The cytokine storm and COVID-19

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Abstract
Coronavirus disease 2019 (COVID-19), which began in Wuhan, China, in December 2019, has caused a large global pandemic and poses a serious threat to public health. More than 4 million cases of COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been confirmed as of 11 May 2020. SARS-CoV-2 is a highly pathogenic and transmissible coronavirus that primarily spreads through respiratory droplets and close contact. A growing body of clinical data suggests that a cytokine storm is associated with COVID-19 severity and is also a crucial cause of death from COVID-19. In the absence of antivirals and vaccines for COVID-19, there is an urgent need to understand the cytokine storm in COVID-19. Here, we have reviewed the current understanding of the features of SARS-CoV-2 and the pathological features, pathophysiological mechanisms, and treatments of the cytokine storm induced by COVID-19. In addition, we suggest that the identification and treatment of the cytokine storm are important components for rescuing patients with severe COVID-19.

Keywords
COVID-19, cytokine storm, literature review, SARS-CoV-2

1 | INTRODUCTION

An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world.1 The initial symptoms of COVID-19 mainly include fever, cough, myalgia, fatigue, or dyspnea. In the later stages of the disease, dyspnea may occur and gradually develop into acute respiratory distress syndrome (ARDS) or multiple organ failure.2 It has been reported that a cytokine storm is associated with the deterioration of many infectious diseases, including SARS (severe acute respiratory syndrome)3 and Middle East respiratory syndrome (MERS).4 The cytokine storm caused by COVID-19 has been suggested to be associated with COVID-19 severity.25 However, there is currently a limited understanding of the cytokine storm in severe COVID-19. Therefore, here, we have discussed the current findings and treatment strategies for the cytokine storm in severe COVID-19.

2 | FEATURES OF SARS-CoV-2

SARS-CoV-2 is the newest coronavirus known to infect humans. SARS-CoV, MERS-CoV, and SARS-CoV-2 cause severe pneumonia, while other human coronaviruses, including 229E, OC43, HKU1, and NL63, cause only the common cold.6 SARS-CoV-2 belongs to the genus Betacoronavirus, which also includes SARS-CoV and MERS-CoV, both of which have caused SARS and MERS, respectively.7 SARS-CoV-2, SARS-CoV, and MERS-CoV have similarities and differences. Genetic sequence analysis has revealed that SARS-CoV-2 shares 79% sequence identity with SARS-CoV and 50% identity with MERS-CoV.8 The genomes of SARS-CoV-2 and the bat coronavirus RaTG13 are 96.2% homologous.9 As of 11 May 2020, COVID-19 has resulted in 278 892 deaths and 4 006 257 cases, with an approximate case fatality rate of 7.0%.10 SARS-CoV and MERS-CoV had a case fatality rate of 9.6% (774/8096) and 34.4% (858/2494), respectively.11 The reproduction number ($R_0$) of COVID-19 is thought to be between 2 and 2.5,12 which is slightly higher than of SARS (1.71.9) and MERS (<1).13 COVID-19 appears to be more infectious than SARS and MERS, but maybe less severe. The origins of SARS-CoV, MERS-CoV, and SARS-CoV-2 are considered to be zoonotic. Both SARS-CoV and MERS-CoV originated in bats and spread directly to humans from marked palm civets and dromedary camels, respectively.14 However, the origin of SARS-CoV-2 remains unclear. SARS-CoV-2 has been reported to be transmitted between humans through direct contact, aerosol droplets, the fecal-oral route, and
intermediate viruses from symptomatic and asymptomatic patients. SARS-CoV and MERS-CoV are also thought to spread from infected to noninfected individuals through direct or indirect contact. The clinical symptoms of SARS, MERS, and COVID-19 range from mild respiratory diseases to severe acute respiratory diseases. Patients with mild cases of SARS, MERS, and COVID-19 primarily exhibit fever, cough, and dyspnea. ARDS is a common severe complication of SARS and MERS. Among 1099 inpatients with COVID-19, 15.6% of the patients with severe pneumonia were reported to have ARDS. Feng et al proposed that SARS-CoV-2 infection triggers an excessive immune response known as a cytokine storm in cases of severe COVID-19. A cytokine storm is a potentially fatal immune disease characterized by the high-level activation of immune cells and excessive production of massive inflammatory cytokines and chemical mediators. It is considered to be the main cause of disease severity and death in patients with COVID-19, and is related to high levels of circulating cytokines, severe lymphopenia, thrombosis, and massive mononuclear cell infiltration in multiple organs.

It has been found that SARS-CoV-2 genomes from different parts of the world have evolved in different clusters. Forster et al reported there to be at least three central variants of SARS-CoV-2 globally, named A, B, and C. The A type is the most similar to the bat coronavirus and is mainly found in the United States and Australia. The B type is more common in East Asia and has evolved through several mutations. The C type is primarily found in Europe. Different viral isolates exhibit significant differences in pathogenicity and viral load. Notably, given the diverse clinical symptoms of patients, it will be challenging to establish a genotype-phenotype relationship. With new sequences being uploaded to the global initiative on sharing all influenza data every day, new results may be produced as more data become available. The emergence of variants may add to the challenges of vaccine development.

3 | LUNG PATHOLOGY OF COVID-19

Pathological alterations in patients with COVID-19 include pulmonary edema, diffuse alveolar injury with the formation of hyaline membranes, the presence of reactive type II pneumocyte hyperplasia, proteinaceous aggregates, fibrinous exudates, monocytes and macrophages within alveolar spaces, and inflammatory infiltration of interstitial mononuclear cells. Electron microscopy has revealed the presence of SARS-CoV-2 virus particles in bronchial and alveolar type II epithelial cells, but not in other tissues. Therefore, although a polymerase chain reaction test may be negative from blood or throat swabs, SARS-CoV-2 viral inclusions may be detected in the lungs. Immunohistochemical staining indicated that CD68+ macrophages, CD20+B cells, and CD8+T cells infiltrated the alveolar cavity and alveoli. The levels of CD8+T cells may be slightly higher than that of CD4+T cells within the alveolar septa. These pathological features are very similar to those of SARS-CoV and MERS-CoV infections, indicating that effective treatments for SARS and MERS may be suitable for COVID-19. Excessive local release of cytokines is considered to be the determinant of pathological alterations and the clinical manifestation of ARDS. Overall, the primary pathological manifestations in the lung tissue are viral cytopathic-like changes, infiltration of inflammatory cells, and the presence of viral particles. Thus, severe lung injury in patients with COVID-19 is considered as the result of both direct viral infection and immune overactivation.

4 | MECHANISMS OF THE CYTOKINE STORM IN COVID-19

Cellular entry of SARS-CoV-2 depends on the binding of S proteins covering the surface of the virion to the cellular ACE2 receptor and on S protein priming by TMPRSS2, a host membrane serine protease. After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak interferon (IFN) response. The proinflammatory immune responses of pathogenic Th1 cells and intermediate CD14+CD16+ monocytes are mediated by membrane-bound immune receptors and downstream signaling pathways. This is followed by the infiltration of macrophages and neutrophils into the lung tissue, which results in a cytokine storm.

Particularly, SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF further activates CD14+CD16+ monocytes to produce large quantities of IL-6, tumor necrosis factor-α (TNF-α), and other cytokines. Membrane-bound immune receptors (eg, Fc and Toll-like receptors) may contribute to an imbalanced inflammatory response, and weak IFN-γ induction may be an important amplifier of cytokine production. Neutrophil extracellular traps, the extracellular nets released by neutrophils, may contribute to cytokine release. The cytokine storm in COVID-19 is characterized by a high expression of IL-6 and TNF-α. Hirano and Murakami proposed a potential mechanism of the cytokine storm caused by the angiotensin 2 (AngII) pathway. SARS-CoV-2 activates nuclear factor-κB (NF-κB) via pattern-recognition receptors. It occupies ACE2 on the cell surface, resulting in a reduction in ACE2 expression, followed by an increase in AngII. In addition to activating NF-κB, the AngII-angiotensin receptor type 1 axis can also induce TNF-α and the soluble form of IL-6Ra (sIL-6Ra) via disintegrin and metalloprotease 17 (ADAM17). IL-6 binds to sIL-6R through gp130 to form the IL-6-sIL-6R complex, which can activate signal transducer and activator of transcription 3 (STAT3) in nonimmune cells. Both NF-κB and STAT3 are capable of activating the IL-6 amplifier to induce various proinflammatory cytokines and chemokines, including vascular endothelial growth factor, monocyte chemotactrant protein 1 (MCP-1), IL-8, and IL-6. IL-6 not only binds to sIL-6R to act in cis-signaling but can also bind to the membrane-bound IL-6 receptor (mIL-6R) through gp130 to act in trans-signaling. The latter can lead to pleiotropic effects on acquired and innate immune cells, resulting in cytokine storms. Collectively, the impaired acquired immune responses and uncontrolled inflammatory innate responses to SARS-CoV-2 may cause cytokine storms.
Earlier studies have indicated that the levels of IL-1β, IL-6, IL-8, IL-12, inducible protein 10 (IP-10), MCP-1, and IFN-γ are increased during SARS-CoV infection. Low levels of the Th2 cytokine IL-4 were also observed in patients with SARS. MERS-CoV infection was also reported to induce increased concentrations of IL-15, IL-17, IFN-γ, and TNF-α. Some studies have found that patients with severe COVID-19 exhibit higher levels of IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF-α, macrophage inflammatory protein 1 alpha, and granulocyte-CSF than patients with mild and moderate infections. The fluctuations of these cytokines (eg, IL-6, IL-10, and TNF-α) are small or within the normal range. In addition, increased levels of proinflammatory cytokines (eg, IL-4 and IFN-γ) are also observed in patients with COVID-19. Liu et al found significant and sustained decreases in lymphocyte counts (CD4⁺ cells and CD8⁺ cells), especially CD8⁺ T cells, but increases in neutrophil counts in the patients with severe COVID-19 compared to the mild patients. T cell loss may lead to increased inflammatory responses, while T cell restoration may reduce inflammatory responses during SARS-CoV-2 infection. Thus, the neutrophil-to-lymphocyte ratio (NLR) may be predictive of COVID-19 outcome. Interestingly, Ong et al revealed that the levels of most cytokines, except IL-1, peaked after respiratory function nadir, indicating that cytokine expression might not be the primary cause of impaired respiratory function in patients with COVID-19. Dynamic cytokine storms and T cell lymphopenia are associated with COVID-19 severity. These findings indicate that clinicians should be able to identify patients at risk of developing severe COVID-19 as early as possible by monitoring dynamic cytokine storms and NLR.

Changes in the major cytokines induced by the three coronaviruses discussed here are shown in Table 1, and cytokine secretion patterns based on COVID-19 severity are shown in Table 2.

**TABLE 1** The major cytokines related to cytokine storms during coronaviruses infection

| cytokines        | SARS-CoV | MERS-CoV | SARS-CoV-2 |
|------------------|----------|----------|------------|
| IL-1β            | ↑        | ↑        | ↑          |
| IL-6             | ↑        | ↑        | ↑          |
| IL-8             | ↑        | ↑        | ↑          |
| IL-12            | ↑        | ↑        | ↑          |
| IP-10            | ↑        | ↑        | ↑          |
| MCP-1            | ↑        | ↑        | ↑          |
| IFN-γ            | ↑        | ↑        | ↑          |
| IL-4             | ↑        | ↑        | ↑          |

Note: ↑ = increased. ↓ = decreased.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IFN-γ, interferon γ; IL, interleukin; IP-10, inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MERS-CoV, Middle East respiratory syndrome coronavirus; MIP1A, macrophage inflammatory protein 1 alpha; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor α.
TABLE 2 Patterns of symptoms, cytokine secretion, and T cell lymphopenia related to the severity of COVID-19.62-64

| State of COVID-19 | Uninfected individual | Mild and moderate COVID-19 | Severe COVID-19 |
|------------------|-----------------------|---------------------------|-----------------|
| Symptoms         | No symptoms           | Fever, myalgia, fatigue, or dyspnea | Fever, myalgia, fatigue, dyspnea, ARDS, or MOF |
| Cytokine patterns| No cytokines          | ↑IL-6, IL-10, and TNF-α | ↑↑IL-6, IL-10, TNF-α, IL-2, and MCP-1 |
| T cell lymphopenia| No changes            | ↓Lymphocytes (CD4+T and CD8+T cells) | ↓↓Lymphocytes (CD4+ T cells, especially CD8+ T cells) |

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MOF, multiple organ failure; TNF-α, tumor necrosis factor-α.

severe side effects of CQ, HCQ may be a better therapeutic option. CQ and HCQ are able to reduce CD154 expression in T cells65 and suppress the release of IL-6 and TNF.53 A test of the pharmacological activities of CQ and HCQ in SARS-CoV-2-infected Vero cells revealed that low doses of HCQ might mitigate cytokine storm in patients with severe COVID-19.54 A small French trial showed significant reductions in viral load and the duration of viral infection for COVID-19 patients who received 600 mg/day HCQ for 10 days, and these effects could be enhanced by cotreatment with azithromycin.55 However, a meta-analysis of clinical trials indicated no clinical benefits of HCQ treatment in patients with COVID-19.56 In fact, HCQ might actually do more harm than good given its side effects, which include retinopathy, cardiomyopathy, neuromyopathy, and myopathy.57 Some clinical trials have suggested that taking high doses of HCQ or CQ may cause arrhythmia.58,59 The role and risks of HCQ and CQ in the treatment of COVID-19 still need more data to further verify.

6.3 | Tocilizumab

Tocilizumab (TCZ), an IL-6 receptor (IL-6R) antagonist, can inhibit cytokine storms by blocking the IL-6 signal transduction pathway.60 Currently, a small-sample clinical trial in China (clinical trial registration ID: ChiCTR2000029765) has found TCZ to be effective in critically ill patients with COVID-19.61 Xu et al.62 found that out of 21 patients with severe COVID-19, 90% recovered after a few days of treatment with TCZ. A retrospective case-control study of COVID-19 patients with ARDS revealed that TCZ might improve survival outcomes.63 However, the risks associated with TCZ (eg, severe infections, thrombocytopenia, neutropenia, and liver damage) should also be noted.64 It is unclear whether there are different effects between IL-6 antagonists (siltuximab) and IL-6R antagonists (TCZ). Siltuximab binds to sIL-6 and inhibits only cis- and trans-signaling. TCZ binds to both mIL-6R and sIL-6R and inhibits both cis- and trans-signaling and trans-presentation.60,65 Of note, IL-6 inhibitors are not able to bind to IL-6 produced by viruses such as HIV and human herpesvirus-8.65 Currently, the application of TCZ for COVID-19 treatment is under study. The three drugs mentioned above (corticosteroids, HCQ, and TCZ) are immunosuppressants. Owing to the overall damage to the immune system caused by autoimmune diseases and the iatrogenic effects of immunosuppressants, the risk of infection in patients with autoimmune diseases will be increased compared to the general population. Currently, rheumatology societies66-69 recommend the use of immunosuppressive drugs (except glucocorticoids) to be suspended in patients with COVID-19.

6.4 | Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have a wide range of immune regulatory functions and can inhibit the abnormal activation of T lymphocytes and macrophages and the secretion of proinflammatory cytokines.70 MSC therapy was found to significantly reduce the mortality of patients with H7N9-induced ARDS and had no harmful side effects.71 A clinical trial of MSC therapy revealed that MSCs were able to rapidly and significantly improve the clinical symptoms of COVID-19 without any observed adverse effects.72 Although the side effects of MSC treatment are rarely reported, the safety and effectiveness of this treatment require further investigation.

6.5 | Other therapies

Anakinra, an IL-1 receptor antagonist that blocks the activity of proinflammatory cytokines IL-1α and IL-1β, has been reported to improve the respiratory function and increase the survival rate of patients with COVID-19.73 IL-1 receptor antagonists increase the risk of bacterial infections, but this is extremely rare for anakinra.74 Janus kinase (JAK) inhibitors can inhibit inflammatory cytokines and reduce the ability of viruses to infect cells.75 A small nonrandomized study reported that patients treated with JAK inhibitors exhibited improved clinical symptoms and respiratory parameters.75 However, JAK inhibitors can also inhibit IFN-α production, which helps us to fight viruses.76 Intravenous immunoglobulin (IVIG) can exert various immunomodulatory effects by blocking Fc receptors, which are related to the severity of the inflammatory state.77 IVIG has been reportedly used to treat patients with COVID-19.78 Given its uncertain effectiveness and the risk of severe lung injury and thrombosis,79 IVIG treatment requires further investigation. Furthermore, convalescent plasma therapy containing coronavirus-specific antibodies from recovered patients can be directly used to obtain artificial passive immunity. This approach has demonstrated promising results in the treatment of SARS and influenza.80,81 However, a Cochrane systematic review revealed weak evidence on the effectiveness and safety of this therapy for patients with COVID-19.82 Some individuals experienced moderate fever or anaphylactic shock after receiving...
CONCLUSION

The cytokine storm leads to deleterious clinical manifestations or even acute mortality in critically ill patients with COVID-19. Impaired acquired immune responses and uncontrolled inflammatory innate responses may be associated with the mechanism of the cytokine storm in COVID-19. Early control of the cytokine storm through therapies, such as immunomodulators and cytokine antagonists, is essential to improve the survival rate of patients with COVID-19. Although many research articles are published each month, the majority of the existing literature about COVID-19 comes from descriptive works. In addition, high-quality evidence will be necessary to understand and treat the cytokine storm of COVID-19.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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| Treatments | Mechanisms | Advantages | Disadvantages |
|------------|------------|------------|---------------|
| Corticosteroids | 1. Inhibiting the inflammatory response | 1. Reducing hospital stay | 1. Impaired clearance of viral RNA |
| | 2. Suppressing the immune response | 2. Reducing mortality | 2. Adverse events (secondary infection, psychosis, diabetes, and avascular necrosis) |
| HCQ and CQ | 1. Reducing CD154 expression in T cells | 1. Reducing viral load | 1. Damage to the heart (arrhythmias) |
| | 2. Suppressing the release of IL-6 and TNF | 2. Reducing the duration of viral infection | 2. Other side effects (retinopathy, cardiomyopathy, neuromyopathy, and myopathy) |
| TCZ | 1. Blocking the IL-6 signal transduction pathway | 1. Improving survival outcome | 1. Adverse events (severe infections, thrombocytopenia, neutropenia, and liver damage) |
| MSCs | 1. Inhibiting the activation of T lymphocytes and macrophages | 1. Reducing mortality | 1. Unclear |
| | 2. Inhibiting the secretion of proinflammatory cytokines | 2. Improving clinical symptoms | |
| IL-1 receptor antagonist | 1. Blocking the activity of proinflammatory cytokines IL-1α and IL-1β | 1. Improving respiratory function | 1. Increasing the risk of bacterial infections |
| | | 2. Increasing survival rate | |
| JAK inhibitors | 1. Inhibiting inflammatory cytokines | 1. Improving clinical symptoms | 1. Blocking the production of beneficial cytokine (IFN-α) |
| | 2. Reducing the ability of infected lung cells of the virus | 2. Improving respiratory parameters | |
| IVIG | 1. Blocking Fc receptors | 1. Exerting various immunomodulatory effects | 1. Severe lung injury |
| | | | 2. Thrombosis |
| Convalescent plasma therapy | 1. Transfusion of plasma with antibodies specific | 1. Obtain artificial passive immunity | 1. Moderate fever |
| | | | 2. Anaphylactic shock |

Abbreviations: COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; IFN-α, interferon α; IL-1, interleukin-1; IVIG, intravenous immunoglobulin; JAK, Janus kinase; MSCs, mesenchymal stem cells; TCZ, tocilizumab; TNF, tumor necrosis factor.
REFERENCES

1. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Potential for global spread of a novel coronavirus from China. J Travel Med. 2020;27(2):taa011.

2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

3. Huang J, Su JI, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. J Med Virol. 2005;75(2):185-194.

4. Zhou J, Chu H, Li C, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. J Infect Dis. 2014;209(9):1331-1342.

5. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.

6. Corman VM, Muth D, Niemeyer D, Drosten C, et al. Chapter eight: coverage and therapeutic options. Lancet. 2020;17:181-192.

7. World Health Organization. Coronavirus disease (COVID-19) situation report, 112. 2020.

8. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and hosts of sources of endemic human coronaviruses. Adv Virus Res. 2018;100:163-188.

9. Coronavirus Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536-544.

10. International Committee on Taxonomy of Viruses. Coronavirus database and metadata. 2020.

11. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and hosts of sources of endemic human coronaviruses. Adv Virus Res. 2018;100:163-188.

12. World Health Organization (WHO). Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf?sfvrsn=2. Accessed June 5, 2020.

13. Rossetto N, Vicentone G, Ergonou O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect. 2020;26:729-734.

14. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. J Med Virol. 2005;75(2):185-194.

15. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. J Clin Med. 2020;9(4):1225.

16. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronavirus—drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-347.

17. Chandrapanavar R, Perlmutter J. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-539.

18. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(19):1708-1720.

19. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severity: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201:1380-1388.

20. Teijaro JR, Walsh KB, Rice S, Rosen H, Oldstone MB. Mapping the innate signaling cascade essential for cytokine storm during influenza virus infection. Proc Natl Acad Sci USA. 2014;111(10):3799-3804.

21. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20:355-362.

22. Jia Y, Shen G, Zhang Y, et al. Analysis of the mutation dynamics of SARS-CoV-2 reveals the spread history and emergence of RBD mutant with lower ACE2 binding affinity. bioRxiv. https://doi.org/10.1101/2020.04.09.034942.

23. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci USA. 2020;117(17):9241-9243.

24. Yao H, Lu X, Chen Q, et al. Patient-derived mutations impact pathogenicity of SARS-CoV-2. medRxiv. https://doi.org/10.1101/2020.04.14.20060160.

25. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-422.

26. Yao XY, He ZC, Li TY, et al. Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient. Cell Res. 2020;30:541-543.

27. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020;395(10235):1517-1520.

28. Zhang H, Zhou P, Wei Y, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med. 2020;172(9):629-632.

29. Akzur AK, Akdis M, Akzur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Alergy. 2020;75(7):1564-1581.

30. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol. 2001;194(3):282-289.

31. Ngl DL, Al Hosani F, Keating MK, et al. Clinopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Ann J Pathol. 2016;186(3):652-658.

32. Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med. 2005;33(1):1-6.

33. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.

34. Hussain JP. Cellular and molecular pathways of COVID-19 and potential points of therapeutic intervention. OSF Preprints. 19 May 2020;Web.

35. Haining W, Xiaoling X, Yonggang Z, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. BioRxiv. https://doi.org/10.1101/2020.02.12.945576.

36. Zuo Y, Avalarthi S, Shi H, et al. Neutrophil extracellular traps in severe and moderate coronavirus disease 2019. J Intern Med. 2020;287(4):595-603.

37. Azkur AK, Akdis M, Akzur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy. 2020;75(7):1564-1581.

38. Eguchi S, Kawai T, Scalia R, Rizzo V. Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology. Hypertension. 2018;71(5):804-810.

39. Murakami M, Kamimura D, Hirano T. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. Immunity. 2019;50(4):812-821.

40. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-474.

41. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136(1):95-103.

42. Mahallawi WH, Khabour OF, Zhang Q, Makdhamoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine. 2018;104:8-13.

43. 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):2620-2629.

44. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.
64. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational use of tocilizumab in the treatment of COVID-19 pneumonia. J Infect Dis. 2020;211(1):80-88.

65. Wu S, Chen R, Chang C-B, Hsu J-M, et al. Hydroxychloroquine inhibits CD154 expression in CD4 T lymphocytes of systemic lupus erythematosus through NFAT, but not STAT5, signaling. Arthritis Res Ther. 2017;19(1):183.

66. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722-727.

67. Gaudart J, Liesenfeld O, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.

68. Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antibiotic Chemother. 2015;70(6):1608-1621.

69. Borba MGS, de Almeida Val F, Sampaio VS, et al. Chloroquine diprophosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 study). medRxiv. 2020. https://doi.org/10.1101/2020.04.14.20065276.

70. Lane JCE, Weaver J, Kostka K, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv. https://doi.org/10.1101/2020.04.08.20045551.

71. Zhang C, Wu Z, Li J-W, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;55(1):105949.

72. Chinese Clinical Trial Registry. A multicenter, randomized controlled trial for baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect. 2020;81(2):318-356.

73. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10233):e30-e31.

74. Liu Q, Zhou Y-H, Yang Z-Q. The cytokine storm of severe influenza and development of immunomodulatory therapy. Mol Cell Med. 2016;13(1):3-10.

75. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.

76. Alijotas-Reig J, Esteve-Valverde E, Belizna C, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review. Autoimmun Rev. 2020;19:102569.

77. Mair-Jenkins J, Saavedra-Campos M, Baille JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211(1):80-90.

78. Kuk E, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52(4):447-456.

79. Vakil SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Syst Rev. 2020;5(5):D013600.