



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

COVID-19 Acute Respiratory Distress Syndrome

One Pathogen, Multiple Phenotypes



Susannah Empson, MD^{a,*}, Angela J. Rogers, MD^b,
Jennifer G. Wilson, MD, MS^c

KEYWORDS

• ARDS • COVID-19 • Subtypes • Phenotypes

KEY POINTS

- COVID-19 acute respiratory distress syndrome (ARDS) represents a distinct subset of ARDS.
- Significant clinical heterogeneity exists within COVID-19 ARDS despite a single causative agent.
- Several physiologically, clinically, and biologically derived phenotypes of COVID-19 ARDS have been identified.
- Phenotypic stratification in COVID-19 ARDS has value for both prognostic and predictive enrichment.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the novel respiratory virus responsible for the COVID-19 pandemic, which in less than 2 years has caused more than 4.5 million deaths worldwide.¹ In its most severe form, COVID-19 causes acute respiratory distress syndrome (ARDS), a syndrome defined by acute onset hypoxemia ($\text{PaO}_2:\text{FiO}_2 < 300$) with bilateral infiltrates not otherwise explained by volume overload or cardiac failure.²

ARDS is a clinically heterogeneous syndrome arising from multiple causes (pneumonia, aspiration, trauma, sepsis, pancreatitis, and so forth) and with a range of clinical severity. Although the landmark ARDS Network trials showed a mortality benefit from lung protective ventilation, subsequent experimental therapies have failed to demonstrate consistent benefit.^{3–9} One plausible explanation for the numerous negative trials, despite high-quality preliminary evidence, is the substantial heterogeneity

^a Department of Anesthesiology, Perioperative, and Pain Medicine, 300 Pasteur Drive, H3580, Stanford, CA 94305, USA; ^b Department of Pulmonary, Allergy & Critical Care Medicine, 300 Pasteur Drive, H3153, Stanford, CA 94305, USA; ^c Department of Emergency Medicine, 900 Welch Road, Suite 350, Stanford, CA 94305, USA

* Corresponding author.

E-mail address: sfempson@stanford.edu

within the ARDS population; this has led to an interest in identifying more homogeneous subgroups or phenotypes within ARDS for both prognostic and predictive enrichment. Prognostic enrichment enables identification of patients at highest risk for poor outcomes, thereby increasing the power to detect a therapeutic benefit with an intervention, should one exist. Predictive enrichment allows for selection of patients most likely to respond to a given therapy, thereby amplifying the effect of a particular treatment of any given sample size. Both strategies are recommended by the Food and Drug Administration and increase the efficacy of clinical trials.¹⁰ Thus far, several physiologically, clinically, and biologically derived subphenotypes have been identified (**Table 1**) with the potential to more efficiently and effectively test and tailor interventions to the unique profile of the patient.^{11,12}

In contrast to the general ARDS population, patients with COVID-19 ARDS have a single unifying causative agent and might therefore be expected to show less clinical heterogeneity. Nevertheless, the spectrum of disease severity observed in COVID-19 can range from asymptomatic to fulminant hypoxemic respiratory failure. The reasons for this marked variation in disease severity are incompletely understood but are hypothesized to include both host and pathogen factors.^{13,14} Even among the subset of COVID-19 patients who develop COVID-19 ARDS, there is a spectrum of physiology, biomarker expression, and outcomes, and controversy remains as to which patients should be treated with which therapies. Furthermore, we remain unable to predict, nor can we fully explain, why some patients improve and others develop

Phenotype	ARDS	COVID-19 ARDS
Physiologic	Hypoxemia (Pao ₂ :Fio ₂) Lung water/weight Dead space fraction Ventilatory ratio Driving pressure	Hypoxemia (level of respiratory support) Lung compliance
Clinical	Direct/indirect Early/late (time of onset, duration) Trauma-related/medical Radiographic patterns (focal/diffuse) Extrapulmonary organ involvement (AKI)	Demographic characteristics Medical comorbidities Radiographic characteristics Early/late (time since symptom onset) Worsening/recovering Extrapulmonary organ involvement
Biological	Genomic (genome-wide association) Transcriptomic (microRNA analysis) Proteomic (biomarkers) <ul style="list-style-type: none"> ● Inflammation ● Endothelial injury ● Epithelial injury ● Impaired coagulation Metabolomic Hyper/hypoinflammatory	Genomic Transcriptomic Proteomic <ul style="list-style-type: none"> ● Pathogen Factors <ul style="list-style-type: none"> ○ Viral variant ○ Viral kinetics (viral load at 7–14 d) ○ Viremia ● Host Factors <ul style="list-style-type: none"> ○ Serostatus ○ Hypo-/hyperinflammatory ○ Coagulation profile Metabolomic

persistent or fatal disease. As with ARDS in general, therefore, there is substantial interest in identifying more homogeneous subgroups of COVID-19 ARDS within the broader population. In order to be clinically meaningful, however, these subgroups must be more than mere descriptions of different clinical presentations and patterns of disease. Phenotypes of COVID-19 ARDS are valuable only if they are¹ feasibly identifiable and² improve our ability to prognosticate or predict treatment response.

In this review, the authors summarize the existing literature on clinically meaningful COVID-19 ARDS phenotypes, including the impact of the timeline of disease progression on phenotypic features, how these phenotypes are compared with known ARDS phenotypes, and how this approach may be leveraged to improve both prognostication and precision therapy.

PHYSIOLOGIC PHENOTYPES IN COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME

Severity of Hypoxemia

Codified within the Berlin consensus definition of ARDS, severity of hypoxemia has been used to stratify patients with ARDS both pre-COVID-19 and post-COVID-19.² Pre-COVID-19, many major clinical trials of ARDS used severity of hypoxemia as an enrichment strategy for their study population, enrolling patients with moderate-to-severe hypoxemia ($\text{PaO}_2:\text{FiO}_2 < 150$).^{4,5,15} To date, the most important clinical trials of therapies for acute hypoxemic respiratory failure due to COVID-19 have analyzed treatment effect based on level of respiratory support at the time of randomization. Although in theory level of respiratory support should correlate with degree of hypoxemia, because of institutional variation in timing of intubation and use of noninvasive positive pressure ventilation, this is likely an imperfect proxy. Nonetheless, multiple recent trials have shown important differences in treatment effect based on level of respiratory support at time of randomization. Most notably, the RECOVERY trial of dexamethasone showed maximal benefit in patients receiving invasive mechanical ventilation, less benefit in patients receiving supplemental oxygen but not mechanically ventilated, and a trend toward harm in patients on no oxygen therapy¹⁶; this raises questions about the mechanisms by which some therapies provide benefit to patients with lower severity of illness, whereas others seem to provide greater benefit to those with more severe disease. As discussed earlier, it may be that the degree of hypoxemia is best understood as a proxy for the time course and underlying biology, providing the clinician with important data on which patient is most likely to benefit from which therapy and when.

Lung Compliance

Early in the pandemic, Marini and Gattinoni noted that severity of hypoxemia alone was not sufficient to understand the “stages” of COVID-19 ARDS. They proposed phenotyping patients with COVID-19 ARDS according to lung compliance and advocated for a ventilation strategy that departed from traditional tenets of lung protective ventilation based on compliance phenotype. It was suggested that patients with preserved compliance (termed “L phenotype”) be ventilated with lower PEEP and slightly higher tidal volumes, whereas patients with poor lung compliance (“H phenotype”) be managed with a traditional lung protective ventilation strategy.¹⁷ It has since been demonstrated, however, that patients with pre-COVID-19 ARDS also had a range of lung compliance early in disease,¹⁸ and therefore current consensus is that a low tidal volume lung protective ventilation approach is appropriate for all patients with COVID-19 ARDS regardless of their compliance profile.¹⁹ Nonetheless, Marini and Gattinoni introduced 2 fundamental

concepts with which most experts now agree¹: not all patients with COVID-19 ARDS have the same phenotype, and² an individual's phenotype may change over time.

CLINICAL PHENOTYPES OF COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME

Baseline Demographics and Comorbidities

Accepted risk factors for severe or fatal COVID-19 include older age, male sex, obesity, cardiovascular disease, diabetes, chronic lung, liver or kidney disease, immunocompromise, and active cancer.^{20,21} Nonwhite race is also associated with higher risk of death from COVID-19 in the United States and United Kingdom, a disparity that is largely attributable to underlying socioeconomic disadvantage.^{22,23} Age and comorbidities have been used as prognostic enrichment criteria for clinical trials in COVID-19, but once COVID-19 ARDS has developed, all patients are at high risk of death from hypoxemic respiratory failure and worsening extrapulmonary organ dysfunction, so these prognostic enrichment factors may be less important in terms of trial design. Beyond providing prognostic value, however, baseline patient phenotypes may help select patients for trials of more targeted therapies such as monoclonal antibodies in immunocompromised patients or SGLT2 inhibitors in diabetic or obese patients.²⁴ As with all subgroups of patients with COVID-19 ARDS, however, these baseline phenotypes may be more precisely characterized by combining them with other physiologic, clinical, or biological variables, all of which are discussed in other sections of this review.

Radiographic Findings

As with pre-COVID ARDS, radiographic findings associated with COVID-19 have been well described and correlate with disease severity.^{25–29} Increasingly, studies have attempted to identify patterns on computed tomography (CT) that might serve as predictors of disease progression and mortality. Ruch and colleagues demonstrated that visual quantification of affected lung parenchyma on hospital admission CT was independently associated with disease severity.³⁰ In one retrospective study, the volume of affected lung as well as the rate of progression on serial CT scans performed within 5 days of symptom onset predicted progression to severe disease in advance of clinical decompensation.³¹

Pellegrini and colleagues used chest CT to describe the progression of lung injury in a small cohort of critically ill patients with COVID-19 ARDS, observing initially a predominantly subpleural distribution of hypo- and nonaerated sections of lung.³² However, in those patients exposed to volutrauma, extensive centripetal progression of disease was noted. Similar radiographic findings were observed in those with a positive fluid balance and elevated ferritin and d-dimer levels and were associated with worsening gas exchange and pulmonary mechanics. Results of this study show that worsening radiographic lung injury correlates with multiple known risk factors for poor outcome, including duration of symptoms, volutrauma, positive fluid balance (and associated increase in lung weight), systemic inflammation, and hypercoagulability. Whether this subset of patients with worsening CT findings represents a distinct phenotype of COVID-19 ARDS or the end stage of disease progression remains unclear, and although radiographic phenotyping can prove prognostically useful, it is uncertain whether or how it should guide management.

Time Since Symptom Onset and Trajectory of Disease

The importance of time since symptom onset in terms of selecting COVID-19 therapies has been apparent from the beginning of the pandemic. Many patients will not

develop severe illness until a week or more after onset of symptoms. In light of this, several clinical trials have limited enrollment to patients who are within a certain window from symptom onset or planned subgroup analyses based on time since symptom onset (ACTIV-3, RECOVERY).^{16,33} The rationale for this is clearly based on the temporal dynamics of peak viral load and antibody/immune response (Fig. 1 below).³⁴ Although point-of-care tests for antibody status are in development, until such tests are available, time since symptom onset may serve as a way to categorize patients, with “earlier” patients more likely to benefit from therapies focused on inhibiting viral replication and enhancing viral clearance (such as antiviral therapy and monoclonal antibodies), and “later” patients more likely to benefit from immunomodulating therapies. In support of this idea, the RECOVERY trial of dexamethasone discussed earlier showed no benefit in patients who were less than 7 days from symptom onset.¹⁶ Of course, the exact timing of onset of symptoms, peak of viral load, and antibody production and inflammasome activation varies from patient to patient. Thus, although time since symptom onset may be a pragmatic way to classify patients, direct measurement of antibody serostatus or inflammatory markers (as discussed in detail later) or combination of time course with other clinical or physiologic markers (such as need for oxygen therapy) is likely a more precise approach to phenotyping patients with COVID-19 with worsening hypoxemic respiratory failure.

Another way to phenotype patients is based on the trajectory of their organ dysfunction. Su and colleagues describe 2 distinct phenotypes of organ failure trajectory among intubated patients with COVID-19 ARDS based on serial daily Sequential Organ Failure Assessment scores over the first 7 days postintubation: worsening or recovering.³⁵ These 2 groups were identified in all strata of illness severity, and baseline demographics, comorbidities, and organ dysfunction did not differ. Patients with the worsening phenotype in the mild and intermediate illness severity strata had worse outcomes than patients with the highest baseline severity of illness who had a recovering phenotype; this suggests that grouping patients with COVID-19 ARDS according to trajectory of extrapulmonary organ dysfunction postintubation is more prognostic than grouping them by baseline risk factors or severity of illness at time of intubation.

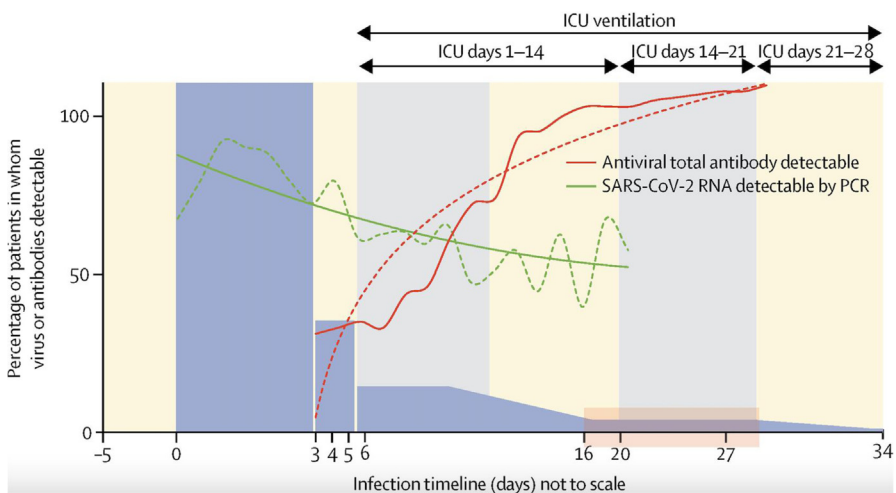


Fig. 1. SARS-CoV-2 clinical course, viral replication, and immune response. (Adapted with permission from [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30230-7/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30230-7/fulltext).)

Further, these findings reinforce the need to investigate the biological pathways driving the progressive extrapulmonary organ dysfunction seen in some but not all patients with COVID-19 ARDS.

Extrapulmonary Organ Dysfunction

Although respiratory failure is the leading cause of death for patients with COVID-19 ARDS, many patients develop multisystem organ dysfunction either before or after the onset of respiratory failure.^{36,37} As one would expect, these patients have worse outcomes, and therefore, presence of extrapulmonary organ dysfunction in patients with worsening hypoxemia may be a low-effort, high-yield strategy for prognostic enrichment. Extrapulmonary organ dysfunction attributable to SARS-CoV-2 infection may also provide important clues about the underlying pathophysiology of severe disease in patients with COVID-19 ARDS. Multiple mechanisms by which SARS-CoV-2 causes multiorgan injury have been postulated, including direct viral toxicity, endothelial inflammation and thrombosis, systemic immune response, and dysregulation of the renin-angiotensin-aldosterone system.³⁸ Focusing future research on the biological profile of this phenotype of patients may therefore help prioritize targets for potential therapeutic intervention.

BIOLOGICAL PHENOTYPES OF COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME

SARS-CoV-2 Variants and Kinetics

As SARS-CoV-2 mutates over time, different variants of concern have emerged, with the B.1.617.2 (Delta) variant predominant in the United States as of Fall 2021.³⁹ Different variants may produce different disease manifestations, likely related to variation in angiotensin-converting enzyme 2 receptor binding affinity and degree of immune escape between different strains.⁴⁰ Certain therapies proved beneficial during a time when previous variants predominated may work differently in patients infected with a new variant; this has already occurred with combination bamlanivimab and etesevimab monoclonal antibody therapy, which had its emergency use authorization revised based on concern about continued use in areas where resistant variants are prevalent.⁴¹ Thus rather than using a one-size-fits-all approach for COVID-19 therapies, tailoring treatments based on SARS-CoV-2 genomics, as well as targeting patients most likely to benefit (eg, seronegative patients) will be an important part of precision care for COVID-19.

Regardless of the viral variant, viral kinetics may also help us identify more homogeneous subgroups within the COVID-19 patient population. As discussed earlier, time from symptom onset to development of symptomatic disease matters in terms of treatment selection. The mechanism underlying this almost certainly relates to the temporal dynamics of infection with SARS-CoV-2 and the nature of the host response. Although nasopharyngeal viral load at admission (as measured by qualitative real-time polymerase chain reaction) is not by itself associated with worse clinical outcomes, persistence of high viral loads at 7 to 14 days postadmission is significantly associated with mortality.^{42,43} In addition, SARS-CoV-2 viremia (as measured by digital PCR in plasma samples) is associated with severe disease and worsened clinical outcomes. Taken together, this suggests that severe disease is in part driven by poor control of the SARS-CoV-2 virus by the immune response.¹⁶ Using viral kinetics and viremia may therefore be a feasible way to identify patients at highest risk for deterioration and most likely to derive benefit from antiviral therapies early in the course of disease.

Host Response: Serostatus

Although monoclonal antibody therapies (largely agents directed at various epitopes on the SARS-CoV-2 spike protein) have demonstrated benefit in high-risk outpatient populations, previous trials of monoclonal antibody therapies in hospitalized patients had failed to show benefit, even when enrollment was limited to patients with less than 12 days of symptoms.^{44,45} The more recently released results from the RECOVERY trial of combination casirivimab and imdevimab for hospitalized COVID-19 suggests that the failure of monoclonal antibodies in previous inpatient trials may be explained by the serostatus of the patients enrolled: in this large randomized trial, although there was no benefit of therapy observed in the combined trial population (both seronegative and seropositive at baseline), there was a 20% reduction in mortality rate among patients who were seronegative at baseline.⁴⁶ Thus serostatus has already been shown to be a phenotypic feature by which treatment effect of antiviral therapies will differ and is more precise than using time since symptom onset as a surrogate marker. Because rapid turnaround antibody tests may not be available in all settings, time since symptom onset and severe immunocompromise may be important clinical features to consider when antibody testing is not feasible.

Host Response: Overview

The cascade of the immune and inflammatory response to SARS-CoV-2 infection is complex and incompletely understood. However, the proposed pathogenesis of COVID-19 ARDS is characterized by a dysregulated host response, leading to local and systemic inflammatory and thrombotic derangements. More specifically, infection triggers an immune response characterized by both T- and B-cell activation, leading to inflammatory cytokine release, activation of the complement and coagulation cascades, and resulting endothelial injury.⁴⁷ Autopsies of deceased patients demonstrate diffuse alveolar damage with leukocyte infiltration, microangiopathy, and thrombosis of the pulmonary capillaries.⁴⁸ The terms “endotheliitis” and “thromboinflammation” have been used to describe the pathogenesis of severe disease.^{49,50} There has therefore been sustained interest in phenotyping patients according to their cytokine or coagulation profile, each of which is discussed later.

Host Response: Inflammatory Profile

Multiple studies have demonstrated high levels of inflammatory biomarkers in patients with COVID-19, and higher levels correlate with disease severity and clinical outcomes.^{26,51–53} These data have therefore sparked an interest in “cytokine storm,” as central to the pathogenesis of severe COVID-19.⁵⁴ Hypo- and hyperinflammatory phenotypes have been well described in the general ARDS population, and Sinha and colleagues were able to identify similar phenotypes in patients with COVID-19 ARDS.^{55–59} As with general ARDS, the hyperinflammatory phenotype was associated with a higher mortality rate but was observed at a much lower prevalence than in the matched non-COVID-19 cohort. Furthermore, although proinflammatory cytokine/cytokine receptor (interleukin-6 [IL-6], soluble tumor necrosis factor receptor) levels were elevated, supporting a state of systemic inflammation, they were similar to or lower than those observed in the matched non-COVID-19-associated ARDS cohort.^{60,61} Finally, mortality among both the hypo- and hyperinflammatory COVID-19 cohorts was higher than their matched counterparts. It is therefore hypothesized that COVID-19 ARDS has distinct pathophysiologic features compared with non-COVID-19 ARDS and that severity of disease is incompletely understood and not explained by “cytokine storm.”

Nonetheless, multiple clinical trials have now demonstrated benefit to using anti-inflammatory therapies in subgroups of patients with COVID-19 ARDS. Dexamethasone is recommended in all patients with COVID-19 who require supplemental oxygen and shows the greatest benefit in patients requiring mechanical ventilation at the time of randomization. In addition, tocilizumab (an anti-IL-6 therapy) and baricitinib (a JAK inhibitor) have now been proved beneficial in patients with markers of systemic inflammation.^{62,63} Trials of these therapies used elevated C-reactive protein (CRP) (in the case of tocilizumab) and elevated D-dimer, lactate dehydrogenase, or ferritin (in the case of baricitinib) as enrollment criteria, thereby enriching the trial population for patients at higher risk for poor outcomes and most likely to benefit based on mechanism of these antiinflammatory therapies. Taken together, these studies add to the growing body of evidence that there is a subset of patients with COVID-19 with an inflammatory phenotype amenable to targeted therapy within a distinct time frame of clinical disease progression.

Unfortunately, with the exception of dexamethasone, little evidence exists to guide the use of antiinflammatory therapies in COVID-19 ARDS requiring intubation beyond the choice of initial therapy before or within 24 hours of intubation. The COV-BARRIER study of JAK inhibition excluded patients on mechanical ventilation at time of study entry.⁶³ The REMAP-CAP trial of anti-IL-6 therapy in the critically ill required randomization within 24 hours of initiating organ support in the intensive care unit, and the RECOVERY trial of anti-IL-6 therapy showed no benefit in patients who were already mechanically ventilated at the time of study entry.^{62,64} Thus, an incredibly important question remains of how to manage patients with COVID-19 ARDS who have persistent organ dysfunction or elevated inflammatory markers despite initial treatment with dexamethasone or IL-6/JAK inhibition.

The multisystem inflammatory syndrome in children is a hyperinflammatory syndrome triggered by recent SARS-CoV-2 infection that has recognized diagnostic criteria and guidelines for suggested therapy.⁶⁵ There is now a working definition for a multisystem inflammatory syndrome in adults (MIS-A) as well, and glucocorticoids, anakinra (an IL-1 receptor antagonist), and intravenous immunoglobulin have been suggested as therapies for patients with this phenotype.^{65–67} Indeed, although several studies have found that inflammatory cytokine levels in patients with COVID-19 ARDS are not markedly different from critically ill patients with sepsis or ARDS from other causes and are lower than those observed in cytokine release syndrome, noncytokine inflammatory biomarkers (D-dimer, CRP, ferritin) are elevated to a greater degree in COVID-19 than in other critical illnesses.^{60,68} In addition to identifying patients with COVID-19 ARDS with potential MIS-A, several investigators have suggested that there is a subset of severely ill patients with a “macrophage activation syndrome” phenotype (identified by marked hyperferritinemia or a clinical score known as the H-score) in which IL-1 blockade should be considered.^{69–71}

In summary, there are numerous approaches to identifying patients with COVID-19 ARDS who are showing signs of maladaptive inflammation and who may benefit from antiinflammatory therapies. The question of which approach should be used, and how signs of hyperinflammation should be interpreted and treated at different timepoints in the disease course will be a central focus for researchers going forward.¹³

Host Response: Coagulation Profile

As discussed earlier, the interaction between inflammation and hypercoagulability is a notable feature of severe COVID-19, and presence of both micro- and macrovascular thrombosis in patients with severe disease and ARDS has been well documented.^{72–75} In addition, serum biomarkers of systemic coagulation have been independently

associated with more severe forms of disease and poorer outcomes.^{53,76–78} Clinically, coagulopathy most commonly manifests as high rates of venous thromboembolic disease, but microthrombosis of the pulmonary vasculature has also been posited as a mechanism for the increased dead space observed in COVID-19 ARDS.⁷⁹ Histopathologically, autopsies of deceased patients with COVID-19 demonstrate widespread platelet-fibrin activation and microthrombi in the alveolar capillaries.^{80,81} Although the exact mechanism of coagulopathy is incompletely understood, it is hypothesized that virus-induced endothelial injury leads to inflammation and thrombosis. Furthermore, microthrombosis, coagulopathy, and subsequent endotheliitis have been theorized to play a central role in the development of extrapulmonary complications and multisystem organ failure.⁴⁷

Despite the recognized role of micro- and macrovascular thrombosis in the pathogenesis of COVID-19, a large multiplatform randomized controlled trial of empirical therapeutic anticoagulation in hospitalized patients with COVID-19 yielded different results in critically and noncritically ill cohorts. In the noncritically ill cohort, therapeutic anticoagulation increased the probability of survival to hospital discharge and reduced the need for organ support, regardless of baseline D-dimer (although the effect was slightly greater in those with D-dimer levels $>2\times$ ULN).⁸² In contrast, no benefit was observed among patients who were critically ill at the time of enrollment, and there was a trend toward harm.⁸³ One explanation posited for this discrepancy in treatment effect is that by the time patients have progressed to critical illness, the cascade of inflammation, thrombosis, and organ dysfunction has progressed to a degree where anticoagulation can no longer make a meaningful difference on outcomes. In this sense, the choice of anticoagulation dose in COVID-19 may depend not only on selecting patients most likely to benefit based on their coagulation profile but also on identifying the time point at which those patients are most likely to derive that benefit.

Aspirin has also been studied by the RECOVERY platform trial and unfortunately did not reduce 28-day mortality.⁸⁴ Studies of P2Y12 inhibitors are ongoing at the time of this review, and other trials of treatments with antithrombotic properties (eg crizanlizumab) are planned. Regardless of the outcomes of these trials, it is clear that endothelial dysfunction and platelet activation are prominent features of severe COVID-19, and future work focuses on identifying subsets of patients with COVID-19 most likely to benefit from antiplatelet and antithrombotic therapies.

Host Response: Genomics and Transcriptomics

The heterogeneity of COVID-19 ARDS has provoked interest in identifying biologically distinct phenotypes, and research has therefore increasingly focused on genomic and transcriptomic signatures with the hope of identifying host factors that predict poor outcomes and pathways for targeted therapies.^{85–89} Preliminary work has focused predominantly on the host immune response, inflammatory, and coagulation cascade and has suggested an association between a cluster of genes encoding chemokine receptors and severe disease, as well as upregulation of genes involving inflammation, immunity, coagulation, and interferon signaling.^{90–92} Furthermore, several multi-omics studies have identified distinct shifts in immunologic and inflammatory profiles between mild, moderate, and severe disease.^{93–95} In addition to identifying targeted pathways for therapeutic intervention, transcriptomics in particular may shed light on the optimal timing of specific interventions. There is, however, significant work to be done to confirm associations between candidate genes, transcriptomic signatures, and clinically meaningful subphenotypes of COVID-19 ARDS. At this point, genomic and transcriptomic phenotyping of COVID-19 ARDS patients remains exploratory and unavailable outside of the research setting.

SUMMARY

Despite a unifying causative agent, the spectrum of disease observed in COVID-19 ARDS is broad, and although research is progressing at a rapid pace, the underlying reasons for this clinical heterogeneity remain incompletely understood. It is becoming increasingly accepted that COVID-19 ARDS is a distinct subset of ARDS with its own subphenotypes that bear some similarities to but also distinct differences from the broader syndrome. As DeMerle and colleagues remind us, however, phenotypic categorization is meaningful only to the extent that it offers plausible, easily identifiable, and reproducible frameworks to prognosticate and tailor treatment.⁹⁶ Although many recent and ongoing clinical trials have used combined physiologic, clinical, and biological phenotypes to identify and target patients most likely to benefit from a particular therapy, precision medicine for COVID-19 ARDS is still in its infancy. Years of work have led to identification of biological subphenotypes of sepsis and ARDS, but the clinical importance of these phenotypes has yet to be rigorously established in prospective clinical trials. For the clinician practicing in the midst of a dynamic global pandemic, therefore, keeping current with the outcomes of high-quality clinical trials for COVID-19 ARDS—and adhering to established evidence-based therapies for ARDS in the interim—remains best practice. The clinical relevance of many of the proposed phenotypes discussed in this review require ongoing prospective validation with the ultimate goal of bringing precision therapies for COVID-19 ARDS to the bedside.

CLINICS CARE POINTS

- Patients with COVID-19 ARDS have a similar range of lung compliance as patients with general ARDS, and adherence to classic ARDS strategies, including low tidal volume ventilation, remains the mainstay of care for COVID-19 ARDS.
- Oxygen requirement, markers of systemic inflammation, and timing since symptom onset can help guide treatment.
- Steroids (dexamethasone), anti-IL-6 therapy, and JAK1/2 inhibition have demonstrated therapeutic benefit in subsets of patients hospitalized with COVID-19.
- The clinical applicability of biological phenotypes in COVID-19 ARDS requires ongoing prospective validation.

DISCLOSURE

S. Empson has no conflict of interest to declare. A.J. Rogers is a pulmonary clinical trials advisor for Merck, not relevant to this work. J.G. Wilson has no conflict of interest to declare.

REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard. Available at: <https://covid19.who.int>. Accessed October 1, 2021.
2. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307(23):2526–33.
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301–8.

4. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363(12):1107–16.
5. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;380(21):1997–2008.
6. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;370(23):2191–200.
7. McAuley DF, Laffey JG, O’Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014;371(18):1695–703.
8. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351(4):327–36.
9. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564–75.
10. FDA. Enrichment strategies for clinical trials to support approval of human drugs and biological products. Available from <https://www-fda-gov.laneproxy.stanford.edu/media/121320/download>. Accessed September 15, 2021.
11. Wilson JG, Calfee CS. ARDS subphenotypes: understanding a heterogeneous syndrome. *Crit Care Lond Engl* 2020;24(1):102.
12. Sinha P, Calfee CS. Phenotypes in acute respiratory distress syndrome: moving towards precision medicine. *Curr Opin Crit Care* 2019;25(1):12–20.
13. Sinha P, Calfee CS. Immunotherapy in COVID-19: why, who, and when? *Lancet Respir Med* 2021;9(6):549–51.
14. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46(6):1099–102.
15. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368(23):2159–68.
16. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384(8):693–704.
17. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* 2020;323(22):2329–30.
18. Panwar R, Madotto F, Laffey JG, et al. Compliance phenotypes in early acute respiratory distress syndrome before the COVID-19 Pandemic. *Am J Respir Crit Care Med* 2020;202(9):1244–52.
19. Botta M, Tsonas AM, Pillay J, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. *Lancet Respir Med* 2021;9(2):139–48.
20. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584(7821):430–6.
21. Harrison SL, Fazio-Eynullayeva E, Lane DA, et al. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. *PLOS Med* 2020;17(9):e1003321.
22. Kabarriti R, Brodin NP, Maron MI, et al. Association of race and ethnicity with comorbidities and survival among patients with COVID-19 at an urban medical center in New York. *JAMA Netw Open* 2020;3(9):e2019795.
23. Muñoz-Price LS, Nattinger AB, Rivera F, et al. Racial disparities in incidence and outcomes among patients with COVID-19. *JAMA Netw Open* 2020;3(9):e2021892.
24. Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised,

- double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2021;9(9):586–94.
25. Warren MA, Zhao Z, Koyama T, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax* 2018; 73(9):840–6.
 26. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet Lond Engl* 2020;395(10223):497–506.
 27. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20(4): 425–34.
 28. Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel Coronavirus (2019-nCoV). *Radiology* 2020;295(1):202–7.
 29. Bernheim A, Mei X, Huang M, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* 2020. <https://doi.org/10.1148/radiol.2020200463>. 200463.
 30. Ruch Y, Kaeuffer C, Ohana M, et al. CT lung lesions as predictors of early death or ICU admission in COVID-19 patients. *Clin Microbiol Infect* 2020;26(10):1417.e5–8.
 31. Li K, Liu X, Yip R, et al. Early prediction of severity in coronavirus disease (COVID-19) using quantitative CT imaging. *Clin Imaging* 2021;78:223–9.
 32. Pellegrini M, Larina A, Mourtos E, et al. A quantitative analysis of extension and distribution of lung injury in COVID-19: a prospective study based on chest computed tomography. *Crit Care Lond Engl* 2021;25(1):276.
 33. University of Minnesota. A multicenter, adaptive, randomized, blinded controlled trial of the safety and efficacy of investigational therapeutics for hospitalized patients with COVID-19. [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT04501978). 2021. Available at: <https://clinicaltrials.gov/ct2/show/NCT04501978>. Accessed September 30, 2021.
 34. McGrath BA, Brenner MJ, Warrillow SJ, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Respir Med* 2020;8(7):717–25.
 35. Su C, Xu Z, Hoffman K, et al. Identifying organ dysfunction trajectory-based subphenotypes in critically ill patients with COVID-19. *Sci Rep* 2021;11(1):15872.
 36. Elezkurta J, Greuel S, Ihlow J, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep* 2021;11(1):4263.
 37. Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with Coronavirus Disease 2019 in the US. *JAMA Intern Med* 2020; 180(11):1436–47.
 38. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020;26(7):1017–32.
 39. CDC. COVID. Data tracker. Centers for Disease Control and Prevention. 2020. Available at: <https://covid.cdc.gov/covid-data-tracker>. Accessed September 30, 2021.
 40. Khateeb J, Li Y, Zhang H. Emerging SARS-CoV-2 variants of concern and potential intervention approaches. *Crit Care* 2021;25(1):244.
 41. Pica N. Bamlanivimab and Etesevimab Authorized States, Territories, and US Jurisdictions. :2.
 42. Argyropoulos KV, Serrano A, Hu J, et al. Association of initial viral load in severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patients with outcome and symptoms. *Am J Pathol* 2020;190(9):1881–7.
 43. Néant N, Lingas G, Le Hingrat Q, et al. Modeling SARS-CoV-2 viral kinetics and association with mortality in hospitalized patients from the French COVID cohort. *Proc Natl Acad Sci U S A* 2021;118(8). e2017962118.
 44. NIH-sponsored ACTIV-3 clinical trial closes enrollment into two Sub-studies. National Institutes of Health (NIH). 2021. Available at: <https://www.nih.gov/news->

events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies. Accessed September 30, 2021.

45. ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2021;384(10):905–14.
46. Group RC, Horby PW, Mafham M, et al. Casirivimab and Imdevimab in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial.; 2021:2021.06.15.21258542. doi:10.1101/2021.06.15.21258542
47. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021;9(6):622–42.
48. Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: a literature review. *Forensic Sci Med Pathol* 2021;17(2):279–96.
49. Talasz AH, Sadeghipour P, Kakavand H, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;77(15):1903–21.
50. Teuwen LA, Geldhof V, Pasut A, et al. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020;20(7):389–91.
51. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130(5):2620–9.
52. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46(5):846–8.
53. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl* 2020;395(10229):1054–62.
54. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020;395(10229):1033–4.
55. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2(8):611–20.
56. Delucchi K, Famous KR, Ware LB, et al. Stability of ARDS subphenotypes over time in two randomised controlled trials. *Thorax* 2018;73(5):439–45.
57. Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;195(3):331–8.
58. Bos LD, Schouten LR, van Vught LA, et al. Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. *Thorax* 2017;72(10):876–83.
59. Sinha P, Calfee CS, Cherian S, et al. Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. *Lancet Respir Med* 2020;8(12):1209–18.
60. Wilson JG, Simpson LJ, Ferreira AM, et al. Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis. *JCI Insight* 2020;5(17):e140289.
61. Kox M, Waalders NJB, Kooistra EJ, et al. Cytokine levels in critically ill patients with COVID-19 and Other Conditions. *JAMA* 2020. <https://doi.org/10.1001/jama.2020.17052>.

62. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Lond Engl* 2021;397(10285):1637–45.
63. Marconi VC, Ramanan AV, Bono S de, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021;0(0). [https://doi.org/10.1016/S2213-2600\(21\)00331-3](https://doi.org/10.1016/S2213-2600(21)00331-3).
64. Investigators TRC. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021. <https://doi.org/10.1056/NEJMoa2100433>.
65. Henderson LA, Canna SW, Friedman KG, et al. American College of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 1. *Arthritis Rheumatol* 2020;72(11):1791–805.
66. Multisystem CDC. Inflammatory syndrome (MIS). Centers for Disease Control and Prevention. 2020. Available at: <https://www.cdc.gov/mis/mis-a/hcp.html>. Accessed September 29, 2021.
67. Ahmad F, Ahmed A, Rajendraprasad SS, et al. Multisystem inflammatory syndrome in adults: a rare sequela of SARS-CoV-2 infection. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis* 2021;108:209–11.
68. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020;8(12):1233–44.
69. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2(6):e325–31.
70. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2(7):e393–400.
71. Dimopoulos G, de Mast Q, Markou N, et al. Favorable anakinra responses in severe Covid-19 patients with Secondary Hemophagocytic Lymphohistiocytosis. *Cell Host Microbe* 2020;28(1):117–23.e1.
72. Mazzaccaro D, Giannetta M, Fancoli F, et al. COVID and venous thrombosis: systematic review of literature. *J Cardiovasc Surg (Torino)* 2021. <https://doi.org/10.23736/S0021-9509.21.12022-1>.
73. Liu Y, Cai J, Wang C, et al. A systematic review and meta-analysis of incidence, prognosis, and laboratory indicators of venous thromboembolism in hospitalized patients with coronavirus disease 2019. *J Vasc Surg Venous Lymphat Disord* 2021;9(5):1099–111.e6.
74. Kollias A, Kyriakoulis KG, Lagou S, et al. Venous thromboembolism in COVID-19: a systematic review and meta-analysis. *Vasc Med Lond Engl* 2021;26(4):415–25.
75. Zhang C, Shen L, Le KJ, et al. Incidence of venous thromboembolism in hospitalized coronavirus disease 2019 patients: a systematic review and meta-analysis. *Front Cardiovasc Med* 2020;7:151.
76. Paliogiannis P, Mangoni AA, Dettori P, et al. D-dimer Concentrations and COVID-19 severity: a systematic review and meta-analysis. *Front Public Health* 2020;8:432.
77. Vidali S, Morosetti D, Cossu E, et al. D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. *ERJ Open Res* 2020;6(2):00260–2020.

78. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020;136(4):489–500.
79. Bhatt A, Deshwal H, Luoma K, et al. Respiratory Mechanics and association with inflammation in COVID-19-related ARDS. *Respir Care* 2021. <https://doi.org/10.4187/respcare.09156>.
80. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;20(10):1135–40.
81. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med* 2020;8(7):681–6.
82. Therapeutic anticoagulation with Heparin in noncritically ill patients with Covid-19. *N Engl J Med* 2021;385(9):790–802.
83. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with Heparin in critically ill patients with Covid-19. *N Engl J Med* 2021;385(9):777–89.
84. Group RC, Horby PW, Pessoa-Amorim G, et al. Aspirin in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial.; 2021:2021.06.08.21258132. doi:10.1101/2021.06.08.21258132
85. Kan M, Shumyatcher M, Himes BE. Using omics approaches to understand pulmonary diseases. *Respir Res* 2017;18(1):149.
86. Rogers AJ, Contrepois K, Wu M, et al. Profiling of ARDS pulmonary edema fluid identifies a metabolically distinct subset. *Am J Physiol Lung Cell Mol Physiol* 2017;312(5):L703–9.
87. Zhu Z, Liang L, Zhang R, et al. Whole blood microRNA markers are associated with acute respiratory distress syndrome. *Intensive Care Med Exp* 2017;5(1):38.
88. Bos LDJ, Scicluna BP, Ong DSY, et al. Understanding heterogeneity in biologic phenotypes of acute respiratory distress syndrome by leukocyte expression profiles. *Am J Respir Crit Care Med* 2019;200(1):42–50.
89. Morrell ED, Radella F, Manicone AM, et al. Peripheral and alveolar cell transcriptional programs are distinct in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2018;197(4):528–32.
90. Pathak GA, Singh K, Miller-Fleming TW, et al. Integrative genomic analyses identify susceptibility genes underlying COVID-19 hospitalization. *Nat Commun* 2021;12(1):4569.
91. Sarma A, Christenson S, Mick E, et al. COVID-19 ARDS is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. *Res Sq* 2021. <https://doi.org/10.21203/rs.3.rs-141578/v1>. rs.3.rs-141578.
92. Bost P, Giladi A, Liu Y, et al. Host-viral infection Maps reveal signatures of severe COVID-19 patients. *Cell* 2020;181(7):1475–88.e12.
93. Su Y, Chen D, Yuan D, et al. Multi-omics resolves a sharp disease-state shift between mild and moderate COVID-19. *Cell* 2020;183(6):1479–95.e20.
94. Wilk AJ, Lee MJ, Wei B, et al. Multi-omic profiling reveals widespread dysregulation of innate immunity and hematopoiesis in COVID-19. *J Exp Med* 2021;218(8):e20210582.
95. Overmyer KA, Shishkova E, Miller IJ, et al. Large-scale multi-omic analysis of COVID-19 severity. *Cell Syst* 2021;12(1):23–40.e7.
96. DeMerle K, Angus DC, Seymour CW. Precision medicine for COVID-19: phenotype Anarchy or promise realized? *JAMA* 2021;325(20):2041–2.