant proportion of COVID-19 patients manifest a disease similar to immunoparalysis in sepsis, which involves decreased human leukocyte antigen (HLA)-DR expression and profound, persistent lymphopenia, including reductions in both CD4 and CD8 T cells. In addition, the remaining immune cells in many COVID-19 patients are functionally impaired: monocytes have been shown to release less TNF-α, whereas T cells release less IFN-γ and demonstrate increased PD-1 expression, consistent with an exhausted phenotype (30–33). The observed downregulation of IL-2 and IL-7 in COVID-19 patients indicates an impairment in the development, differentiation, and homeostatic expansion of T cells (34).

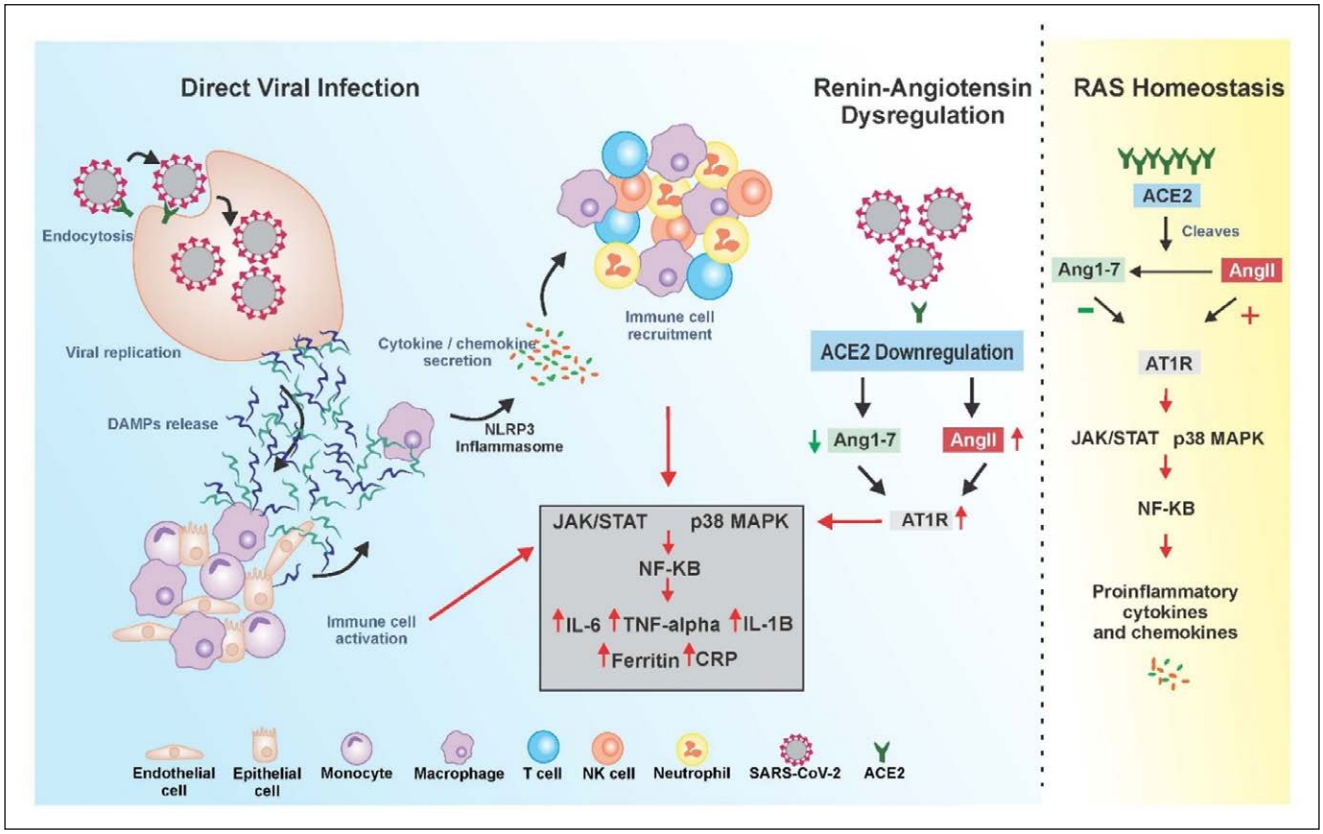

Figure 2. Proposed host immune responses secondary to severe acute respiratory syndrome–associated coronavirus 2 (SARS-CoV-2) infection. Although several host immune responses are activated by SARS-CoV-2 infection, all mechanisms appear to activate janus kinase/signal transducer and activator of transcription (JAK/STAT), p38 mitogen-activated protein kinase (MAPK), and/or nuclear factor–κB (NF-κB) pathways. This leads to release of proinflammatory cytokines (tumor necrosis factor [TNF] α, interleukin [IL]–6, IL-1β) and chemokines (C-X-C motif ligand [CXCL] 1, CXCL10), and immune cell recruitment. Current evidence implicates three potential mechanisms. 1) Direct viral infection induces host cell death and the release of multiple damage/danger-associated molecular patterns (DAMPs), which increase proinflammatory cytokine and chemokine secretion. 2) Activation of NLRP3 inflammasome and pyroptosis triggers a cascade of proinflammatory cytokines such as IL-1β. 3) Viral infection dysregulates the renin-angiotensin system (RAS) by down-regulating the ACE2 receptor, which leads to decreased angiotensin (Ang) 1–7, increased AngII, and subsequent AngII-receptor type 1 (AT1R) activation. This ultimately activates JAK/STAT, p38 mitogen-activated protein kinase (MAPK), and NF-κB pathways and induces a proinflammatory state. CRP = C-reactive protein, NK = natural killer, NLRP3 = nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing-3.

Such patients may benefit from immune stimulation, rather than immune suppression. Indeed, recent work suggests that treatment with the inhaled antiviral cytokine interferon-α2b results in accelerated viral clearance and reduced lung injury (35).

In contrast, the hyperinflammatory response subphenotype involves elevated levels of IL-6, IL-10, IL-8, and chemokines (e.g., C-X-C motif ligand [CXCL]–8, CXCL1, CXCL10, and C-C motif chemokine ligand-5) (21, 34, 36–40). CXCL10 reflects recent IFN-γ activity within 14 days, suggesting that the elevated CXCL10 levels at the time of ICU admission might be indicative of increased T helper 1, natural killer (NK), or natural killer T cell activity early in the illness, even though IFN-γ levels were not elevated among these patients (34). TNF-α levels range from low to normal or increased, indicating that the hyperinflammatory immune response is distinct from the classical cytokine storm associated with diseases like macrophage-activation syndrome in which TNF-α is both a lead cytokine and a therapeutic target (34). IL-1β levels are variable, reported as increased or decreased, and there are currently trials using anakinra, which blocks IL-1β activity, for treatment of the hyperinflammatory phase of COVID-19 (34).

Despite these overall patterns, IL-6 levels are orders of magnitude lower in patients with severe or critical COVID-19 disease (median 26–210 pg/mL) than in patients with non–COVID-19 ARDS (median

578–1,618 pg/mL) (21, 36–43). Elevated IL-6 levels are needed to activate and potentiate the adaptive immune response and promote T cell regulation. By contrast, excessive IL-6 levels can block lymphopoiesis and induce lymphocyte death (44). All distinct lymphocyte subsets (NK cells, B cells, and T cells) may be affected by this innate overactivation (34). The degree of IL-6 elevation has been correlated with adverse outcomes in COVID-19 patients and has led to trials of anti–IL-6 therapy for COVID-19 patients, with variable success (45, 46).

Other contributors to the hyperinflammatory state that are observed in many patients include dysregulation of the renin-angiotensin system (RAS) and its interaction with the host immune response. ACE2 regulates RAS homeostasis by cleaving angiotensin II (proinflammatory/profibrotic) into angiotensin 1–7, which leads to an anti-inflammatory/antifibrotic/antioxidant response (47–59). Angiotensin II is elevated in preclinical ARDS models and elicits proinflammatory effects by activating angiotensin II receptor type 1 (AT1R), nuclear factor–κB, janus kinase/signal transducer and activator of transcription, and p38 mitogen-activated protein kinase pathways; activation of these signaling pathways has stimulated interest in trials of kinase inhibitors for COVID-19. The cleaved peptide (angiotensin 1–7) reduces inflammation by binding the Mas receptor to antagonize AT1R (56). Previous studies report that SARS-CoV-1 infection down-regulates ACE2 in mice, which correlated with severe acute lung pathologies mediated by increased angiotensin II and AT1R activation (57). Angiotensin II was elevated in a small cohort of COVID-19 patients and appeared to correlate with viral load and lung injury, thus supporting the hypothesized role of RAS-immune axis dysregulation (60).

The role of ACE2 in COVID-19 pathophysiology led to hypotheses regarding the therapeutic use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with COVID-19. One hypothesis suggests that ACEI-mediated ACE2 inhibition could reduce morbidity and mortality by down-regulating RAS (57). By contrast, ACEIs, and ARBs could hypothetically increase ACE2 expression, leading to increased host susceptibility to viral invasion of target cells (52). Several small observational studies investigated the clinical outcomes of these hypotheses in patients with COVID-19, and current data suggest no benefit or harm from ACEIs and ARBs on risk of developing COVID-19 or clinical outcomes (61, 62).

The primary site of SARS-CoV-2 infection in the lungs is type 2 alveolar epithelial cells (AT2 cells). Other cell types also express the ACE2 receptor and may contribute to the multiple organ inflammatory response observed in patients with COVID-19 disease. ACE2 expression is essentially ubiquitous and has been detected in the brain, heart, oral and nasal mucosa, nasopharynx, liver, kidney, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, and spleen (16, 58). ACE2 expression has been reported on lymphocytes, and SARS-CoV-2 viral particles can be detected in lymphocytes (63, 64). Therefore, direct lymphocyte infection and cell death may be responsible for lymphopenia in COVID-19 patients and explain the mechanism by which cytokine release syndrome can develop in severe COVID-19 infections (65).

SARS-CoV-1 and SARS-CoV-2 have been isolated from macrophages, and viral infection of these cells in vitro appears to be associated with increased cytokine release (66, 67). However, it remains difficult to distinguish these inflammatory mechanisms from direct cellular infection effects due to ubiquitous ACE2 expression on immune cells (i.e., macrophages and dendritic cells) and in multiple organs. Alternatively, MOF may be due to damage resulting from a combination of the systemic inflammatory response or ongoing immune suppression and persistent viral replication. Finally, the emerging postinfectious inflammatory syndrome in children (termed "multisystem inflammatory syndrome in children") is likely mediated by inflammatory cytokines, although this remains an area of active exploration and will not be the subject of this review (68).

METHODS

We performed a narrative review of the literature retrieved from searches of Medline via the PubMed portal, Directory of Open Access Journals, Excerpta Medica database, Latin American and Caribbean Health Sciences Literature, and Web of Science originally from December 2019 to October 15, 2020, and revised twice to December 10, 2020, and February 3, 2021. We included data prior to December 2019 when relevant for the reported or proposed mechanisms in each organ system. Searches were not limited by date, language, or publication status. Publication bias

was limited by searching clinical trial registries including ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and the Australian New Zealand Clinical Trials Registry. We also searched the medRxiv and Research Square preprint servers to limit publication bias. Grey literature was eligible for inclusion if the authors responded affirmatively to correspondence with the requested information.

We used the following National Library of Medicine Mesh search terms: SARS-CoV-2 [Mesh], COVID-19 [Mesh], Middle East Respiratory Syndrome Coronavirus [Mesh], SARS virus [Mesh]; Respiratory Distress Syndrome [Mesh], and Pneumonia [Mesh]. Additional search terms included 2020 pandemic and individual organ system terms. Articles were not assessed using standardized and validated scales to assess risk-of-bias or evidence quality. The data were not pooled, so statistical analyses were not performed.

COVID-19 DISEASE MECHANISMS IN ORGAN FAILURE

Respiratory Manifestations and Failure

SARS-CoV-2 was first identified via a bronchoalveolar lavage sample from a patient with severe ARDS in Wuhan, China, indicating that the predominant location of viral replication and shedding is the respiratory tract (69). Patients with COVID-19 develop a wide spectrum of pulmonary diseases with varying severities, suggesting multiple mechanisms of disease propagation. Early evaluation of TMPRSS2 and ACE2 expression reported that both receptors were localized in nasal epithelial cells and AT2 cells (16, 70). AT2 cells have a critical role in normal pulmonary physiology because they secrete surfactant and produce alveolar type 1 cells during acute lung injury (ALI). Children have lower illness severity than their adult counterparts, which may be partly explained by an age-dependent decrease in ACE2 expression in nasal epithelium (71). The exact mechanism of SARS-CoV-2 infection of AT2 cells is under investigation, although it is clear that AT2 viral infection leads to significant lung injury and may partly explain pulmonary sequela observed in patients.

SARS-CoV-2 is a promiscuous virus with multiple mammalian hosts and hijacks a variety of different receptors and enzymes to invade cells. SARS-CoV-2 enters cells (by exploiting Spike protein sites) via ACE2, dipeptidyl peptidase 4 (DPP4), CD147 (a highly glycosylated cell surface protein with wide tissue expression), or the cathepsin pathway to cleave and facilitate viral entry (72–75). Blocking DPP4 attenuates ALI in a murine model, and DPP4 has been studied in airway remodeling and fibrosis, whereas CD147 has been implicated in mucus hypersecretion (76–78). Thus, identifying all receptors/proteases involved in SARS-CoV-2 respiratory infection will enhance our mechanistic insight into disease pathogenesis.

Autopsy of COVID-19 patient lungs reveals several mechanistic clues for respiratory failure. First, there is evidence of increased angiogenesis based on imaging and gene expression data (79). Second, COVID-19 patients with ARDS display significant pulmonary fibrosis in the later disease stages, which impairs oxygenation (80). Third, significant deposition of microthrombi is common and may partly explain the proposed "L" (low lung weight, low elastance, and low inspiratory driving pressures) and "H" (high lung weight, high elastance, and high inspiratory driving pressures) ARDS phenotypes (81), although some experts have refuted the presence of the L phenotype. Fourth, COVID-19 patients are reported to have increased susceptibility to ventilator-associated pneumonia, for as yet undefined reasons compared with non–COVID-19 patients receiving invasive ventilation (82). Respiratory effects also occur along with MOF, profound alterations in coagulation, and hyperinflammatory cytokine profiles that are observed in other critical illnesses. Inflammation and tissue injury do not necessarily associate with the distribution of SARS-CoV-2 RNA and protein in post mortem examinations of lungs from COVID-19 patients, indicating that the inflammatory response itself is responsible for much of the respiratory failure (83).The extrapulmonary mechanisms by which SARS-CoV-2 infection triggers respiratory failure are discussed in subsequent sections.

Hematologic Dysfunction

COVID-19 disease significantly impacts the hematologic system and hemostasis. Prothrombin time (PT) and activated partial thromboplastin time are prolonged and D-dimer levels are elevated, suggesting the presence of a consumptive coagulopathy such as disseminated intravascular coagulation. Diffuse alveolar hemorrhage has been reported in COVID-19 patients, although a hypercoagulable phenotype with micro/macrothrombi formation

in venous and arterial sites is more prevalent (12, 64, 65). Thrombi have been documented in the pulmonary, renal, brain, hepatic, and cardiac vasculature. Marked D-dimer elevation accompanied by normal or increased platelet count and fibrinogen levels (84–86) is predictive of severe disease in COVID-19 infection (62). This pattern, along with increased clot tensile strength without increased fibrinolysis on thromboelastomeric assays in COVID-19 patients (66), suggests that D-dimer elevation likely reflects the patient's inflammatory response rather than consumptive coagulopathy. This is supported by differences in thrombi types between COVID-19 patients and other critically ill patients, and the reduced effectiveness of anticoagulation therapy (either prophylactic or therapeutic) in COVID-19–related thrombosis (87, 88).

It remains unclear why COVID-19–related coagulopathy generates a thrombotic phenotype rather than a hemorrhagic phenotype. Recent data suggest that the thrombotic phenotype likely results from specific interactions between the host inflammatory response (e.g., complement) and activation of coagulation, platelets, and endothelial cells. SARS-CoV-2 infection promotes cytokine release through DAMPs, viral nucleic acid recognition, and RAS axis disruption. Reduced ACE2 levels may increase bradykinin levels (89), which may promote coagulopathy in at least two distinct ways: 1) enhancing complement activation (27, 87) and 2) promoting neutrophil activation and NET formation. Inflammation generally activates the complement system, and subsequent depletion of plasma complement is associated with increasing disease severity and a prothrombotic state (**Fig. 3**) (90–94). Separately, bradykinin-induced neutrophil recruitment initiates a positive feedback pathway of thrombin-mediated platelet activation promoting NET formation, which further enhances inflammation and platelet activation and leads to NET colocalization with microthrombi (26, 95). Inhibition of NET formation reduces ARDS progression and thrombus formation in non–COVID-19 ARDS (96), whereas increased NET formation is associated with ARDS and COVID-19 severity, supporting a role for NETs in increased thrombi risk in COVID-19 patients (88, 97–99).

SARS-CoV2 infection also elicits endotheliopathy, which likely has a role in thrombotic events (100). Several markers of platelet and endothelial activation/injury, including soluble P-selectin, soluble thrombomodulin, and von Willebrand factor (vWf), were higher in critically ill COVID-19 patients than in noncritically ill patients and healthy controls, suggesting that platelets and endothelial cells are involved in the infection pathophysiology. The frequency of thrombotic events is approximately nine-fold higher in COVID-19 patients with dyslipidemia than in those without (101, 102). A recent report linked dyslipidemia, hypertension, and endotheliopathy and demonstrated that lipids (enhanced by low-density lipoproteins), rapid blood flow, and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) modulate the formation of secreted vWf into long fibrils tethered to endothelial cells (103, 104). These studies suggest causative links between platelets, endothelial cells, and lipids in the venous and thrombotic events observed in COVID-19 patients and may explain the need for therapeutic anticoagulation.

Another relevant hematologic perturbation is an association between blood type and COVID-19 frequency and severity. A study of 2,173 COVID-19 patients reported that more COVID-19 cases had type A blood (38% vs 32% community control) than type O blood (26% vs 35% community control) (105). Although there may be a protective effect of anti-A antibodies, the type A antigen itself is likely to be involved in stabilizing vWf levels in blood, as blood group type A-vWf is more resistant to proteolysis than blood group type O-vWF (106, 107). African Americans with type A blood have higher baseline vWf levels than Caucasians (108), which could increase the risk of thrombotic disorders. A/B blood types are similar across ethnic groups and do not fully account for ethnic disparities in COVID-19 disease. Ethnic groups most affected by COVID-19 are more likely to inherit null traits for three lesser-known blood antigens. 1) The Duffy antigen receptor for chemokines (DARC) is a glycoprotein receptor for *Plasmodium falciparum* and is expressed on erythrocytes (109). 2) The DARC-null phenotype confers resistance to malaria and is carried by 68% of African Americans and 5% of Hispanics (110) compared with 0% of Caucasians and 0% Chinese (109). DARC serves as a decoy receptor and is a "sink" for several chemokines; loss of the DARC receptor in COVID-19 could enable the cytokine storm and ARDS (111). 3) Lewis-null/Secretor-null individuals lack blood group system (AB) glycosylated antigens along epithelial linings in airways, gut, and kidney (109). Lewis antigens

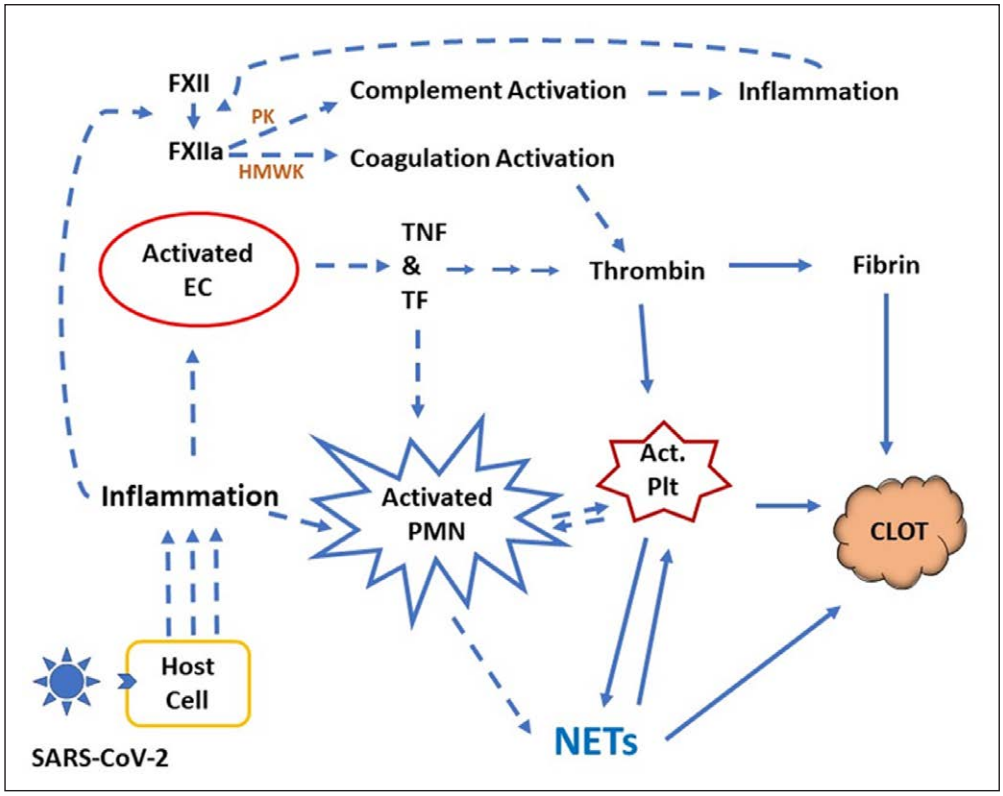

Figure 3. Proposed mechanism for severe acute respiratory syndrome–associated coronavirus 2 (SARS-CoV-2)–induced coagulopathy and thrombotic microangiopathy. The SARS-CoV-2 virus directly injures cells/tissues and induces local and systemic inflammatory cascades, which induce the release of cytokines and damage/danger-associated molecular patterns (DAMPs) and activate three interconnected procoagulation pathways. Coagulation factor XII is activated during the contact phase of coagulation, thereby activating complement, thrombin, and a positive feedback loop for inflammation. Inflammation damages endothelial cells, further activating thrombin and polymorphonucleated cells (PMNs) via tumor necrosis factors (TNFs) and tissue factor (TF). Cytokines and DAMPs also directly activate PMNs, which initiates the development of NETosis and activates platelets. Activated platelets, neutrophil extracellular traps (NETs), and fibrin combine to form clinically significant clots in patients with coronavirus disease 2019 infections. CLOT = clot formation, EC = endothelial cell, FXII = factor XII, FXIIa = activated factor XII, HMWK = high molecular weight kininogen, NETosis = neutrophil extracellular traps, PK = prekallikrein, Plt = platelet.

are fucosyl groups that are up-regulated in bronchial epithelium after inflammation (112) and have discrete roles in dendritic cell activation (113) and neutrophil transepithelial migration (110). Secretor status promotes some viral infections and inhibits others (109), although the effect on SARS-CoV-2 infection remains unclear. Lewis-null/Secretor-null is a rare phenotype that is three- to four-fold more frequent in African Americans and Brazilians than in Whites and Chinese (109). Thus, in addition to socioeconomic factors (e.g., healthcare access, nutrition, crowded housing, employment conditions) (114), DARC and Lewis-null/Secretor-null alleles may contribute biological factors that drive ethnic disparities in severe COVID-19.

Future research on complement, coagulation, platelet activation, NETs, thrombotic microangiopathy (TMA), vWf, ADAMTS13, RAS axis, bradykinin, and blood type in COVID-19 disease will enhance our understanding of how SARS-CoV-2 viral infection affects numerous tissues and organs through its effect on the vasculature. In addition, given recent reports about the potential protective effects of aspirin therapy, the effects of antiplatelet agents (including aspirin, colchicine or P2Y12 inhibitors) in preventing thrombotic events observed in COVID-19 patients should be further investigated (115).

Cardiac Manifestations

Early population studies on COVID-19 detected a disproportionate number of deaths in patients with preexisting cardiovascular disease (36, 116). Patients with hypertension likely have RAS axis dysregulation, which may increase morbidity and mortality. There is evidence that elevated troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels are mortality risk factors in patients with and without preexisting cardiovascular disease (117). COVID-19 patients without preexisting cardiovascular disease can develop cardiovascular manifestations such as arrhythmias, myocarditis, and heart failure (117), and sudden cardiac failure can occur 1–3 weeks after initial infection, even while patients' MOF is improving (116). These combined results indicate that SARS-CoV-2 infection impacts the cardiovascular system during both acute and convalescent phases.

A simple hypothesis of SARS-CoV-2–induced cardiac dysfunction is through direct infection of the myocardium and/or coronary endothelium. ACE2 and TMPRSS2 are expressed in both tissues; although the myocardium could theoretically act as a host for SARS-CoV-2, there are no documented reports myocardial infection (118, 119). Viral RNA has been detected in the bloodstream, but infectious viral particles have not been isolated from blood, which may limit the potential for viral infection of myocardium or cardiac endothelium (69, 120–124). There are reports of viral detection in myocardial tissue samples with possible myocarditis, although this could be explained by migration of infected macrophages from the lung into the myocardium (125–127).

An alternative hypothesis of SARS-CoV-2–induced cardiac dysfunction is that the proposed hypercoagulable state predisposes patients to develop coronary artery thromboses and subsequent sudden heart failure, with elevated troponin and NT-proBNP levels reflecting direct myocardial injury. Only two studies reported ST-segment elevation in COVID-19 patients (128, 129), thus limiting current data in support of this hypothesis. However, myocardial infarctions are unlikely to be a common occurrence in spite of the high prevalence of hypercoagulability, as myocardial biomarkers are not detected at high frequency.

The prominent hyperinflammatory response may be responsible for the cardiac manifestations of COVID-19 disease. Proinflammatory cytokines decrease left ventricular function and lead to left ventricle dilation (130). Immune complexes and autoantibodies generated during hyperinflammatory states may precipitate acute cardiomyopathy (131). Hyperinflammatory states associated with recruitment of macrophage and T cells to the heart may cause substantial cardiac injury and the development of fulminant myocarditis (121, 125, 131, 132). Research investigating the underlying mechanisms of hyperinflammation in COVID-19 should focus on its impact on cardiac function and the development of myocarditis.

Gastrointestinal and Hepatic Involvement

Various symptoms and laboratory abnormalities indicative of gastrointestinal and hepatobiliary involvement have been reported in COVID-19 patients. Reports of nausea, vomiting, diarrhea (up to 10%), and abdominal discomfort are common, and SARS-CoV-2 RNA is detectable in the stool (133–135). Up to 31% of patients with COVID-19-associated ARDS were found to have elevated lipase levels without pancreatitis, suggesting possible impairment in pancreatic microcirculation (136). Liver injury is more common in those with gastrointestinal symptoms and in the critically ill (133, 137). Gastrointestinal symptoms correlate with more severe COVID-19 illness (133). Possible routes for COVID-19 involvement in gastrointestinal include trachea-esophagus-ileum-colon and disruption of the gut-liver and gut-pulmonary axes (133, 138). ACE2 and TMPRSS are expressed by absorptive enterocytes in the small and large bowel and likely have mechanistic roles in gastrointestinal involvement (133, 138). Once infected, enterocyte malabsorption may lead to increased gastrointestinal wall permeability and enteric symptoms such as diarrhea (139).

In normal liver tissue, ACE2 expression in bile duct epithelial cells (cholangiocytes) is higher than that in hepatocytes (16, 133, 140). Hepatocyte ACE2 expression increases in chronic liver diseases and during hypoxia (125, 133). Isolated severe liver injury is rare and generally accompanies shock, respiratory failure, cardiac insufficiency, and/or renal insufficiency (137). Hepatocyte injury biomarkers (AST, ALT, LDH) may be increased, whereas liver synthetic function may be impaired as manifested by decreased albumin and increased PT (137).

Pathologic examination of COVID-19 patients may reveal moderate microvascular steatosis, mild sinusoidal dilatation, minimal lymphocytic infiltration, mild lobular and portal activity, multifocal hepatic necrosis, and rarely canalicular cholestasis (126, 141–143). Intranuclear or intracytoplasmic viral inclusions have not been reported (126, 141). These results suggest that COVID-19–mediated hepatic injury has multifactorial etiology that may differ in individual patients (144). Potential mechanisms include: 1) direct viral effects; 2) treatment-associated toxicity; 3) underlying disease predisposing to secondary injury; and 4) inflammatory response and other effects of severe illness (e.g., parenteral nutrition, hypotension, hypoxia, mechanical ventilation with high positive end-expiratory pressure [18–20 cm H_2O]) (133, 144, 145). Identifying the subset of mechanisms that are operating for a given patient may enable personalization of therapies to optimize outcomes.

Renal Manifestations

The frequency of AKI in severe COVID-19 disease appears variable. Cohort studies using consensus definitions report AKI rates of 0–39%, and 5–19% of critically ill patients require renal replacement therapy (146–151). The underlying pathophysiology of COVID-19–associated AKI may share similarities with other forms of multifactorial AKI in the setting of critical illness (152, 153). Current evidence from postmortem samples and limited biopsy series suggests a myriad of renal injuries (154–156), predominantly loss of proximal tubular brush border and acute tubular injury or the presence of inflammatory cells/infiltrates, viral particles in the parenchyma, and fibrin thrombi (in approximately 10% of samples). These results suggest a TMA/endothelial injury process (157) but do not identify a specific cause of AKI. In many cases, injury may be from hypotension-induced ischemia and hemodynamic sequelae of positive pressure ventilation that reduces renal perfusion, reduces cardiac output, and increases renal venous pressures (158–162). Tubular injury may stem from nephrotoxin exposure, which traditionally accounts for up to 25% of all hospital-based AKI. Given the COVID-19 polypharmacy in select scenarios, nephrotoxins undoubtedly complicate this issue (163).

There are conflicting reports regarding the virus in urine, although SARS-CoV-2 RNA/particles have been identified in urine (47, 154, 164, 165). In early AKI with a slightly injured tubule, the virus Spike protein may bind the ACE2 receptor and enter renal tubular epithelial cells, where it can then replicate (55). Epithelial cell entry may explain some of the pathologically observed renal injury patterns (16, 148). Genetic variations in the ACE2 receptor may contribute to the disproportionate impact of COVID-19 in certain subpopulations. Several reports suggested associations between COVID-19–mediated AKI and collapsing glomerulopathy (157, 166–168). Collapsing glomerulopathy is characterized by tuft collapse with podocyte hypertrophy and intracytoplasmic protein resorption droplets. It has been associated with high-risk *APOL1* alleles in individuals of African descent, thus providing a biologic factor that may explain ethnic disparities in COVID-19 outcomes (168, 169). Collapsing glomerulopathy has been associated with other viral infections including HIV, Zika, and Dengue. The exact mechanisms and links of collapsing glomerulopathy to the *APOL1* gene remain under intense investigation. Future investigations into COVID-19–associated AKI should examine the specific impact of ACE2 and apolipoprotein L1 on the development of severe AKI.

Neurologic Manifestations

CNS involvement of human coronavirus infections has been extensively documented (170–172). CNS manifestations of SARS-CoV-2 infection have been reported in 14–36% of hospitalized patients, including altered mental status, temporary anosmia, seizures, encephalitis, and ischemic stroke (173–175). These CNS pathologies may be related to direct viral neurotropism, CNS migration of infected peripheral immune cells, or secondary to systemic infection (176, 177). Autopsy of COVID-19 patients revealed virus in brain tissue, primarily in neurons (64, 178). Neurons and the capillary endothelium express ACE2 receptors, providing two possible routes for brain invasion (59). Intranasal inoculation of SARS-CoV-2 in transgenic mice expressing human ACE2 resulted in rapid and widespread infection of primarily neurons and astrocytes in the brain (179). Anosmia is reported in patients infected with SARS-CoV-1 and SARS-CoV-2, thus supporting this route of entry, but olfactory tract abnormalities have not been observed in MRI (174, 180, 181). Coronaviruses infect macrophages and glial cells, but there is currently little evidence that peripheral immune cell infection leads to CNS access (182, 183). COVID-19–induced MOF may result in brain tissue hypoxia/ischemia and blood-brain barrier disruption, thereby potentially allowing SARS-CoV-2 access to the CNS via the blood stream, although further data are needed to support this hypothesis. Further work also is needed to optimize testing modalities and procedures as the duration of SARS-CoV-2 in cerebrospinal fluid after symptom onset is unknown.

Up to 31% of critically ill COVID-19 patients have thromboembolic complications (184, 185). The frequency of ischemic stroke in COVID-19 patients is currently unknown, although one retrospective study reported an frequency as high as 2.8% in hospitalized COVID-19 patients with severe disease (173). A case series of six patients with COVID-19 and ischemic stroke reported that patients had moderate to critical disease and an 8–24-day interval from COVID-19 symptom onset to stroke symptoms (186). Possible indications and patient selection criteria for systemic anticoagulation therapy to reduce stroke risk in

COVID-19 patients remain to be determined, along with any beneficial changes in the approach to systemic thrombolysis or endovascular therapy. Several studies reported that mechanically ventilated COVID-19 patients require unusually high levels of sedation with a markedly higher frequency of delirium (187–198). Increased delirium rates may be due to direct virus or inflammation-mediated effects, greater sedation requirements, or other yet unidentified factors.

Influenza pandemics before the 20th century were historically followed by increased reports of neuropsychiatric symptoms including psychosis, depression, anxiety, insomnia, and mania (199, 200). Recent viral pandemics and epidemics (influenza H1N1, SARS-CoV-1, and Middle East respiratory syndrome–associated coronavirus) have been associated with neuropsychiatric sequelae including narcolepsy, seizures, and demyelinating processes (201–203). It will be crucial to institute longitudinal studies to assess COVID-19 association with long-term neuropsychiatric sequelae to determine the disease burden and identify possible therapeutic interventions, particularly given the emerging recognition of post-ICU syndrome and long-haul disease among COVID-19 survivors.

Endocrine Manifestations

Obesity and type 2 diabetes mellitus (DM) are important risk factors associated with COVID-19 severity, morbidity, and mortality (204–207). Adiposity promotes chronic low-grade inflammation and immune dysregulation, leading to a more robust inflammatory response, profound adaptive immune suppression, and reduced viral clearance during infection with SARS-CoV-2. Patients with obesity or type 2 DM may have a chronic endotheliopathy and prothrombotic state associated with dyslipidemia and high levels of circulating vWf, as noted above (208); when combined with COVID-19–mediated coagulation perturbations, the risk of cardiovascular and CNS thrombotic events increases (209).

Uncontrolled hyperglycemia is associated with poor outcomes in COVID-19 (209, 210). This may result from hyperglycemia-associated glycosylation of ACE2 and viral Spike proteins that facilitate entry into target host cells, thus increasing viral loads and suppressing viral clearance. Studies on SARS-CoV-1 suggest that the virus may directly infiltrate ACE2-expressing pancreatic islet cells, thereby reducing insulin production and causing hyperglycemia (210). It is currently unknown whether islet cell damage is transient or permanent in COVID-19 survivors. Growing evidence suggests that SARS-CoV2 infection may trigger new onset diabetes, either via direct pancreatic invasion or due to the immune response to the virus (211–213).

Adrenal insufficiency is an uncommon early finding in COVID-19, and higher serum cortisol levels have been associated with increased mortality (214). Persistent fatigue and malaise following SARS-CoV-2 infection may be related to postinfection adrenal insufficiency. Direct viral CNS infiltration may enable infection of pituitary gland cells, leading to transient suppression of the hypothalamic-pituitary-adrenal axis. Alternatively, adrenal insufficiency may be caused by immune-mediated hypophysitis (215). Bilateral adrenal hemorrhage secondary to renal vein and adrenal plexus thrombosis was reported in a COVID-19 patient who had positive antiphospholipid antibodies (216). Systemic corticosteroid therapy has been quite successful in treating patients with severe COVID-19, which may reflect both the anti-inflammatory effects of steroids but also partial treatment of adrenal insufficiency.

Patients often develop low levels of thyroid-stimulating hormone and triiodothyronine during the early phases of critical COVID-19 illness, which typically normalize during recovery (215). Although this may represent euthyroid sick syndrome, there is evidence that SARS-CoV-1 virus can directly invade and affect thyroid tissue (205, 217, 218). This could explain late-onset subacute thyroiditis observed in COVID-19 patients, possibly secondary to immune-mediated processes that cause thyrotoxicosis to hypothyroidism. However, these mechanisms have yet to be elucidated (217, 218).

Dermatologic Manifestations

Cutaneous manifestations have been reported in 5–20% of symptomatic COVID-19 patients (219–221). Erythematous macules or papules over the trunk and extremities, comparable with those observed in other viral exanthems, occur early in the infection and are the most common cutaneous manifestation. The rash may be pruritic, lasts for a median of 10 days, and generally is associated with a more favorable clinical course (222). The exanthem results from perivascular dermatitis and vasculitis with neutrophilic and lymphocytic

infiltration as a response to the virus (223). Urticaria, with or without angioedema, comprises up to 20% of the rashes observed in COVID-19, particularly in those with more severe disease (224, 225). Vesicular eruptions (similar to those of chickenpox) are associated with moderate disease severity, exhibit acantholysis with dyskeratosis, and may be due to a cytopathic effect of viral invasion (226). Purpura or petechiae are uncommon and have been reported in patients with thrombocytopenia and coagulopathy (221). Livedo racemosa resembles livedo reticularis but is more diffuse and likely secondary to small or medium vessel vasculopathy with occlusive microthrombi or immune complexes, complement deposition, and reperfusion injury. The term "COVID toes" is used to describe a chilblain-like lesion in COVID-19 patients. Unlike their idiopathic counterpart, COVID-related chilblains occur in the absence of exposure to cold. These acral lesions are often the only presenting symptom of COVID-19 infection and are likely caused by immune complex deposition or microthrombi (227–231). Two recent studies present comprehensive depictions of the most common cutaneous manifestations of COVID-19 (230, 231).

FUTURE AREAS FOR RESEARCH AND CONCLUSIONS

The COVID-19 pandemic will persist well in to 2021 and beyond. Further investigations on the mechanisms underlying the frequency, prevention, and treatment of COVID-19–related organ failure are urgently needed. The current hypotheses of hyper- and hypoinflammation driving the clinical disease course do not facilitate consensus views for therapeutic approaches. Future research should use multiomic methods to refine descriptive findings and identify relevant signaling pathways. These studies should include patients with different age, sex, and race, as potential therapies may not be efficacious across heterogeneous populations. Although a vaccine holds the most promise, it is likely that adjunctive immunorestoration or antiviral therapies are needed to improve outcomes. These approaches should be based on specific immune signaling pathways rather than observed changes in nonspecific biomarkers. Given that there are several distinct strategies for vaccine development (messenger RNA, viral vector, adjuvanted protein, and inactivated virus), the impact of these different strategies on the immune response, as well as the impact on organ dysfunction among immunized individuals who become infected, remains an unanswered question. For example, given the now known early induction of cellular immune exhaustion by SARS-CoV-2 infection that limits T and B cell responses, vaccine development must include induction of both of these responses including antiviral CD8+ T cells to provide robust protection from severe disease (232). However, it is unclear how patients that have already acquired the disease when the optimal time for vaccination should occur to maximize protection? In addition, the recent emergence of SARS-CoV-2 variants raises additional translational research questions: what is the nature of the immune response triggered by such variants, and is their increased transmissibility a reflection of a distinct immune response? Do these variants result in differential organ dysfunction among infected patients? The critical care research community is well poised to merge basic science with translational, clinical, and big data approaches to tackle this devastating illness.

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