Insights into COVID-19-associated critical illness: a narrative review

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Background and Objective: Since the outbreak of the 2019 novel coronavirus disease (COVID-19), acute respiratory distress syndrome (ARDS) and sepsis resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have surged in intensive care units around the world. The heterogeneity of ARDS and sepsis has long been observed, and multiple subphenotypes and endotypes correlated with different outcomes and treatment response have been identified in the search for treatable traits. Despite their similarity to typical ARDS and sepsis, COVID-19-associated ARDS and sepsis harbor distinct features, raising the question as to whether they could be considered as subphenotypes or endotypes of the historical syndromes and, accordingly, benefit from specific therapeutic strategies. This review aimed to summarize and discuss the current knowledge of COVID-19-associated critical illness and the intrinsic subphenotypes or endotypes.

Methods: Literature on the pathogenesis of COVID-19 and the subphenotyping of COVID-19-associated critical illness was derived from the PubMed database and reviewed.

Key Content and Findings: Accumulating evidence, varying from clinical observation to basic research, has contributed to revealing the fundamental pathophysiological features of severe COVID-19 and has advanced our knowledge of the disease. COVID-19-associated ARDS and sepsis exhibit some distinctive features compared to the classic syndromes, including remarkable vascular abnormality and coagulopathy, and distinct respiratory mechanics and immune response. Some conventional subphenotypes derived from classic ARDS and sepsis have been validated in COVID-19, while novel subphenotypes and endotypes have also been identified in patients with this disease, who experience variable clinical outcomes and treatment responses.

Conclusions: Subphenotyping of COVID-19-associated ARDS and sepsis can provide new insights into the development and management of these illnesses.

Keywords: 2019 novel coronavirus disease (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); acute respiratory distress syndrome (ARDS); sepsis; subphenotype

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Introduction

The 2019 novel coronavirus disease (COVID-19) pandemic has caused massive mortality worldwide since its outbreak (1). Although COVID-19 has identical causal injury to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2) infection, it nonetheless exhibits a broad spectrum of clinical manifestations—ranging from mild symptoms of upper respiratory tract infection to severe hypoxic respiratory failure with multiple organ dysfunction, which usually results in the diagnosis of acute respiratory distress syndrome (ARDS) and sepsis (3-5).

Both ARDS and sepsis have long been considered to be highly heterogeneous, and related studies have focused on subphenotyping the syndromes to better understand them and to identify beneficial treatments. For example, two phenotypes of ARDS, "hyperinflammatory" and "hypoinflammatory" (6), have consistently been identified through studies and have shown different responses to treatments and clinical outcomes (7-9). Similarly, previous studies have also revealed different subphenotypes or endotypes of sepsis (10-14).

Although ARDS and sepsis are diagnosed in most cases of severe COVID-19, some features of COVID-19-associated ARDS and sepsis are distinct from those of ARDS and sepsis with non-COVID etiologies. For example, coagulopathy and vascular dysfunction are often observed in the pathogenesis of COVID-19-associated ARDS but are rarely involved in non-COVID ARDS (5,15,16). In addition, multi-organ dysfunction in severe COVID-19 is acknowledged to be a result of a dysregulated host immune response against SARS-CoV-2 infection, which is characterized by an excessive inflammatory response mediated not only by tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 production and signaling, but also by dysregulated type I interferon (IFN) response (17-20). In this regard, COVID-19-associated ARDS and sepsis could possibly represent distinct subphenotypes or endotypes of historical ARDS and sepsis.

Since the outbreak of the COVID-19 pandemic, numerous studies have investigated COVID-19-associated critical illness from the molecular to the clinical aspects, and given the intrinsic heterogeneity of COVID-19, emerging studies have moved on to investigating subphenotyping of critically ill patients with COVID-19. In this review, we aimed to summarize the current knowledge of COVID-19-associated critical illness, discuss its inherent distinctions and connections to historical ARDS and sepsis, and identify the intrinsic subphenotypes in order to shed light on the discovery of treatable traits of COVID-19 and the development of personalized treatment in the future. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2541/rc).

Methods

A literature search was performed in the PubMed database on March 30, 2022. The following terms were used in various combinations to search for relevant literature: "COVID-19", "ARDS", "sepsis", "critical illness", "subphenotype", and "endotype". Literature was considered regardless of year of publication. The search strategy is summarized in *Table 1*.

Pathobiology of COVID-19

Acute respiratory failure is the predominant manifestation in a substantial proportion of severe COVID-19 cases. According to a pathological investigation of lung tissue samples from a series of patients with COVID-19, diffuse alveolar damage was identified as the principal pattern of lung lesion; specifically, capillary congestion, necrosis of pneumocytes, hyaline membrane formation, interstitial edema, pneumocyte atypical hyperplasia, and inflammatory infiltrate (macrophage and lymphocyte) were observed, which were different to the lung lesions induced by SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) infection (5). Notably, the presence of alveolar capillary thrombosis with microangiopathy has frequently been reported in patients with COVID-19, which indicates that coagulopathy and microangiopathy may also play an important role in the pathogenesis of the disease (5,15). Moreover, under electron microscopy, Carsana *et al.* observed type 1 and type 2 pneumocytes to be the main target cells of SARS-CoV-2 in the lung, while very few viral particles were found in alveolar macrophages (5).

Aside from the lung, COVID-19 involves injury to many other organ systems, which gives rise to various extrapulmonary manifestations (21-23). Histopathological investigation has shown cardiac injury (myocarditis, vasculitis, inflammatory infiltrate, pericarditis, vascular fibrosis, etc.), hepatic injury (inflammatory infiltrate, congestion, steatosis, etc.), renal injury (inflammatory infiltrate, glomerulosclerosis, interstitial fibrosis, etc.), and splenic and bone marrow abnormalities, among other

Table 1 Summary of the literature search strategy

Items	Specification
Date of search	March 30, 2022
Databases and other sources searched	PubMed database
Search terms used	"COVID-19", "ARDS", "sepsis", "critical illness", "subphenotype", and "endotype"
Timeframe	From inception to July 31, 2022
Inclusion and exclusion criteria	Inclusion criteria: English language
Selection process	The authors jointly screened the titles and abstracts to assess eligibility

manifestations (24).

Although the pathophysiology of COVID-19 is not fully understood at present, the key mechanisms are considered to include direct viral toxicity of the target cells, endothelial cell damage, coagulopathy and microangiopathy, dysregulation of immune response, and systemic release of inflammatory cytokines (1,23). The entry of SARS-CoV-2 into target cells mainly depends on two host proteins: angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). The spike (S) protein binds to the entry receptor ACE2, which facilitates viral attachment to the surface of target cells; then, the cellular protease TMPRSS2 cleaves the S protein into S1 and S2 subunits to allow fusion of the viral and cellular membranes (25). Given the high expression of ACE2 in multiple epithelial cell types of the airway, particularly alveolar pneumocytes, SARS-CoV-2 has a tropism for the respiratory tract and commonly causes direct tissue damage in the lung (23). Studies have also confirmed the expression of ACE2 and TMPRSS2 in esophageal keratinocytes, gastrointestinal epithelial cells, colonocytes, renal proximal tubules and podocytes, cholangiocytes, and pancreatic β-cells, among other cells, which is correlated with the extrapulmonary manifestations of COVID-19 (23,26-29).

Malfunction of the renin-angiotensin-aldosterone system (RAAS) secondary to SARS-CoV-2 infection also contributes to the pathophysiology of COVID-19. ACE2 is a membrane-bound aminopeptidase that serves as a potent restriction factor of the RAAS pathway. It cleaves angiotensin I into inactive angiotensin 1–9 and angiotensin II into angiotensin 1–7, which has vasodilator, antiproliferative, and antifibrotic properties (30-32). When ACE2 binds to the SARS-CoV-2 S protein, it becomes reduced in number, resulting in decreased cleavage of angiotensin I and II, which in turn leads to increased vasoconstriction, vascular permeability, inflammation, and tissue injury (23).

Endothelial cell damage and subsequent thromboinflammation have been reported to be another pathophysiological mechanism of COVID-19. With ACE2 expression, pulmonary and renal endothelial cells have been shown to be infected by SARS-CoV-2 in some patients with COVID-19, which leads to endothelial injury and endothelialitis characterized by von Willebrand factor production and neutrophil and macrophage activation (15,33,34). Consequently, coagulation and complement pathways are activated, while fibrinolysis is inhibited, leading to microthrombus formation and microvascular dysfunction (35,36). The activation of neutrophils and macrophages results in the release of proinflammatory cytokines, which further damages the endothelium and initiates the local and systemic immune response (37,38). Moreover, hypoxia-mediated hyperviscosity and upregulation of the hypoxia-inducible factor 1 (HIF-1) signaling pathway also contribute to coagulopathy (39).

Dysregulation of immune response in patients with COVID-19 is characterized by the overactivation of innate immunity, T-cell lymphodepletion, inhibition of IFN signaling, and robust production of proinflammatory cytokines, particularly IL-6 and TNF-α (40). In patients with moderate to severe COVID-19, immune profiling revealed an overall increase in innate cell lineages, with a concomitant reduction in T-cell number (40). Studies have revealed that different IFN signaling phenotypes are correlated with divergent disease trajectories in patients with COVID-19. For example, SARS-CoV-2 was reported to induce limited IFN-I and -III response *in vitro*, *ex vivo*, and *in vivo* (18-20,40,41), while *in vivo*

study showed early IFN-I signaling to be associated with reduced virus titer, regulated inflammation, and mild disease; however, delayed IFN-I signaling promoted pathogenic monocyte-macrophage accumulation, leading to lung immunopathology, vascular leakage, and impaired T-cell response (41). Immune profiling studies have also reported that patients with severe COVID-19 tend to have a low IFN-I and -III and high chemokine signature (18,20,40). However, one immune profiling study reported a coordinated immune response to SARS-CoV-2, which found an increased IFN-α response for all major immune cell types (42). Using single-cell transcriptomics, proteomics, and functional experiments, Krämer *et al.* longitudinally analyzed the detailed characteristics of natural killer cells in severe COVID-19 and found early and prolonged IFN-α-induced natural killer cell response to be associated with disease severity (43).

Intriguingly, multiomics studies have provided valuable insights into the full spectrum of immune responses in patients with COVID-19. Using longitudinal plasma proteomic analysis of severe COVID-19, Filbin *et al.* identified the death of infected lung epithelial cells as a key feature of severe disease, which was possibly attributable to early monocyte activation driving T-cell recruitment, activation, and exhaustion (44). Su *et al.*'s multiomics analysis of serial blood from 139 patients with COVID-19 revealed novel immune cell subsets associated with disease severity, including a proliferative exhausted $CD8^+$ T cell subpopulation [characterized by intermediate levels of effector markers and upregulated exhaustion markers including Lymphocyte Activating 3 (LAG3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), and CD279), and two distinct $CD4^+$ T cell subpopulations (which were characterized by cytotoxic and exhaustion markers, respectively] (42). Furthermore, another single-cell multiomics analysis of peripheral blood mononuclear cells in patients with COVID-19 revealed that severe disease was accompanied by clonally expanded $CD8^+$ T cells and an increased ratio of $CD8^+$ effector T cells to effector memory T cells (45). Additionally, elevated levels of $CD8^+$ T cells expressing inhibitory killer cell immunoglobulin-like receptors in patients with COVID-19 have also been reported to be correlated with disease severity and vasculitis (46). Recently, a landmark study conducted by the COVID-19 Multi-omic Blood Atlas (COMBAT) consortium identified the hallmarks of COVID-19 severity. In the study, plasma proteomic analysis of patients with COVID-19 identified two clusters of patients associated with disease severity, with multiple proteins (including IL-6, IL-8, CCL2, CLEC11A, CCL20, CXCL10, and CCL19) being the main discriminatory features distinguishing the clusters. This multiomics study of blood samples revealed both similarities and specific features of COVID-19 compared to historical sepsis (47).

Metabolomics analysis has also demonstrated increased COVID-19 severity to be associated with certain metabolite alterations, which reflects that elements of the COVID-19 immune response are produced through altered metabolic processes. Through proteomic and metabolic analysis, Shen *et al.* reported the involvement of dysregulated metabolites in lipid metabolism and significant activation of the kynurenine pathway in sera from severe COVID-19 cases, which probably resulted from dysregulated macrophage function (48). Another multiomics study reported that elevated inflammatory signaling was accompanied by the loss of specific classes of metabolites and metabolic processes, especially the massive suppression of amino acid and lipid catabolism (42). In a more recent study involving single-cell resolution, Lee *et al.* identified a metabolically hyperactive $CD8^+$ T cell subpopulation and found that increasing disease severity was correlated with a bifurcation of monocytes into two metabolically distinct subsets (an inflammatory, metabolically activated subpopulation and a potentially immunomodulatory, metabolically repressed nonclassical subpopulation) (49).

COVID-19-associated ARDS versus classic ARDS

Although it has the novel etiology of SARS-CoV-2 infection, COVID-19-associated ARDS has similar pathological changes and respiratory mechanics to ARDS of other causes, which suggests that COVID-19-associated ARDS is basically ARDS (50,51). As mentioned above, the predominant pathological change in the lung of patients with COVID-19 is not identical to that of historical ARDS, which is characterized by diffuse alveolar damage manifesting as interstitial edema, hyaline membrane formation, neutrophil infiltration, and pulmonary microvascular thrombosis in the exudative phase. However, COVID-19 ARDS still presents with distinct pathological features; for example, inflammatory infiltrates in the lungs of patients with COVID-19 mainly consist of lymphocytes rather than neutrophils, and pulmonary microvascular thrombosis is more severe in COVID-19 ARDS than in

ARDS of other etiologies (15,51,52).

Furthermore, the remarkable coagulopathy and microvascular thrombosis in patients with COVID-19 also greatly contribute to the discrepancy between COVID-19 ARDS and classic ARDS. Studies have reported that the D-dimer concentration, which is associated with increased inflammation, fibrin degradation, and vascular endothelial injury, was markedly elevated in most patients with COVID-19 (53,54). Patients whose D-dimer concentration was equal to or less than the median had normal perfusion regardless of compliance, whereas most patients with a D-dimer concentration greater than the median had bilateral, diffuse areas of hypoperfusion regardless of whether their compliance was high or low (53). In this context, the hypothesis that COVID-19 ARDS is a distinct endotype or, more specifically, a vascular endotype of ARDS has been proposed (15,16,55).

The potential mechanisms that contribute to the "vascular endotype" are probably related to the viral receptor ACE2 and the renin-angiotensin system, the complement system, and inflammation. Theoretically, ACE2 is downregulated by binding to the SARS-CoV S protein, which consequently reduces the cleavage of angiotensin I and II. Dysregulation of the renin-angiotensin system has been found to induce prolonged vasoconstriction, microvascular thrombosis, and endothelial injury (56,57). However, the loss of ACE2 induced by viral entry has only been investigated with the original SARS-CoV S protein (58), and whether the SARS-CoV-2 S protein has similar properties remains unclear (55). Moreover, as in non-COVID ARDS, dysregulation of complement activation and systemic inflammation in COVID-19 ARDS could also contribute to vascular damage. Preclinical studies have revealed that the nucleocapsid protein of several coronaviruses, including SARS-CoV-2, could directly bind to and activate MBL Associated Serine Protease 2 (MASP-2), a key protease in the lectin pathway of the complement system (59,60). Complement-mediated damage to pulmonary vascular endothelial cells has also been reported as a prominent feature of COVID-19 ARDS (55,61).

With regard to respiratory mechanics, a primary characteristic of COVID-19 ARDS is dissociation between the relatively well-preserved lung mechanics and the severity of hypoxemia. Gattinoni *et al.* reported that patients with COVID-19 ARDS could exhibit entirely different lung morphology and respiratory mechanics even with a similar extent of hypoxemia (62); furthermore, according to their observation of a small cohort of patients with COVID-19, a large discrepancy between respiratory compliance (50.26±14.3 mL/cmH_2O) and shunt fraction (0.50±0.11) was observed, which is not typical in classic ARDS (63). A multicenter prospective observational study further reported that the median static compliance of the respiratory system was 28% higher in patients with COVID-19 (n=297; 41 mL/cmH_2O; IQR, 33–52 mL/cmH_2O) than in those with classic ARDS (n=960; 32 mL/cmH_2O, IQR, 25–43 mL/cmH_2O; P<0.0001) (53). In general, a relatively high respiratory compliance indicates a well-preserved lung gas volume, which is in sharp contrast to the severe hypoxemia in severe COVID-19 ARDS. A possible explanation for this discrepancy is lung perfusion dysregulation and hypoxic vasoconstriction. Gattinoni *et al.* reported that marked hyperperfusion of the poorly aerated and nonaerated lung tissue could be observed in patients with COVID-19, with a shunt fraction to gasless tissue fraction ratio of 3.0±2.1, as measured on computed tomography scans (63). Another observational study reported that the estimated physiologic dead-space ratio of a cohort of patients with COVID-19 who underwent intubation and mechanical ventilation was 0.45 (IQR, 0.38–0.58) (64).

Based on the current knowledge of the molecular mechanisms and pathophysiology of COVID-19 ARDS, the conventional therapeutic strategies for classic ARDS have been reevaluated, and some adjustments have been proposed. Although early reports suggested that phenotypic heterogeneity exists in patients with COVID-19-associated ARDS, large observational studies have indicated that the respiratory system mechanics of patients with COVID-19 ARDS and those with non-COVID ARDS are broadly similar (50,64-68). In this regard, therapeutic strategies for patients with COVID-19 ARDS, including respiratory support and pharmacotherapy, are recommended based on the current evidence-based management of classic ARDS with consideration given to some distinctive phenotypes of COVID-19 ARDS.

Lung-protective ventilation with limited tidal volume or pressure remains the fundamental respiratory support strategy recommended for COVID-19 ARDS, and has been shown to be effective in a heterogeneous ARDS population with a wide range of physiological parameters (50,69). Specifically, the current paradigm of ventilatory support in ARDS includes limiting the tidal volume to 6 mL/kg predicted body weight, the plateau pressure to <30 cmH_2O, and the driving pressure to <15 cmH_2O (70). Moreover,

prolonged prone positioning (>16 h/day) is endorsed in early moderate to severe ARDS [with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) <150 mmHg], while venovenous extracorporeal membrane oxygenation is recommended after prone positioning with PaO_2/FiO_2 <80 mmHg or where safe ventilation is difficult (70). Furthermore, given the increasing understanding of the pathophysiology of COVID-19 ARDS, the ventilatory strategy has, to some extent, been tailored with consideration given to the heterogenous respiratory mechanics of patients. For example, patients with scattered ground-glass infiltrates in the lung and relatively high respiratory compliance are usually less responsive to positive end-expiratory pressure (PEEP); therefore, lower PEEP (<10 cmH_2O) and a more liberal tidal volume (7–9 mL/kg) should serve as better options for these patients to minimize pulmonary stress and optimize oxygenation. In contrast, patients with lower respiratory compliance and extensive infiltrates of atelectasis and edema are more PEEP responsive, which is more consistent with typical ARDS (71).

Regarding pharmacotherapy, a number of studies have evaluated the efficacy of corticosteroids in patients with respiratory failure due to COVID-19. Notably, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated that treatment with low-dose dexamethasone for 10 days could reduce mortality in hospitalized patients with COVID-19 receiving oxygen or respiratory support (72). The REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) clinical trial demonstrated that the administration of systemic corticosteroids improved 28-day all-cause mortality compared to usual care or placebo in critically ill patients with COVID-19 (73). Thus, early administration of low-dose dexamethasone is recommended for patients with COVID-19. However, the role of corticosteroids in early ARDS with other causes remains unclear, although there is some evidence to support its use from small cohorts of patients with classic ARDS (74-76).

COVID-19-associated sepsis

With the dysregulated immune response to SARS-CoV-2 infection, severe cases of COVID-19 usually progress to multi-organ dysfunction, meeting the diagnostic criteria for sepsis or septic shock according to the Sepsis-3 International Consensus (77). Considering that bacterial, fungal, and viral infection tend to induce different immune responses, the notion of "viral sepsis" has been proposed to distinguish COVID-19-associated sepsis from sepsis with other causes (78).

In clinical practice, typical clinical manifestations of sepsis or septic shock that are often observed in critically ill patients with COVID-19 include hypotension with cold extremities and weak peripheral pulses, metabolic acidosis indicating microcirculation dysfunction, and impaired liver and kidney function, in addition to severe lung injury. As in historical sepsis, the dysregulated immune response secondary to SARS-CoV-2 infection is acknowledged as the predominant driving force of the multi-organ dysfunction in COVID-19 sepsis; nevertheless, the immune response induced by SARS-CoV-2 infection has distinctive features.

As the front line of SARS-CoV-2 infection, the antiviral immune response in the lung under attack plays a pivotal role in the pathogenesis of sepsis. Immune profiling has revealed macrophage infiltration to be the hallmark of COVID-19 pneumonia, whereas neutrophil infiltration is commonly seen in bacterial pneumonia. Rendeiro *et al.* performed a thorough investigation of the interactions between infected cells and the immune system at sites of infection, and reported that disease progression was associated with increased macrophage extravasation, an increased number of mesenchymal cells and fibroblasts, and increased proximity between these cell types (79). Furthermore, by examining the bronchoalveolar lavage fluid samples of patients with COVID-19, the researchers found enrichment of T cells and monocytes in the alveolar space, and bulk and single-cell transcriptomic profiling revealed that SARS-CoV-2 had also infected alveolar macrophages, leading to the release of T-cell chemoattractants. The recruited T cells produced IFN-γ, which in turn induced the release of inflammatory cytokines from the alveolar macrophages and further promoted T-cell activation (80).

Aside from the pulmonary immune response, systemic inflammation characterized by TNF-α, IL-1β, and IL-6 upregulation has been recognized as contributing to the multi-organ dysfunction in COVID-19, which represents a difference to non-COVID sepsis. Intriguingly, single-cell RNA sequencing revealed that a type I IFN response coexisted with TNF-α/IL-1β-driven inflammation in classical monocytes in patients with severe COVID-19, but this was hardly seen in patients with mild COVID-19. Based on this, a type I IFN response was considered

to play a pivotal role in exacerbating inflammation in severe COVID-19 and to possibly be a distinctive feature of COVID-19 sepsis (17). Intriguingly, Zheng *et al.* integrated over 5,000 bulk transcriptome and single-cell transcriptome profiles from patients infected with 1 of 16 viruses, including SARS-CoV-2, Ebola, chikungunya, and influenza, and identified that disease severity was associated with a conserved host response, which included increased hematopoiesis, myelopoiesis, and myeloid-derived suppressor cells. Moreover, their study further identified protective and detrimental gene modules that defined distinct trajectories associated with mild versus severe outcomes, in which the IFN response was decoupled from the protective host response in patients with severe disease (81). Given that the metabolic needs of immune responses depend on their function, metabolomics has also identified important immunological distinctions and connections between COVID-19 and non-COVID sepsis. For example, one study found that compared to non-COVID sepsis, the $S100A9^{high}$ inflammatory subpopulation of monocytes in COVID-19 sepsis showed distinctively high expression of 417 metabolic genes in mitochondrial protein synthesis-related processes, which was suggestive of increased oxidative phosphorylation. On the other hand, metabolically hyperactive, proliferative-exhausted $CD8^+$ T cells emerged in both COVID-19 and sepsis, comprising a small fraction of $CD8^+$ T cells and presenting with increased amino acid metabolism and protein synthesis (49).

Another distinctive contributing factor of COVID-19-associated sepsis is coagulopathy and vascular injury. Observational studies have reported increases in fibrin degradation products like D-dimer to be significantly associated with a poor prognosis in patients with COVID-19, and that overt disseminated intravascular coagulation appears in a great proportion of nonsurvivors of COVID-19 (82,83).

Based on our knowledge of the pathogenesis of COVID-19, several therapeutic strategies have been proposed and investigated by randomized clinical trials, particularly the RECOVERY trials (72,73,84-88); these strategies include the use of corticosteroids, immunomodulators (tocilizumab and azithromycin), and direct-acting antiviral agents (lopinavir-ritonavir). Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors (89). Azithromycin, a macrolide antibiotic, is known to exert immunomodulatory activity by decreasing proinflammatory cytokine production and inhibiting neutrophil activation (90-92). Lopinavir is an HIV-1 protease inhibitor that has been shown to have an inhibitory effect on SARS-CoV-2 in several preclinical studies (93,94). The RECOVERY trials have revealed that among these therapeutics, hydroxychloroquine, lopinavir-ritonavir, and azithromycin did not improve survival in patients hospitalized with COVID-19 (84,85,87); however, corticosteroids and tocilizumab could provide better survival and improvements in other clinical outcomes in certain groups of critically ill patients with COVID-19 (72,73,88,89). Additionally, based on randomized clinical trials, baricitinib, an oral selective Janus kinase 1/2 inhibitor with known anti-inflammatory properties, has been found to be associated with both a reduced recovery time in patients with COVID-19 receiving high-flow oxygen or noninvasive ventilation (95) and reduced mortality in hospitalized adults with COVID-19 (96). Given the current evidence, the latest World Health Organization (WHO) guideline on drugs for COVID-19 recommends treatment with corticosteroids, IL-6 receptor blockers, or baricitinib for patients with severe or critical disease (97). Furthermore, for patients with immunodeficiency-associated antibody disorders who are at high risk of prolonged/persistent COVID-19 infection with few viable treatment options, the monoclonal antibody combination of casirivimab and imdevimab (REGEN-CoV, Ronapreve) has been reported to promote rapid viral clearance and reduce mortality (98,99).

Subphenotypes and endotypes of COVID-19

With a growing body of evidence pointing to the heterogeneity of COVID-19, studies have been looking into the intrinsic subphenotypes or endotypes that are associated with different characteristics of pathophysiology, clinical outcomes, and treatment response.

Inflammatory status has long been recognized as an important indicator for subphenotyping patients with ARDS. The breakthrough study by Calfee *et al.* first derived the hypo- and hyperinflammatory subphenotypes of ARDS from the patient cohorts of the ARMA and ALVEOLI clinical trials using latent class analysis (LCA) (6), and these subphenotypes have consistently been observed in later studies and showed different responses to certain treatments (7,9). Similarly, LCA conducted in COVID-19-associated ARDS has identified the similar hypo- and

hyperinflammatory subphenotypes, and has revealed the hyperinflammatory subphenotype of COVID-19 ARDS to be associated with a worse clinical outcome but a better response to corticosteroid treatment than the hypoinflammatory subphenotype (100,101).

Concerning respiratory mechanics, COVID-19-associated ARDS can be classified into two subphenotypes: H type (characterized by high elastance, high shunt, and high lung weight) and L type (characterized by low elastance, low shunt, and low lung weight) (62,63,102). The respiratory compliance in L type is nearly normal, indicating a nearly normal amount of gas in the lungs; in this case, the hypoxemia might be due to the loss of regulation of perfusion and hypoxic vasoconstriction. Moreover, Gattinoni *et al.* reported that only ground-glass densities located subpleurally and along the lung fissures were present on computed tomography scans, which could explain the moderate increase in lung weight (62). Therefore, in patients with L-type COVID-19 ARDS, lower tidal volumes may not be necessary, and higher PEEP could possibly create dead space and adversely redirect blood flow. In contrast, H type COVID-19 ARDS is considered to have low respiratory compliance due to increased edema and atelectasis, which makes it closer to typical ARDS; therefore, lower tidal volume and higher PEEP strategies should be appropriate (71). However, these subphenotypes of COVID-19 ARDS are only conceptual models representing extreme conditions, and the characteristics of some patients with COVID-19 could lie between the two types, or transit from L to H type as the disease progresses.

Bos *et al.* identified two distinct respiratory subphenotypes of COVID-19 ARDS using longitudinal LCA, of which, subphenotype 2 is associated with fewer ventilator-free days and more venous thrombotic events. Furthermore, individual trajectories of single variables were evaluated by group-based trajectory modelling, which revealed that upward trajectories of the ventilatory ratio and mechanical power over the first 4 days of invasive mechanical ventilation overlapped with subphenotype 2. In this regard, the authors proposed that the subphenotype with increasing dead-space ventilation could be associated with worse outcomes and might benefit from anticoagulation therapy, whereas the subphenotype with increasing mechanical power was an indicator of inappropriate use of high PEEP (103).

Similarly, using longitudinal body temperature measurements, Bhavani *et al.* identified four temperature trajectory subphenotypes correlated with immune response in patients with sepsis (11,13). Recently, they also classified patients with COVID-19 into the four previously defined subphenotypes using the validated group-based trajectory model, and these subphenotypes were found to be correlated with different inflammatory and coagulation abnormalities. Specifically, hypothermics were correlated with hypercoagulable state, while hyperthermic slow resolvers were correlated with hyperinflammatory state and had the highest odds of mortality (104,105). These results suggest that patients with specific temperature subphenotypes of COVID-19 could benefit from targeted antithrombotic and anti-inflammatory strategies, but this proposition requires further investigation and validation.

In a prospective single-center observational study of COVID-19, Sweeney *et al.* confirmed the three robust sepsis endotypes (inflammopathic, adaptive, and coagulopathic) they had previously identified from multiple data sets of patients with bacterial sepsis through unsupervised analysis of transcriptomics (106). In patients with COVID-19, the coagulopathic group, which had the highest D-dimer concentrations, showed the highest mortality rate (42%) among the groups (107). Moreover, Grasselli *et al.* stratified patients with COVID-19 ARDS by D-dimer concentration and static compliance and reported different clinical outcomes; in their multicenter prospective observational study, patients with COVID-19 ARDS who had a reduction in respiratory system compliance together with increased D-dimer concentrations had high mortality rates (53). Given the remarkable contribution of coagulopathy in the pathogenesis of COVID-19 (108), anticoagulation therapy is anticipated to benefit patients with severe COVID-19. In this context, a single-center retrospective cohort study investigated the efficacy of anticoagulation therapy in patients with COVID-19, revealing that anticoagulation therapy was associated with lower in-hospital mortality in critically ill patients with COVID-19; however, unsupervised machine learning analysis revealed that the subgroup of patients with multiorgan dysfunction and excessive inflammation might not benefit from anticoagulation therapy (109).

Regarding immune subphenotypes and endotypes, a recent deep multiomics, longitudinal study of 309 patients with COVID-19 reported on four immune endotypes that exhibited divergent acute severity and postacute sequelae.

The type 1 group was characterized by T helper type 1-like signatures in $CD4^+$ T cells, M1-like proinflammatory signatures in monocytes, cytotoxic effector signatures in $CD8^+$ T cells and natural killer cells, and memory signatures in B cells. In contrast, the type 2 group was enriched for T helper type 2-like $CD4^+$ T-cell signatures, M2-like anti-inflammatory monocyte signatures, and a plasma B-cell signature. The intermediate group exhibited a transitional immune status between type 1 and type 2, while the naïve group exhibited naïve-like T- and B-cell signatures, and resting natural killer cell signatures (110).

Recent studies have also focused on identifying novel subphenotypes in patients with COVID-19 based on different clinical characteristics and disease courses. For example, Vasquez *et al.* categorized four subphenotypes within a heterogeneous population of patients with COVID-19: subphenotype 1 (12%) presented with shock, acidemia, and multi-organ dysfunction; subphenotype 2 (29%) required early invasive mechanical ventilation and had the highest rate of ARDS; subphenotype 3 (22%) had the highest rate of associated comorbidities; and subphenotype 4 (37%) had fewer chronic medical conditions than the other subphenotypes and showed milder physiologic abnormalities. Mortality rates at day 28 were found to decrease from subphenotype 1 to subphenotype 4 (52.9% to 20.6%) (111,112). Additionally, based on the prospective COVID-19 registry database consisting of 20,572 patients, Wang *et al.* identified seven phenotypes by demographics, comorbidities, and presenting symptoms using hypothesis-free LCA, and then identified five subphenotypes with additional blood biomarkers (113). This type of information highlights the value of stratified analyses of clinical trial data.

Finally, after more than 2 years of the COVID-19 pandemic, investigations of postacute sequelae of COVID-19 (PASC) have begun to provide thorough and compelling evidence. A recent study investigated PASC symptoms and quality of life by following up 179 patients with COVID-19 for 8 months from disease onset and reported bothersome symptoms with variable patterns of persistence and impact on quality of life, suggesting the existence of multiple subphenotypes of PASC (114). However, most of the patients enrolled in the study experienced only mild disease, and PASC in severe COVID-19 remains to be further investigated.

The studies on subphenotyping of COVID-19 are summarized in *Table 2*.

Conclusions and future directions

With a wide spectrum of clinical manifestations, COVID-19 is a heterogenous syndrome with crossover with ARDS and sepsis in severe cases. The pathophysiology of COVID-19-associated critical illness includes diffuse alveolar damage, dysregulation of the RAAS, endothelial cell damage and microvascular thrombosis, and dysregulated immune response and hyperinflammation. In COVID-19, ARDS commonly arises in critically ill patients and exhibits some distinctive features compared to classic ARDS, including remarkable vascular abnormality and coagulopathy as well as different respiratory mechanics and immune response. However, no adequate evidence has been unearthed to differentiate COVID-19-associated ARDS from ARDS of other causes, and therapeutic strategies for COVID-19 ARDS are still recommended based on the standards of care for classic ARDS with consideration given to pathophysiological rationales. Similarly, although COVID-19 can lead to multi-organ dysfunction in severe cases and thus meet the diagnostic criteria of sepsis, the underlying immune response might differ from that of bacterial sepsis to some extent; for example, the dysregulation of IFN response is considerably greater in COVID-19 than it in sepsis from other causes. Moreover, as a heterogenous syndrome itself, COVID-19 can be subphenotyped in a similar fashion to historical ARDS and sepsis. Some conventional subphenotypes derived from classic ARDS and sepsis have been validated in COVID-19, and novel subphenotypes and endotypes have also been identified in patients with COVID-19, showing different clinical outcomes and treatment response.

Since the outbreak of the COVID-19 pandemic, numerous COVID-19-associated studies—varying from controlled clinical to molecular investigations, case reports to randomized clinical trials, and correspondence to original basic science research—have been published. Obtaining such an ocean of information to put together a relatively clear picture of the disease has been a huge challenge for both clinicians and scientists. This review has endeavored to summarize the current knowledge of pathophysiology of COVID-19, focusing on the comparison of COVID-19-associated ARDS and sepsis to the historical syndromes, in addition to the subphenotypes or endotypes of COVID-19-associated critical illness. At this moment, research to understand the stratification of patients with COVID-19, including the basic pathophysiology, prognostic and predictive factors, and treatment response, should be encouraged.

Table 2 Subphenotypes or endotypes of COVID-19

Reference No.	Subphenotype	Characteristics
(100,101)	Hypoinflammatory	–
	Hyperinflammatory	Elevated inflammatory biomarkers, worse clinical outcome, better response to corticosteroid treatment
(62,63,102)	H type	High elastance, high shunt, and high lung weight
	L type	Low elastance, low shunt, and low lung weight
(103)	Subphenotype 1	–
	Subphenotype 2	Fewer ventilator-free days, more venous thrombotic events, and upward trajectories of ventilatory ratio and mechanical power over the first 4 days of invasive mechanical ventilation
(104,105)	Hyperthermic slow resolvers	Highest C-reactive protein, ferritin, and IL-6 levels; highest odds of mechanical ventilation and vasopressor requirement, and mortality
	Hyperthermic fast resolvers	–
	Normothermics	–
	Hypothermics	Highest D-dimer and fibrin monomers, highest prevalence of cerebrovascular accidents, highest thromboembolism rate
(106,107)	Inflammopathic	Highest C-reactive protein and IL-6 levels
	Adaptive	Lower rates of severe respiratory failure and no deaths
	Coagulopathic	Highest D-dimer concentrations and highest mortality rates
(53)	HDHC	High D-dimers and high compliance
	HDLC	High D-dimers, low compliance, and highest mortality
	LDHC	Low D-dimers and high compliance
	LDLC	Low D-dimers and low compliance
(110)	Type 1 group	Th1-like signatures in $CD4^+$ T cells, M1-like proinflammatory signatures in monocytes, cytotoxic effector signatures in $CD8^+$ T cells and NK cells, and memory signatures in B cells
	Type 2 group	Th2-like $CD4^+$ T cell signatures, M2-like anti-inflammatory monocyte signatures, and a plasma B-cell signature
	Intermediate group	A transitional immune status between type 1 and type 2
	Naïve group	Naïve-like T and B cell signatures, and resting NK cell signatures
(111,112)	Subphenotype 1	Shock, acidemia, multi-organ dysfunction, and highest mortality
	Subphenotype 2	Early invasive mechanical ventilation and highest rate of ARDS
	Subphenotype 3	Highest rate of associated comorbidities
	Subphenotype 4	Fewer chronic medical conditions, milder physiologic abnormalities, and lowest mortality

COVID-19, coronavirus disease 2019; IL, interleukin; HDHC, high D-dimers and high compliance; HDLC, high D-dimers and low compliance; LDHC, low D-dimers and high compliance; LDLC, low D-dimers and low compliance; Th1, T helper type 1; Th2, T helper type 2; NK, natural killer; ARDS, acute respiratory distress syndrome.

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Footnote

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