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REVIEW ARTICLE

# Coronavirus disease 2019 (COVID-19): cytokine storms, hyper-inflammatory phenotypes, and acute respiratory distress syndrome

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**Abstract** Coronavirus Disease 2019 (COVID-19) was first identified in China at the end of 2019. Acute respiratory distress syndrome (ARDS) represents the most common and serious complication of COVID-19. Cytokine storms are a pathophysiological feature of COVID-19 and play an important role in distinguishing hyper-inflammatory subphenotypes of ARDS. Accordingly, in this review, we focus on hyper-inflammatory host responses in ARDS that play a critical role in the differentiated development of COVID-19. Furthermore, we discuss inflammation-related indicators that have the potential to identify hyper-inflammatory subphenotypes of COVID-19, especially for those with a high risk of ARDS. Finally, we explore the possibility of improving the quality of monitoring and treatment of COVID-19 patients and in reducing the incidence of critical illness and mortality via better distinguishing hyper- and hypo-inflammatory subphenotypes of COVID-19.


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## Introduction

An ongoing outbreak of the 2019 novel coronavirus (2019-nCoV) pneumonia was first identified in Wuhan, within the Hubei province of China, at the end of 2019. The current outbreak of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO).[1] COVID-19 is a betacoronavirus that affects the lower respiratory tract and manifests as pneumonia in humans.[2] The full spectrum of disease severity, as shown in the guidelines for diagnosis and treatments for COVID-19 issued by the National Health Commission of China, has already been updated seven times by March 8, 2020.[3] As of March 8, 2020, the locations with confirmed SARS-CoV-2 cases included 101 countries/territories/areas. Globally, as of 3:47 pm CEST, June 7, 2020, there have been 6,799,713 confirmed cases of COVID-19 reported to WHO,[4] including 83,040 cases in China.[5] Moreover, a total of 397,388 patients, including 4634 cases in China, have died from this devastating viral infection.[4,5]

COVID-19 may be grouped into 4 subtypes; the severe cases subtype was defined as patients who met at least one of the following clinical criteria: (1) respiratory rates$\geq$30 breaths/min; (2) oxygen saturation$\leq$93% with resting state; (3) the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2) is $\leq$ 300 mmHg. The critical cases subtype defined patients who met at least one of the following criteria: (1) requiring mechanical ventilation (MV); (2) shock; (3) combined other organ failure.[3] The largest current epidemiological study of COVID-19, published by the Chinese Center for Disease Control (CDC), showed that 13.8% of patients were severe cases, and 4.7% patients were critical cases.[6] Critically ill patients infected with SARS-CoV-2 can quickly progress to ARDS, followed by septic shock, refractory metabolic acidosis, coagulation dysfunction, and multiple organ failure if the disease cannot be controlled.[37] Correspondingly, critically ill patients, with a 49% fatality rate, are at the greatest risk of death from COVID-19.[6] Preliminary estimates of case fatalities have been mostly due to ARDS, acute kidney injury (AKI), and myocardial injury.[8] ARDS is the most common and serious complication of COVID-19. For patients in severe or critical condition, tracheal intubation, protective mechanical ventilation (MV), and extracorporeal membrane oxygenation (ECMO) are the primary approaches for treating ARDS. Related to noteworthy phenotypes, cytokine storms are a pathophysiological feature that has been prominent during the course of COVID-19. Cytokine storms promote uncontrolled inflammation and underlie a core mechanism of ARDS, but there are differences in this phenotype across individuals. Hence, further elucidation of cytokine storms exacerbating ARDS in COVID-19 may lead to earlier efficacious interventions in otherwise critically ill COVID-19 patients.

To better understand the effects of differences in host inflammatory responses of ARDS during cytokine storms in COVID-19 patients, it is necessary to analyze and synthesize the characteristics and mechanisms of cytokine storms, host responses, severe complications of ARDS, and their relationships with one another in COVID-19, the ultimate goals of which are to aid in the identification of early warning signs and facilitate management and therapeutic approaches for severe COVID-19 patients. In this review, we confine our discussion to hyper-inflammatory host responses in ARDS that play a critical role in the differentiated development of COVID-19.

## COVID-19: severe cytokine storms and ARDS

To date, most SARS-CoV-2-infected patients have developed mild symptoms and have spontaneously recovered. The fundamental pathophysiology of severe viral pneumonia is severe ARDS. Some infected individuals develop various fatal complications from ARDS, including multiple organ failure.[9] Importantly, ARDS is the most common and serious complication of COVID-19. Multiple observational studies from Wuhan (Hubei province, China) have shown that the COVID-19 incidence of ARDS was 14—29%[9—12] and was even as high as 67% (35/52) among critically ill patients.[13,14] Another previous study has suggested that the mortality rate at 28 days of severe SARS-CoV-2 pneumonia was similar to the mortality rate of severe ARDS, which was near 50%.[15] In new retrospective case series studies from New York, the COVID-19 incidence of ARDS was 35.2% (299/850) and was even as high as 89.8% (212/236) among critically ill patients.[16] Moreover, the rapid increase in Western patients requiring MV (the important therapeutic tool for ARDS) was 23.6% (647/2741)[17] and was as high as 88.5% (1150/1300) among critically ill patients.[18] The median time from the onset of symptoms to ARDS was 9·0 days (range, 8·0—14·0 days).[12] Compared with parameters in survivors, non-survivors exhibited a significantly lower ratio of partial pressure of oxygen (PaO2) to FiO2 (PaO2/FiO2) and were more likely to develop ARDS (26 [81%] vs. 9 [45%]).[13] Meanwhile, the criteria for identifying severe cases also fulfill some of the core elements of the ARDS Berlin definition.[19]

ARDS is caused by widespread endothelial-barrier disruption and uncontrolled cytokine storms.[20] Excessive inflammatory reactions during a cytokine storm in the lungs have historically been regarded as the primary cause of fatal ARDS. Experimental models of acute lung injury (ALI) and human genome-wide association studies (GWAS) of ARDS have suggested a central pathophysiologic role of cytokine storms in ARDS.[20,21] However, there is currently no direct evidence for the involvement of pro-inflammatory cytokines or chemokines in lung pathology during COVID-19. Correlative evidence from patients with severe SARS or Middle East respiratory syndrome (MERS) suggests a role of hyper-inflammatory responses in human coronavirus pathogenesis.[22] Viral infections can trigger cytokine storms, which can cause endothelial damage/dysfunction and deregulation of coagulation, which consequently alter microvascular permeability to induce tissue edema and shock, ultimately resulting in ALI and ARDS.[22,23] SARS-CoV-2 spreads and invades through respiratory mucosa, triggers a series of immune responses, and induces cytokine storms *in vivo*, resulting in changes in immune components, such as peripheral blood leukocytes and lymphocytes.[24] Hence, cytokine storms likely represent one of the most important

mechanisms underlying the deterioration of critically ill COVID-19 patients.[25]

However, there is currently little clinical data available in regard to evidence for cytokine storms in COVID-19. The expression levels of interleukin-2 receptor (IL-2R) and IL-6 in the sera of critical care cases were found to be significantly higher ($P < 0{\cdot}05$) than those of severe cases of COVID-19.[26] In contrast, there were no statistically significant differences in serum tumor necrosis factor alpha (TNF-$\alpha$, IL-1, IL-8, or IL-10 between these two groups ($P > 0{\cdot}05$).[26] However, following initially high expression of Th1 cytokines (e.g., interleukin (IL)-1$\beta$, interferon (IFN)-$\gamma$, interferon-inducible protein 10 (IP10), and monocyte chemoattractant protein-1 (MCP1) Th2 cytokines (e.g., IL-4 and IL-10) may subsequently suppress inflammation during SARS-CoV-2 infection.[12,27] Furthermore, other observational COVID-19 studies have suggested that cytokine storms (comprised of IL-1$\beta$, IL-1RA, IL-7, and IL-8) may be associated with disease severity.[7,12,28] For example, higher concentrations of granulocyte colony-stimulating factor (GCSF), IP10, MCP1, MIP1A, and TNF-$\alpha$ were found in patients who required admission into an intensive care unit (ICU).[12,27] Taken together, we posit that cytokine storms may be associated with the severity of COVID-19. However, it is not feasible to conduct a prospective study of COVID-19 at present, and current evidence for cytokine storms in COVID-19 has been derived from small sample sizes. It is also important to consider that patients at different phases of inflammation when corresponding samples are collected will likely also contribute to increased variability of cytokine storm metrics. However, the close relationship between cytokine storms and ARDS strongly suggests that excessive and maladaptive cytokine release contributes to the unfavorable initiation, strengthening, and promotion of ARDS in COVID-19.

## ARDS: hyper-inflammatory subphenotypes confer greater risks

ARDS is a clinical feature of COVID-19 comprised of several different mechanisms and exhibits both biological and clinical heterogeneities. As such, there is likely no single form of treatment that will cure every patient with ARDS due to the heterogeneity in host responses.[29] Hyper-inflammatory subphenotypes of ARDS are associated with a higher severity of illness, worse clinical outcomes, and trajectories of persistently elevated biomarkers of host injury and inflammation in acute critically ill patients.[30] Subsets of critically ill patients have a higher risk of disease-related outcomes and/or differential responses to therapy.[31,32] Clinical characteristics and biomarkers of ARDS patients have demonstrated hypo-inflammatory and hyper-inflammatory subgroups.[33] Latent class analysis (LCA), highlighted by Lazarsfeld in the 1950s, can potentially identify these ARDS subgroups.[34] Calfee et al reported a hyper-inflammatory subgroup in ARDS, characterized by a higher prevalence of shock, greater inflammation and endothelial injury, and higher mortality, using LCA of data from the ARMA, Assessment of Low tidal Volume, and elevated End-expiratory volume to Obviate Lung Injury (ALVEOLI) and randomized controlled trials (RCTs).[33] Furthermore, a significant interaction was found between subphenotypes and responses to positive end-expiratory pressure (PEEP).[35] Additionally, hyper-inflammatory subphenotypes exhibited significantly different responses to randomly assigned PEEPs and fluid-management strategies.[36,37] Faced with higher inflammation and a greater risk of mortality, a previous study showed a potential heterogeneity of treatment effects in hyper-inflammatory subphenotypes of ARDS.[38–41] In the HARP-2 study, evidence of improved survival at both 28- and 90-days post-ARDS was uniquely found among patients with hyper-inflammatory subphenotypes of ARDS.[38]

Hyper-inflammatory subphenotypes comprise approximately one-third of all ARDS patients, who exhibit higher plasma levels of inflammatory biomarkers, higher vasopressin use, and lower serum bicarbonate.[33] This subgroup also exhibits higher mortality, higher severity of illness, and worse clinical outcomes, accompanied by trajectories of persistently elevated biomarkers of host injury and inflammation.[33] Biomarkers that represent distinct pathways are important in understanding the pathophysiology of ARDS and can be used to identify subgroups who may benefit from targeted therapies.[42] Eight plasma biomarkers have already been validated, including surfactant protein-D (SP-D), von Willebrand factor antigen, soluble intercellular adhesion molecule 1 (sICAM-1), IL-6 and IL-8, soluble tumor necrosis factor receptor 1 (TNFR 1), plasminogen activator inhibitor-1 (PAI-1), and protein C.[36] Previous studies have reported that the hyper-inflammatory ARDS subphenotype can be accurately identified using as few as three variables (IL-8, sTNFr1, and bicarbonate).[36,37] More recently, it has been shown that a selection of four biomarkers, IL-6, interferon gamma (IFN-$\gamma$), angiopoietin $^1/_2$, and PAI-1, can be used to cluster ARDS into two biological phenotypes with different mortality rates.[33,43] Our previous studies have shown that cytokines (e.g., IL-27 and IL-33) with proinflammatory effects are critical biomarkers in ARDS.[44,45] Additionally, we found that IL-33 has different inflammatory-promoting effects in ARDS with different inducements (i.e., pulmonary and non-pulmonary).[45] Moreover, in additional studies, we found that cytokines (e.g., IL-35 and IL-38) with protective effects were significantly elevated in ARDS patients.[46,47] The protective effects of these cytokines in ARDS were mediated through promoting regulatory T cells (Tregs) or downregulating Th17 differentiation.[46,47] Therefore, it is plausible to infer that hyper-inflammatory subphenotypes of ARDS include reactive protective effects via a subset of inflammatory factors. Regardless, taken together, these findings demonstrate that cytokine storms play an important role in distinguishing hyper-inflammatory subphenotypes of ARDS.

Some other biological indicators are also closely related to hyper-inflammatory subphenotypes of ARDS. As a novel indicator of inflammation, endocan is a promising biomarker to predict disease severity and mortality in patients with ARDS.[48] A decrease in the plasmatic endocan cleavage ratio (ECR) is associated with hyper-inflammatory phenotypes of ARDS. Also, a change in ECR $< -4{\cdot}5\%$ is the optimal cutoff value for the diagnosis of a hyper-inflammatory subphenotype (sensitivity of 0·86; specificity of 0·82).[49] Early vascular injury and disrupted alveolar-capillary barrier integrity can also reflect

differences in subtypes of inflammatory responses. Early-onset ARDS is associated with higher levels of the biomarkers sRAGE and Ang-2.[42] Subphenotypes with higher Ang-2 levels, which are characterized by higher inflammatory biomarkers and hypotension, may reflect more endothelial permeability and predilection for extravascular fluid accumulation that responds favorably to fluid restriction.[37] However, uncertainty remains regarding how diverse initial environmental injuries result in a sequence of events culminating in the clinical syndrome of ARDS, involving various molecular pathways along with a general imbalance between injurious and reparative mechanisms. Classification of patients with ARDS into hyper- and hypo-inflammatory subphenotypes using plasma biomarkers may facilitate more effective targeted therapies.[30] Therefore, further elucidation of phenotypes and identifying treatable traits represent the future of personalized medicine for ARDS.

In COVID-19, there is also suggestive evidence of hyper-inflammatory subphenotypes of ARDS. Pathological evidence of COVID-19 associated with ARDS from autopsies has shown differentiated histological changes of ARDS, including desquamation of pneumocytes and hyaline membrane formation (indicating ARDS) or pulmonary edema with hyaline membrane formation (suggestive of early-phase ARDS).[50,51] Additionally, adenocarcinomas from lung lobectomies at the time of surgery represent another pathological feature of COVID-19. Pathological examinations have also revealed that edema and proteinaceous exudate, without hyaline membranes, likely represent an early phase of the lung pathology of COVID-19 pneumonia.[52] In COVID-19 patients who died from ARDS, flow cytometric analysis of peripheral blood showed overactivation of CD4 and CD8 T cells and increased concentrations of highly proinflammatory $CCR6^{+}$ Th17 in CD4 T cells.[50] CD4+ and CD8+ T cells were also significantly reduced in the spleen and lymph nodes.[51] This suggests severe immune injury in these patients. Thus, nodes of onset times may also affect host responsiveness of ARDS in COVID-19. Therefore, identification of hyper-inflammatory subphenotypes of ARDS and focusing on patients at risk for ARDS (ARFA) may improve the management and treatment of severe and critical cases of COVID-19.

## MV: more timely interventions exhibit greater efficacies

Clinical evidence helps to progress patient-level and population-level decision making. Therefore, we need to build upon prior experience and identify similarities versus differences among COVID-19 patients.[53] From the evidence that we were able to retrieve, we found that 61·5—62·0% of critically ill patients died at 28 days.[13,14] In the same way, a newly prospective cohort study among 5279 people with COVID-19 showed that 67.2% (665/990) of patient with critical illness died or went to hospice care.[17] Additionally, about 16·2—26·1% of consecutive hospitalized patients were transferred to the ICU.[11,54] The median duration from admission to ICU to death was 7 days (interquartile range [IQR], 3—11 days) for non-survivors.[13] Although this research sample was small, this is still an astonishing number. Additionally, another study reported that the cumulative risk in severe COVID-19 cases was 20·6%.[54] Even for the previous incident in Singapore, which was considered to be a less virulent strain, 33% of SARS-CoV-2 infections required supplemental oxygen.[55] Furthermore, 55% of patients developed dyspnea, for which the median duration from disease onset to dyspnea was 8 days (interquartile range (IQR), 5·0—13·0 days), while the median time from the onset of symptoms to ICU admission was 10·5 days (IQR, 8·0—17·0 days).[12] Moreover, if a COVID-19 patient progresses from a severe to a critical condition, the situation is likely exacerbated.

Invasive or noninvasive MV was required in 71% of critically ill patients.[14] MV was initiated in more patients with severe disease (non-invasive ventilation, 32·4%; invasive ventilation, 14·5%).[54] Additionally, 63·5% of patients were treated with high-flow nasal cannulae (HFNCs).[13] In influenza, a small cohort of patients showed that HFNCs were associated with avoidance of intubation in 45% of patients.[56] However, this finding was not recapitulated in COVID-19 cases. Studies have shown that 8·3—71% of patients underwent invasive ventilation, while 11·5% of patients underwent prone-position ventilation.[13,54] However, 81% of patients requiring MV had died by 28 days.[13] We observed such a phenomenon in the clinical treatment of critically ill patients with COVID-19, such that if non-invasive ventilation (NIV) or HFNCs could not achieve a satisfactory PaO2/FiO2 (>150 mmHg) and improve respiratory distress within a short time frame (1—2 h), tracheal intubation and MV needed to be performed as early as possible.[3] During the time from the onset of symptoms to MV, which was reported to be 10·5 days (7·0—14·0 days),[12] if patient was identified as having a hyper-inflammatory subphenotype of COVID-19 and given targeted therapy, this approach would be expected to ameliorate the probability of the patient progressing to a severe or critical condition. Therefore, the key treatment for ARDS, a key factor in COVID-19 deterioration, is closely related to the identification and monitoring of hyper-inflammatory subphenotypes.

## Hyper-inflammatory subphenotypes of COVID-19: earlier recognition enables earlier interventions for high-risk patients

It is difficult to distinguish the hyper/hypo inflammatory subphenotypes of COVID-19 since there is currently little data on this phenomenon. C-reactive protein (CRP) levels of most patients are above the normal range.[9,24] Additionally, hypersensitive CRP (hs-CRP) has also been found to be increased.[26] CRP (47·6 vs 28·7, $P < 0.001$) levels in severe cases, compared with those in non-severe cases, may represent more prominent inflammation.[57] Furthermore, CRP within lung injury prediction scores (LIPS) might improve the accuracy of predicting ARDS in high-risk ICU patients.[58] Laboratory features of COVID-19 include lymphopenia with depletion of CD4 and CD8 lymphocytes.[11] The overactivation of T cells, manifested by an increase in Th17 cells and high cytotoxicity of CD8 T cells, was confirmed in deaths resulting from COVID-19-related ARDS.[50] In malaria-associated (MA) ALI/ARDS, $CD8^{+}$T cells

participate in the production of IFN-γ and drive lung injury.[59,60] In addition, the ratio of Th17/Treg cells can be regarded as a risk indicator in early ARDS.[61] Angiotensin-converting enzyme 2 (ACE2) may have dual opposing effects on SARS-induced lung injury, including initially acting as a receptor for the infection of SARS coronavirus and subsequently downregulating ACE2, promoting lung injury.[57,62] The angiotensin-II level in plasma samples from 2019-nCoV infected patients was markedly elevated and linearly associated with viral load and lung injury.[63] Furthermore, some cytokines may be associated with disease severity with infection of SARS-CoV-2. IL-6, IL-8, and IFN-γ, identified via a clustering approach in ARDS,[33,36,37,43] were reported to be increased in COVID-19.[7,12,27,28] IL-1β, a cytokine closely related to inflammatory immunity of ARDS, has also been confirmed to have abnormally high expression in COVID-19.[12,27] The IL-10-1082 G/G genotype was associated with lower mortality of ARDS in a Chinese population.[64] Although IL-10 levels did not predict the development of ARDS,[65] IL-10 could initiate suppression of inflammation in COVID-19.[12,27] Therefore, these inflammation-related indicators have the potential to identify hyper-inflammatory subphenotypes in COVID-19, especially in patients with high risk of ARDS. As such, it is worthwhile to speculate which specific indicators may be most useful in early detection of COVID-19 patients at risk of hyper-inflammatory ARDS.

The use of glucocorticoids in the treatment of COVID-19 is controversial. Specifically, 8·6—58% of patients received glucocorticoid therapy,[11,13,54,66] among whom there was a greater percentage with severe disease than with non-severe disease (44.5% vs. 13.7%, respectively).[54] Prior experience with viral pneumonia, including influenza and MERS coronavirus, suggests that steroids may contribute to higher mortality, increased viral replication with longer periods of viral clearance, and more superinfections (including invasive pulmonary aspergillosis, as previously reported in the Wuhan cohort).[53,67,68] However, COVID-19 patients exhibit respiratory deterioration by 7—9 days after onset, which is double the 3—5-day period documented for influenza, suggesting that such deterioration is not related to the viral load. This interpretation may justify the high rate of use of steroids in recent Wuhan reports.[13,53] Although corticosteroid treatment is a double-edged sword, short treatment courses of corticosteroids at low-to-moderate doses should be of benefit for critically ill COVID-19 patients.[69] Early administration of glucocorticoids (dexamethasone) has been shown to reduce the duration of MV and the overall mortality in patients with established moderate-to-severe ARDS.[70] According to the pathological findings of pulmonary edema and hyaline membrane formation, timely and appropriate use of corticosteroids together with ventilator support should be considered for severe-condition patients to prevent ARDS development.[50] Therefore, proper timing of glucocorticoids may be a critical factor in the treatment of COVID-19 patients, and proper dosing and treatment durations are also important considerations (e.g., methylprednisolone, 40 mg, q12 h, 5 days)".[3] When the potential risk of hyper-inflammatory subphenotypes can be distinguished, the use of glucocorticoids may reduce the chance of early cytokine storms.

In addition to the continued attention on the anti-inflammatory effects of glucocorticoids, traditional Chinese medicines and immunotherapies for cytokine storms have also been investigated. Xuebijing injection (XBJ) improves organ function and decreases both MV duration and ICU duration in ARDS patients.[71,72] A potential protective effect of XBJ has also been attributed to downregulation of inflammatory mediators, reduction in neutrophil infiltration, and upregulation of IL-10 (ChiCTR-TRC-14004628).[72] Furthermore, XBJ has been recommended for severe and critical illness.[3] As a clinically approved immune modulator, chloroquine shows inhibitory effects against SARS-CoV-2 (EC50 = 1·13 μM in Vero E6 cells) (ChiCTR2000029609).[73] Tocilizumab (TCZ), an anti-IL-6 receptor antibody, represents another promising drug candidate. Excessive or sustained production of IL-6 is involved in various diseases. TCZ provides control of severe cytokine-release syndrome (CRS) induced by CAR T cells without being directly T-cell toxic.[74] Furthermore, CRS was registered in the multicenter clinical RCT study of effectiveness and safety in COVID-19 (ChiCTR2000029765, ChiCTR2000030442) and has been included in treatment guidelines (draft).[3] However, it is unclear whether CRS would represent an efficacious treatment for COVID-19 cytokine storms since the effects of IL-1β and TNF-α are stronger and occur earlier in the development of ARDS. Similarly, it is unclear how TCZ-mediated antagonism of IL-6 would ultimately affect COVID-19 cytokine storms. In addition, IL-10 also has therapeutic potential. Studies have shown that recombinant IL-10 (human or mouse) can reduce ventilator-induced lung injury (VILI) and transfusion-related acute lung injury (TRALI) via regulating inflammatory responses in lung tissue, improving lung tissue oxygenation, and inhibiting oxidative stress.[75] In the future, IL-10 will also face similar questions and concerns to those raised for TCZ. In terms of molecular therapy, TMPRSS2 (transmembrane protease serine 2) is a host-cell factor that is critical for the spread of several clinically relevant viruses, including influenza-A viruses and coronaviruses.[76] SARS-CoV-2 uses the SARS-CoV receptor, ACE2, for entry and the serine protease, TMPRSS2, for S-protein priming. Therefore, TMPRSS2 inhibitors that are approved for clinical use block viral entry and might constitute a treatment option for COVID-19 patients.[77]

Taken together, we recommend judicious and limited use of various anti-inflammatory treatments against cytokine storms in COVID-19 patients. Moreover, further elucidation of cytokine storms in COVID-19 is required, upon which we may be able to distinguish the severity and progression of ARDS in COVID-19—via identification of patients with hyper-inflammatory subphenotypes—and apply targeted and early treatments. This prescribed strategy epitomizes individualized diagnostics and treatments for COVID-19 patients.

## Conclusion

Cytokine storms induced by viral invasion, acute organ injury related to direct viral effects, and subsequent hypoxia and shock may be associated with mortality in COVID-19 patients. ARDS caused by cytokine storms represents an

important part of COVID-19 cases progressing to severe and critical conditions. Moreover, distinguishing between hyper- and hypo-inflammatory subphenotypes of ARDS may improve the quality of monitoring and treatment of COVID-19 patients and reduce the incidence of critical illness and mortality.

## Author Contributions

SH. L and FX wrote this manuscript. FX revised this manuscript. FC. Z and DX. Z participated in discussion about the structure of the manuscript, YS. Z, SH. L, and FX searched and collected the bibliography.

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## Conflict of Interest

The authors declare that there are no competing interests regarding the publication of this paper.

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