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.

Clinical Immunology 222 (2021) 108615

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

An enlightening role for cytokine storm in coronavirus infection

Zhongyi Zhao [1], Yinhao Wei, Chuanmin Tao [*]

Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

ARTICLE INFO

Keywords:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Inflammatory cytokines
Coronavirus disease 2019 (COVID-19)
Multiple organ dysfunctions
Cytokine storm

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Wuhan, China has dispersed rapidly worldwide. Although most patients present with mild fever, cough with varying pulmonary shadows, a significant portion still develops severe respiratory dysfunction. And these severe cases are often associated with manifestations outside the respiratory tract. Currently, it is not difficult to find inflammatory cytokines upregulated in the blood of infected patients. However, some complications in addition to respiratory system with the coronavirus disease 2019 (COVID-19) are impossible to explain or cannot be attributed to virus itself. Thus excessive cytokines and their potentially fatal adverse effects are probably the answer to the multiple organ dysfunctions and growing mortality. This review provides a comprehensive overview of the mechanisms underlying cytokine storm, summarizes its pathophysiology and improves understanding of cytokine storm associated with coronavirus infections by comparing SARS-CoV-2 with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

1. Introduction

A novel coronavirus named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the World Health Organization (WHO) is blamed for the recent pneumonia outbreak that started in December 2019 in Wuhan, Hubei, China [1]. The rapid epidemic spread of this highly contagious virus, to date, have caused around 91,554 cases that were confirmed virus infection in China along with 40 million cases across the globe [2]. Some clinical physicians and researchers noticed that infected patients, especially severe patients, are liable to progress into respiratory failure and many of them even have suffered from multiple organ injuries, involving respiratory tract, gastrointestinal tract, kidney, liver, heart, etc. [3–6]. The pathogenesis of these complications has not been elucidated as information on the clinical features of infected patients is limited. However, we are easy to discover relevant tracks in the long history of epidemic disease.

Cytokine storm is a potentially fatal immune condition and caused by a large number of inflammatory mediators derived from unchecked feed forward immune activation and amplification [7,8]. If left untreated, cytokine storm can lead to severe pathological complications including sepsis, shock, tissue damage, multiple organ failure and ultimately death [7–11]. The factors sparking the cytokine storm are heterogeneous but infection is the most frequent cause clinically [12]. In graft versus host disease cytokine storm is also known as hypercytokinemia, a high inflammatory response causing injury of vascular endothelial cells and alveolar epithelial cells, as well as infiltration of neutrophils and macrophages into lung [13]. Recently, hypercytokinemia was seen in severe COVID-19.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CoV, coronavirus; WHO, World Health Organization; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; IL, interleukin; IFN, interferons; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; IL-1RA, IL-1 receptor antagonist; IP-10, IFN-γ-inducible protein-10; Th, helper T cell; DC, dendritic cell; NK, natural killer cell; B, B lymphocyte; Th2, T-helper-2 cell; BMSC, bone marrow stromal cell; Th1, T-helper-1 cell; PBMC, peripheral blood mononuclear cell; CCL, chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; GCSF, granulocyte colony stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; FGF, fibroblast growth factor; PDGF, platelet derived growth factor; VEGF, vascular endothelial cell growth factor; MIP1A, macrophage Inflammatory Protein 1 Alpha; MIP1B, macrophage Inflammatory Protein 1 beta; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; PAMPs, pathogen-associated molecular patterns; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; COVID-CSS, COVID-19 related cytokine storm syndrome; ACE2, angiotensin-converting enzyme 2; NF-κB, nuclear factor κB; JAK, Janus kinase; STAT, signal transducer and activator of transcription; IRF3, IFN regulatory factor-3.

* Corresponding author.
E-mail address: taocm@scu.edu.cn (C. Tao).
[1] First author: Zhongyi Zhao, Email: zzycan@tom.com

https://doi.org/10.1016/j.clim.2020.108615
Received 19 February 2020; Received in revised form 20 October 2020; Accepted 21 October 2020
Available online 23 October 2020

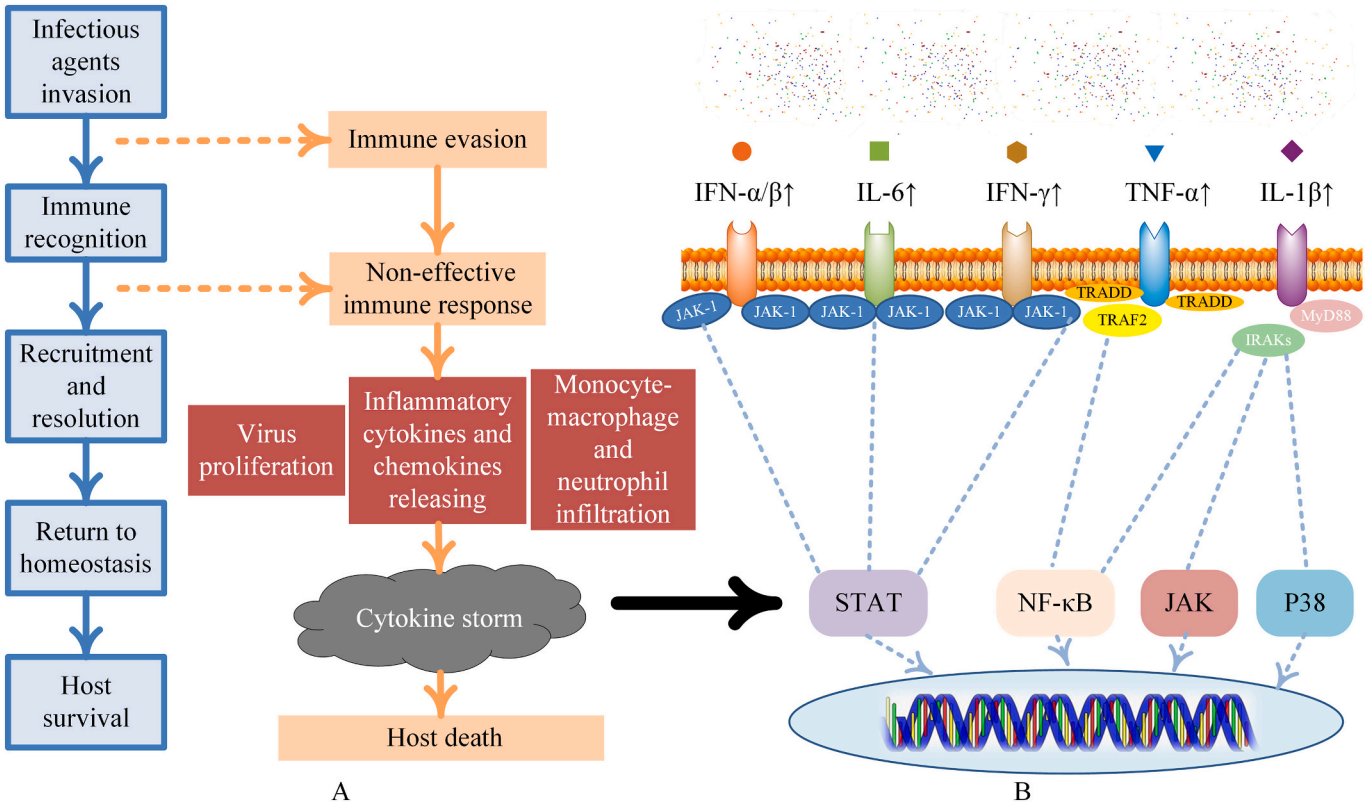

Fig. 1. Schematic diagram of cytokine storm during viral infection. (A) An effective immune response could clear out infectious agents, thus facilitate homeostasis restoring and host survival. While in some infections, immune evasion or delay, causing a non-effective response and this leads to virus proliferation, inflammatory cell infiltration, and cytokine storm that leads to tissue damage and death of the host. (B) Abundant functional cytokines and chemokines produced by local immune cells circulating to different organs and then binding to their cognate receptors that activates inflammatory signaling cascades and finally results in some clinical outcomes associated with the cytokine storm.

Evidence from coronavirus disease 2019 (COVID-19) patients indicated that serum inflammatory markers increased excessively, especially in severe patients with some obvious complications, and the term of COVID-19 related cytokine storm syndrome (COVID-CSS) emerged to denote patients with markedly excessive immune activation [3–6,14]. Previously, SARS-CoV, MERS-CoV, Ebola and other virus have been demonstrated to induce hypercytokinemia and contributes to the high fatality rate [9,11,15]. Studies also support the cytokine storm rather than virus is the real killer, triggering the immune system to attack the human body systemically and fiercely [8,16]. Herein, we comprehensively reviewed the current literature regarding the physiology of cytokine storm in the context of coronavirus infection and also discussed about the complicated interactions among the cytokine storm, immune response and organ functions. We hope to provide some inspirations to SARS-CoV-2 therapeutics and present evidence that could help understand some unexplainable complications.

2. Definition of cytokine storm

Cytokines are a large number of small signaling proteins secreted by immune cells for the purpose of intercellular communication, taking part in cell proliferation and differentiation, regulating immune and inflammatory responses, and being main executors of the cytokine storm [17,18]. Cytokine storm generally describes that pro-inflammatory cytokines are releasing excessively and uncontrollably during severe infection [7,8]. In most cases, multiple cytokines have positive implications in promoting disease progression, such as providing a defense against pathogens, modulating the inflammatory process and facilitating tissue repair, thus present as a complex, overlapping and cross-linked interplay [19]. Whereas, this can be detrimental if excessive. A cytokine storm can bring severe damages to the host and lung is always the first to be affected, such as diffuse alveolar damage, hyaline membrane formed, increased pulmonary capillary permeability and alveolar exudative inflammation, etc. [18,20]. The direst consequences of all lies in that lung injury disrupts immune system and further results in multiple organ dysfunctions [21].

3. The origin of cytokine storm

Inflammatory response is the first line of defense that protects human from infection or damage, responding to endogenous or exogenous challenges by activating both innate and adaptive immune responses [22]. The main signs for inflammation usually consist of heat, redness, swelling and pain [23]. In terms of classical self-limiting inflammatory response, four steps are included: (1) recognition of the infectious agents; (2) recruitment of immune cells and other components; (3) clearance of the infection; (4) retrogression of inflammation [24] (Fig. 1A). However, the procedure doesn't fit into certain pathogens since they are so cunning that they have developed strategies to deceive the immune system and thus unable to induce an effective and defensive immune response [25–27]. On the contrary, some microorganisms cannot be neglected as they could hyperstimulate the immune system and give rise to so-called cytokine storm [28] (Fig. 1B). This extremely dangerous pathogen, like SARS-CoV-2, MERS-CoV and SARS-CoV, can hamper the elimination of infection and induce severe tissue damages [29–32]. Throughout the process, numerous cytokines with pro-inflammatory/anti-inflammatory properties act on different parts of the inflammatory response.

More specifically, cytokine storm is triggered by some signaling pathways. Viral spike protein, like SARS-CoV spike protein, firstly binds

Table 1
Main characteristics of cytokine profile during different coronavirus infections.

Major cytokines	Origin	Major actions	COVID-19	MERS	SARS
TNF-α	Th, Monocyte, Macrophages, DC, NK, B, Mastocyte	Proinflammatory; activates cytotoxic T-lymphocytes	↑ [4]	↑ [41]	↑ Healthy group(n = 12):3.77(3.40)ng/L SARS group(n = 24):4.79 (14.48)ng/L [40]
IL-1α	Monocyte, Macrophages, DC, NK, B, Endotheliocyte	Growth and differentiation of lymphocytes; proinflammatory; cytokine expression			
IL-1β			↑ [4]		↑ SARS group(*n* = 20):>3.9 ng/L [39]
IL-6	Th-2, Monocyte, Macrophage, DC, BMSC	Differentiation of stem cells and lymphocytes; proliferation of T-lymphocytes; proinflammatory	↑↑ Mild group(*n* = 102):13.41 ± 1.84 ng/L Severe group(*n* = 21):37.77 ± 7.80 ng/L [37]	↑ [42]	↑ SARS group(*n* = 20):>3.1 ng/L [39]
IL-RA	Synovial tissue, PBMC	Inhibit IL-1, anti-inflammatory	↑ [4]	↑ [42]	
IL-12	Monocyte, Macrophage, DC, B	Differentiation of Th1; proliferation of T-lymphocytes; proinflammatory			↑ SARS group(n = 20): 7.8 ng/L [39]
IFN-α	Leukocyte	Antiviral properties; regulation MHC II		↑ [42]	
IFN-β	Th, B, Macrophage, Mastocyte	Proinflammatory or anti-inflammatory; promote tissue repairing			
IFN-γ	Th1, Tc1, NK	Antiviral properties; regulation of innate immunity; antiproliferative effects	↑ [4]	↑ [41,43]	↑ SARS group(*n* = 20):>15.6 ng/L [39]
IL-8	Monocyte, Macrophage, Endotheliocyte	Control of chemotaxis; leukocyte recruitment	↑ [4]		↑ SARS group(*n* = 20):>5.0 ng/L [39] Healthy group(*n* = 12):6.28(3.43)ng/L SARS group(*n* = 24): 431.23(78.51)ng/L [40]
IL-10	Th2, Monocyte, Macrophage	Cytokine inhibition; immunosuppression; anti-inflammatory	↑ [4]		
IP-10	CD4+ T, CD8+ T, NK	Control of chemotaxis; leukocyte or lymphocyte recruitment; proinflammatory	↑ [4]	↑ [43]	↑ [39]
MCP-1	Endotheliocyte, Fibrocyte, Monocyte, Macrophage, B	Chemotactic for monocytes and T-lymphocytes; proinflammatory	↑ [4]	↑ [43]	↑ [39]

Abbreviations: COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; IL, interleukin; IFN, interferons; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; IL-1RA, IL-1 receptor antagonist; IP-10, IFN-γ-inducible protein-10; Th, helper T cell; DC, dendritic cell; NK, natural killer cell; B, B lymphocyte; Th2, T-helper-2 cell; BMSC, bone marrow stromal cell; Th1, T-helper-1 cell; PBMC, peripheral blood mononuclear cell.

to angiotensin-converting enzyme 2 (ACE2) for virus entry, and then viral RNAs, one of the most important pathogen-associated molecular patterns (PAMPs), are identified by the pattern recognition receptors (PRRs) mainly consisting of the family of Toll-like receptors (TLRs) [33]. Downstream transduction pathways, including nuclear factor κB (NF-κB), JAK (Janus kinase)/STAT (signal transducer and activator of transcription), IRF3 (IFN regulatory factor-3) are subsequently activated to fight the virus [34–36].

4. Cytokine responses during coronavirus infection

Infection is often the root of cytokine storm. Though no direct evidence can demonstrate that pro-inflammatory cytokines involve in pathogenesis of coronavirus, some patients with severe disease provide the correlative facts that excessive immune response play an irreplaceable role [3,4,37,38]. SARS-CoV-2 has caused a mounting number of COVID-19 cases in Wuhan. It is noteworthy that a group of cytokines elevated significantly in critically ill COVID-19 patients [4,5,37].

Early studies of SARS patients showed that increased amounts of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, MCP-1, IP-10, IL-8, TNF-α and IFN-γ) in serum were connected with severe pulmonary inflammation as well as extensive lung damage [39,40]. Also, compared to mild patients, severe patients had higher levels of pro-inflammatory cytokines (IL-1, IL-6, IL-12, IFN-γ and TGF-β) and chemokines (IL-8, CCL2, CXCL9 and CXCL10), and among them, the classic anti-inflammatory cytokine, IL-10, was at comparatively low level [39]. In addition, elevation of IFN-α, IFN-γ and IFN-stimulated genes (CXCL10 and CCL2) was observed in patients with lethal SARS [29,39,40]. Similarly, MERS-CoV was also demonstrated to induce increased levels of pro-inflammatory cytokines (MCP-1, IFN-α, IFN-γ, IP-10, TNF-α, IL-1RA, IL-6, IL-15 and IL-17) [41,42]. Researchers also found pro-inflammatory cytokines (IFN-α and IL-6) and chemokines (IL-8, CCL5 and CXCL10) in patients with severe MERS increased more than those with mild or moderate disease [42]. High level of cytokines and chemokines was followed by the increased number of neutrophil and monocyte in lungs as well as blood, suggesting that immunocompetent cells possibly participate in lung pathology [30,41].

Two early researches of SARS-CoV-2 also reported the cytokine response. According to a set of data from Jin Yin-tan Hospital, a COVID-19 designated hospital in Wuhan, patients infected with SARS-CoV-2 had higher concentrations of TNF-α, IFN-γ, IP10, MCP-1, IL-1RA, IL-1β, IL-7, IL-8, IL-9, IL10, GCSF, GMCSF, basic FGF, PDGF, VEGF, MIP1A and MIP1B than healthy adults [4]. Moreover, the levels of IL-2, IL-7, IL-10, GCSF, MCP-1, IP-10, MIP1A, and TNF-α were significantly higher in intensive care unit (ICU) patients than those in non-ICU patients, suggesting that cytokine storm was more likely to happen in severe patients and associated with disease severity [4]. Intriguingly, both T-helper-1 (Th1) cell and T-helper-2 (Th2) cytokines were activated and this indicated Th2 cytokines suppressing inflammation were also involved in this process, which differs from SARS-CoV infection [4,39]. Another research group from Chongqing reported the abnormal cytokines in peripheral blood of SARS-CoV-2 infected patients as well. Specifically, 30.39% of the mild patients had higher IL-6 value than normal, but this proportion for severe patients was up to 76.19%, which was significantly higher than that in the mild group [37]. This is in line with the concept of cytokine storm, which serves as a must step experienced by patients with mild illness to become severe. Recent studies further confirmed IL-1, IL-10 and TNF-α in patients with severe COVID-19 were 2 to 100 times greater than normal levels, whereas IL-6 showed larger increases, even more than 1000 fold over the normal. Paralleled studies found markedly

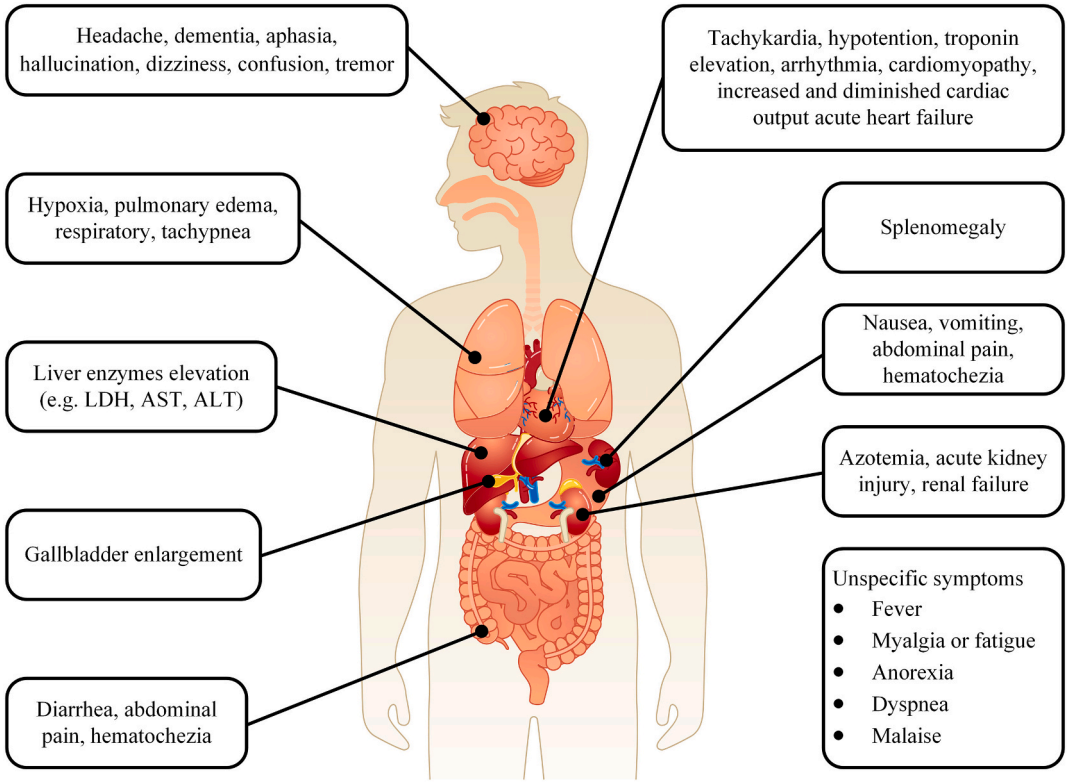

Fig. 2. The associated clinical manifestations with cytokine storm. Beginning with fever or other unspecific symptoms, the systemic cytokine response might impact most organ systems. The mild cases might only present as flu-like symptoms, but severe cases may develop into multiple organ dysfunctions, followed by rapid deterioration and death.

elevated IL-6 ranging from 100 to 10000 pg/mL in severe patients [43–46]. While the emerging coronaviruses present similar clinical symptoms, the laboratory findings are characterized by distinct cytokine profiles (Table 1).

Clinically, it is urgent to diagnose or discern cytokine storm in COVID-19. Result from a global meta-analysis including 33 laboratory biomarkers indicated that elevated serum levels of IL-6 and ferritin, positively and significantly correlated with white blood cells and inversely correlated with lymphocyte and platelet counts, could provide a diagnostic clue for COVID-19 [47]. In another study, severe symptoms were characterized by high levels of IL-6, fibrinogen, sialic acid, C-reactive protein (CRP) and neutrophils [48]. Also, higher neutrophil-to-lymphocyte ratio (NLR) and decreased lymphocyte counts may indicate the dysregulated immune response [48]. Some large studies imply that an IL-6 threshold $\geq$ 80 pg/mL has predictive value in COVID-CSS outcomes [43,49,50]. Though IL-6 measurement became an inexpensive and simple assay for many clinical laboratories to evaluate prognosis of COVID-19, the value of it has been challenged. This is because COVID-19 IL-6 had a relatively low median level in several studies [51]. The temporal heterogeneity makes it difficult to specify effects of IL-6, but treatment with IL-6 blockade is perhaps more informatively [14]. Cytokines modulators have been purposed as therapeutic strategy to mitigate the COVID-19. Such drugs include anti-TNF-α agents, corticosteroids, IL-1 inhibitors, IL-6 receptor antagonists, JAK inhibitors, chloroquine, hydroxychloroquine and azithromycin and some of them have shown clinical benefit [52–63].

5. Cytokine storm involving in multiple organ failures

Cytokine storm could affect all the vital organs of the human body. Acute lung injury (ALI) is a common consequence of a cytokine storm and always associated with confirmed or suspected infections in the lung or other organs [29]. The main characteristic of ALI is inflammatory cell (granulocyte and monocyte) infiltration followed by collagen distribution and deposition [64,65]. Virus-induced lung injury could rapidly progress to ALI or acute respiratory distress syndrome (ARDS), a severe form of ALI, as seen with SARS-CoV and highly pathogenic influenza virus infections [66,67]. Some crucial cytokines in cytokine storm (e.g. IL-1β and TNF-α) drive pro-inflammatory activity in patients with lung injury [68]. Intensive inflammation originated from lungs can have other systemic effects, for instance, the severe lung injury combined with mechanical ventilation makes for cell apoptosis in renal tubular epithelial and renal dysfunction [69].

Systemic effects for cytokine storm starts from local inflammation spilling over into the circulation, producing systemic sepsis, as marked by persistent hyperpyrexia or hypothermia, leukocytosis or leukopenia, thrombocytopenia and often hypotension [70]. Study reported, among the COVID-19 patients, 25% of them had leukopenia and 5% had thrombocytopenia [4]. When it comes to histopathological changes, the highly pathogenic influenza virus (H5N1 and H7N9) was researched most deeply, but more attention has been devoted to coronavirus in recent decades [71,72]. Studies showed SARS-CoV infection induces ALI that may progress rapidly to life-threatening ARDS [73]. MERS-CoV infection could result in a more severe pneumonia than SARS-CoV infection [74].

In addition to pulmonary lesions, a cytokine storm could involve in nervous system, digestive system urinary systems, cardiovascular system and other areas [75–77]. Currently, part of patients with COVID-19 manifested intestinal sign, nervous system symptom, renal damage, hepatic lesion and even cardiac injury, besides respiratory problems [3–5,78]. Zhongnan Hospital of Wuhan University reported common complications among the 138 infected patients, including shock (8.7%), ARDS (19.6%), arrhythmia (16.7%), and acute cardiac injury (7.2%) [3]. Moreover, the ICU patients were more likely to get one of these complications than non-ICU patients [3]. Earlier, Jin Yin-tan Hospital of Wuhan had suggested patients in ICU were more likely to report

dizziness, abdominal pain, and anorexia compared with the non-ICU patients [4]. Besides, a remarkable reduction of lymphocytes, especially T lymphocytes, was observed, suggesting the cytokine storm have caused changes in peripheral immune cells, as does SARS-CoV [3–5,37,78–80]. Actually, many of the similar signs or symptoms have been reported in SARS and MERS. Patients infected with either MERS-CoV or SARS-CoV both had diarrhea [81,82]. In addition to respiratory symptoms, gastrointestinal distress and neurological sequelae have been seen in MERS patients [81]. As to SARS, the most severe cases died after the onset of non-specific symptoms (e.g. cough, myalgia and dyspnea) [82,83]. And follow-up studies revealed that immunopathologic damage resulting from exaggerated immune response, rather than unbridled viral replication, is the lethal cause [29,82]. Studies on cytokine responses in extra-respiratory organs or tissues during coronavirus infection are insufficient, but in the field of influenza virus, systemic cytokine responses have been demonstrated to increase the severity of influenza [71,72,83]. Severe influenza virus infections are associated with central nervous system (CNS) and cardiovascular disease [84,85]. The associated clinical manifestations with cytokine storm are shown in Fig. 2.

6. Conclusions

After several years of silence, appearance of SARS-CoV-2 alarms researchers about the dreadful consequences of immoderate immune response. This virus has caused a widespread and fast-spreading epidemic that poses a major threat to global public health. As a recently emerging and highly contagious coronavirus, SARS-CoV-2 remains mysterious and thus current treatments continue to tamp down symptoms rather than address causes. Several studies have demonstrated that cytokine storm following infection could be the most crucial factor for exacerbation and even death of patients. Therefore, in the present review, we suggested appropriate immunomodulation therapy might become a potential complement to supportive treatment and have significant implications in reducing the mortality of patients. Although scientists have gain more insight into overactive immune response over the last decades, some of the findings still have difficulties in translating into effective treatments. A further understanding of the emergence, spread and pathology of SARS-CoV-2 may halt its emergence and epidemic in the human population.

Declaration of Competing Interest

The authors declare no conflicts of interest related to the manuscript.

Acknowledgments

We thank Dr. Feng for assistance with images disposal.

References

[1] L. Zhang, Y. Liu, Potential interventions for novel coronavirus in china: a systemic review, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25707.
[2] Baidu, Real-time data on the novel coronavirus-infected pneumonia epidemic, 2020. https://voice.baidu.com/act/newpneumonia/newpneumonia/?from=osari_pc_3.
[3] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China, JAMA (2020), https://doi.org/10.1001/jama.2020.1585.
[4] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[5] L. Kui, Y. Fang, Y. Deng, W. Liu, M. Wang, J. Ma, W. Xiao, Y. Wang, M. Zhong, C. Li, G. Li, H. Liu, Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province, Chinese Med J-Peking 1 (2020), https://doi.org/10.1097/CM9.0000000000000744.
[6] Z. Wang, X. Chen, Y. Lu, F. Chen, W. Zhang, Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment, Biosci Trends (2020), https://doi.org/10.5582/bst.2020.01030.
[7] B.G. Chousterman, F.K. Swirski, G.F. Weber, Cytokine storm and sepsis disease pathogenesis, Semin. Immunopathol. 39 (2017) 517–528, https://doi.org/10.1007/s00281-017-0639-8.
[8] A. Srikiatkhachorn, A. Mathew, A.L. Rothman, Immune-mediated cytokine storm and its role in severe dengue, Semin. Immunopathol. 39 (2017) 563–574, https://doi.org/10.1007/s00281-017-0625-1.
[9] P. Younan, M. Iampietro, A. Nishida, P. Ramanathan, R.I. Santos, M. Dutta, N. M. Lubaki, R.A. Koup, M.G. Katze, A. Bukreyev, Ebola Virus Binding to Tim-1 on T Lymphocytes Induces a Cytokine Storm, MBIO 8 (2017), https://doi.org/10.1128/mBio.00845-17.
[10] S.J. Tavernier, V. Athanasopoulos, P. Verloo, G. Behrens, J. Staal, D.J. Bogaert, L. Naesens, M. De Bruyne, S. Van Gassen, E. Parthoens, J. Ellyard, J. Cappello, L. X. Morris, H. Van Gorp, G. Van Isterdael, Y. Saeys, M. Lamkanfi, P. Schelstraete, J. Dehoorne, V. Bordon, R. Van Coster, B.N. Lambrecht, B. Menten, R. Beyaert, C. G. Vinuesa, V. Heissmeyer, M. Dullaers, F. Haerynck, A human immune dysregulation syndrome characterized by severe hyperinflammation with a homozygous nonsense Roquin-1 mutation, Nat. Commun. 10 (2019) 4779, https://doi.org/10.1038/s41467-019-12704-6.
[11] N. Nagata, N. Iwata, H. Hasegawa, S. Fukushi, A. Harashima, Y. Sato, M. Saijo, F. Taguchi, S. Morikawa, T. Sata, Mouse-passaged severe acute respiratory syndrome-associated coronavirus leads to lethal pulmonary Edema and diffuse alveolar damage in adult but not young mice, Am. J. Pathol. 172 (2008) 1625–1637, https://doi.org/10.2353/ajpath.2008.071060.
[12] E.M. Behrens, G.A. Koretzky, Review: cytokine storm syndrome: looking toward the precision medicine era, Arthritis Rheum. 69 (2017) 1135–1143, https://doi.org/10.1002/art.40071.
[13] I.A. Clark, The advent of the cytokine storm, Immunol. Cell Biol. 85 (2007) 271–273, https://doi.org/10.1038/sj.icb.7100062.
[14] L.Y.C. Chen, R.L. Hoiland, S. Stukas, C.L. Wellington, M.S. Sekhon, Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome, Eur. Respir. J. 2003006 (2020), https://doi.org/10.1183/13993003.03006-2020.
[15] S.K.P. Lau, C.C.Y. Lau, K.H. Chan, C.P.Y. Li, H. Chen, D.Y. Jin, J.F.W. Chan, P.C. Y. Woo, K.Y. Yuen, Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment, J Gen Virol 94 (2013) 2679–2690, https://doi.org/10.1099/vir.0.055533-0.
[16] S. Chen, G. Liu, J. Chen, A. Hu, L. Zhang, W. Sun, W. Tang, C. Liu, H. Zhang, C. Ke, J. Wu, X. Chen, Ponatinib protects mice from lethal influenza infection by suppressing cytokine storm, Front. Immunol. 10 (2019) 1393, https://doi.org/10.3389/fimmu.2019.01393.
[17] J. Steinke, L. Borish, 3. Cytokines and chemokines, J. Allergy Clin. Immunol. 117 (2006) S441–S445, https://doi.org/10.1016/j.jaci.2005.07.001.
[18] H. Wang, S. Ma, The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome, Am. J. Emerg. Med. 26 (2008) 711–715, https://doi.org/10.1016/j.ajem.2007.10.031.
[19] S.O. Gollnick, S.S. Evans, H. Baumann, B. Owczarczak, P. Maier, L. Vaughan, W. C. Wang, E. Unger, B.W. Henderson, Role of cytokines in photodynamic therapy-induced local and systemic inflammation, Brit J Cancer 88 (2003) 1772–1779, https://doi.org/10.1038/sj.bjc.6600864.
[20] Q. Liu, Y. Zhou, Z. Yang, The cytokine storm of severe influenza and development of immunomodulatory therapy, Cell. Mol. Immunol. 13 (2016) 3–10, https://doi.org/10.1038/cmi.2015.74.
[21] Y. Imamura, Inflammation and Brain: Regulation of Systemic Inflammation in Sepsis, Biochem. Pharmacol: Open Access 01 (2012), https://doi.org/10.4172/2167-0501.1000e127.
[22] S.L. Oke, K.J. Tracey, The inflammatory reflex and the role of complementary and alternative medical therapies, Ann. N. Y. Acad. Sci. 1172 (2009) 172–180, https://doi.org/10.1196/annals.1393.013.
[23] A. Scott, What is "inflammation"? Are we ready to move beyond Celsus? Brit J Sport Med 38 (2004) 248–249, https://doi.org/10.1136/bjsm.2003.011221.
[24] D.A. Willoughby, A.R. Moore, P.R. Colville-Nash, D. Gilroy, Resolution of inflammation, Int. J. Immunopharmacol. 22 (2000) 1131–1135, https://doi.org/10.1016/S0192-0561(00)00064-3.
[25] X. Chen, S. Liu, M.U. Goraya, M. Maarouf, S. Huang, J. Chen, Host immune response to influenza a virus infection, Front. Immunol. 9 (2018) 320, https://doi.org/10.3389/fimmu.2018.00320.
[26] M. Georgieva, C.O. Buckee, M. Lipsitch, Models of immune selection for multi-locus antigenic diversity of pathogens, Nat. Rev. Immunol. 19 (2019) 55–62, https://doi.org/10.1038/s41577-018-0092-5.
[27] J.A. Linderman, M. Kobayashi, V. Rayannavar, J.J. Fak, R.B. Darnell, M.V. Chao, A. C. Wilson, I. Mohr, Immune escape via a transient gene expression program enables productive replication of a latent pathogen, Cell Rep. 18 (2017) 1312–1323, https://doi.org/10.1016/j.celrep.2017.01.017.
[28] H. Gerlach, Agents to reduce cytokine storm, F1000Research 5 (2016) 2909, https://doi.org/10.12688/f1000research.9092.1.
[29] R. Channappanavar, S. Perlman, Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology, Semin. Immunopathol. 39 (2017) 529–539, https://doi.org/10.1007/s00281-017-0629-x.
[30] B. Alosaimi, M.E. Hamed, A. Naeem, A.A. Alsharef, S.Y. AlQahtani, K.M. AlDosari, A.A. Alamri, K. Al-Eisa, T. Khojah, A.M. Assiri, M.A. Enani, MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower

respiratory tract, Cytokine 126 (2020) 154895, https://doi.org/10.1016/j.cyto.2019.154895.
[31] K. Hong, J. Choi, S. Hong, J. Lee, J. Kwon, S. Kim, S.Y. Park, J. Rhee, B. Kim, H. J. Choi, E. Shin, H. Pai, S. Park, S. Kim, Predictors of mortality in Middle East respiratory syndrome (MERS), Thorax 73 (2018) 286–289, https://doi.org/10.1136/thoraxjnl-2016-209313.
[32] M. Bassetti, A. Vena, D.R. Giacobbe, The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm, Eur. J. Clin. Investig. (2020), https://doi.org/10.1111/eci.13209 e13209.
[33] M. de Marcken, K. Dhaliwal, A.C. Danielsen, A.S. Gautron, M. Dominguez-Villar, TLR7 and TLR8 activate distinct pathways in monocytes during RNA virus infection, Sci. Signal. 12 (2019), https://doi.org/10.1126/scisignal.aaw1347.
[34] J. Olejnik, A.J. Hume, E. Mühlberger, Toll-like receptor 4 in acute viral infection: too much of a good thing, PLoS Pathog. 14 (2018), e1007390, https://doi.org/10.1371/journal.ppat.1007390.
[35] W. Wang, L. Ye, L. Ye, B. Li, B. Gao, Y. Zeng, L. Kong, X. Fang, H. Zheng, Z. Wu, Y. She, Up-regulation of IL-6 and TNF-α induced by SARS-coronavirus spike protein in murine macrophages via NF-κB pathway, Virus Res. 128 (2007) 1–8, https://doi.org/10.1016/j.virusres.2007.02.007.
[36] A. Banerjee, D. Falzarano, N. Rapin, J. Lew, V. Misra, Interferon regulatory factor 3-mediated Signaling limits middle-east respiratory syndrome (MERS) coronavirus propagation in cells from an insectivorous bat, Viruses 11 (2019) 152, https://doi.org/10.3390/v11020152.
[37] Q.Y.S.F. Suxin Wan, Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP), medRxiv (2020), https://doi.org/10.1101/2020.02.10.20021832.
[38] D.S. Hui, E.I. Azhar, Y. Kim, Z.A. Memish, M. Oh, A. Zumla, Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission, Lancet Infect. Dis. 18 (2018) e217–e227, https://doi.org/10.1016/S1473-3099(18)30127-0.
[39] C.K. Wong, C.W. Lam, A.K. Wu, W.K. Ip, N.L. Lee, I.H. Chan, L.C. Lit, D.S. Hui, M. H. Chan, S.S. Chung, J.J. Sung, Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome, Clin. Exp. Immunol. 136 (2004) 95–103, https://doi.org/10.1111/j.1365-2249.2004.02415.x.
[40] J. Xie, Y. Han, T.S. Li, Z.F. Qiu, X.J. Ma, H.W. Fan, W. Lu, Z.Y. Liu, Z. Wang, H. L. Wang, G.H. Deng, Dynamic changes of plasma cytokine levels in patients with severe acute respiratory syndrome, Zhonghua Nei Ke Za Zhi 42 (2003) 643–645.
[41] W.H. Mahallawi, O.F. Khabour, Q. Zhang, H.M. Makhdoum, B.A. Suliman, MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile, Cytokine 104 (2018) 8–13, doi:10.1016/j.cyto.2018.01.025.
[42] H.S. Shin, Y. Kim, G. Kim, J.Y. Lee, I. Jeong, J.S. Joh, H. Kim, E. Chang, S.Y. Sim, J. S. Park, D.G. Lim, Immune responses to Middle East respiratory syndrome coronavirus during the acute and convalescent phases of human infection, Clin. Infect. Dis. 68 (2019) 984–992, https://doi.org/10.1093/cid/ciy595.
[43] R.L. Hoiland, S. Stukas, J. Cooper, S. Thiara, L.Y.C. Chen, C.M. Biggs, K. Hay, A.Y. Y. Lee, K. Shojania, A. Abdulla, C.L. Wellington, M.S. Sekhon, Amelioration of COVID-19-related cytokine storm syndrome: parallels to chimeric antigen receptor-T cell cytokine release syndrome, Brit J Haematol 190 (2020) e150–e154, https://doi.org/10.1111/bjh.16961.
[44] T. Herold, V. Jurinovic, C. Arnreich, B.J. Lipworth, J.C. Hellmuth, M. von Bergwelt-Baildon, M. Klein, T. Weinberger, Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19, J. Allergy Clin. Immunol. 146 (2020) 128–136, e4, https://doi.org/10.1016/j.jaci.2020.05.008.
[45] A.G. Laing, A. Lorenc, I. Del Molino Del Barrio, A. Das, M. Fish, L. Monin, M. Muñoz-Ruiz, D.R. McKenzie, T.S. Hayday, I. Francos-Quijorna, S. Kamdar, M. Joseph, D. Davies, R. Davis, A. Jennings, I. Zlatareva, P. Vantourout, Y. Wu, V. Sofra, F. Cano, M. Greco, E. Theodoridis, J. Freedman, S. Gee, J.N.E. Chan, S. Ryan, E. Bugallo-Blanco, P. Peterson, K. Kisand, L. Haljasmägi, L. Chadli, P. Moingeon, L. Martinez, B. Merrick, K. Bisnauthsing, K. Brooks, M.A.A. Ibrahim, J. Mason, F. Lopez Gomez, K. Babalola, S. Abdul-Jawad, J. Cason, C. Mant, J. Seow, C. Graham, K.J. Doores, F. Di Rosa, J. Edgeworth, M. Shankar-Hari, A.C. Hayday, Author Correction: A dynamic COVID-19 immune signature includes associations with poor prognosis, Nat. Med. (2020), https://doi.org/10.1038/s41591-020-1079-x.
[46] K. Patel, T.A. Gooley, N. Bailey, M. Bailey, L. Hegerova, A. Batchelder, H. Holdread, V. Dunleavy, T. Downey, J. Frisvold, S. Megrath, K. Pagarigan, J. Szeto, J. Rueda, A. Islam, C. Maree, S. Nyatsatsang, S.E. Bork, A. Lipke, D.S. O. Mahony, T. Wagner, J. Pulido, J. Mignone, S. Youssef, M. Hartman, J. D. Goldman, J.M. Pagel, Use of the IL-6R Antagonist Tocilizumab in Hospitalized COVID-19 Patients, J. Intern. Med. (2020), https://doi.org/10.1111/joim.13163.
[47] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (2020) 420–422, https://doi.org/10.1016/S2213-2600(20)30076-X.
[48] Z. Zhu, T. Cai, L. Fan, K. Lou, X. Hua, Z. Huang, G. Gao, Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019, Int. J. Infect. Dis. 95 (2020) 332–339, https://doi.org/10.1016/j.ijid.2020.04.041.
[49] L.Y.C. Chen, A. Hayden, A. Mattman, Extreme hyperferritinaemia, soluble interleukin-2 receptor, and haemophagocytic lymphohistiocytosis, Brit J Haematol 185 (2019) 605–606, https://doi.org/10.1111/bjh.15579.
[50] R. Laguna-Goya, A. Utrero-Rico, P. Talayero, M. Lasa-Lazaro, A. Ramirez-Fernandez, L. Naranjo, A. Segura-Tudela, O. Cabrera-Marante, E. Rodriguez De Frias, R. Garcia-Garcia, M. Fernández-Ruiz, J.M. Aguado, J. Martinez-Lopez, E. A. Lopez, M. Catalan, A. Serrano, E. Paz-Artal, IL-6–based mortality risk model for hospitalized patients with COVID-19, J. Allergy Clin. Immunol. (2020), https://doi.org/10.1016/j.jaci.2020.07.009.
[51] P. Sinha, M.A. Matthay, C.S. Calfee, Is a "cytokine storm" relevant to COVID-19? JAMA Intern. Med. 180 (2020) 1152, https://doi.org/10.1001/jamainternmed.2020.3313.
[52] S. Zhang, L. Li, A. Shen, Y. Chen, Z. Qi, Rational use of tocilizumab in the treatment of novel coronavirus pneumonia, Clin Drug Investig 40 (2020) 511–518, https://doi.org/10.1007/s40261-020-00917-3.
[53] D. Wu, X.O. Yang, TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib, J. Microbiol. Immunol. Infect. 53 (2020) 368–370, https://doi.org/10.1016/j.jmii.2020.03.005.
[54] S. Atal, Z. Fatima, IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy? Pharm Med 34 (2020) 223–231, https://doi.org/10.1007/s40290-020-00342-z.
[55] D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E. C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M. P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, K.H. Hullsiek, A randomized trial of hydroxychloroquine as Postexposure prophylaxis for Covid-19, New Engl J Med 383 (2020) 517–525, https://doi.org/10.1056/NEJMoa2016638.
[56] J. Geleris, Y. Sun, J. Platt, J. Zucker, M. Baldwin, G. Hripcsak, A. Labella, D. K. Manson, C. Kubin, R.G. Barr, M.E. Sobieszczyk, N.W. Schluger, Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19, New Engl J Med 382 (2020) 2411–2418, doi:2020, https://doi.org/10.1056/NEJMoa2012410.
[57] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez De Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D. A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the Treatment of Covid-19 — Preliminary Report, New Engl J Med 2020 (2020), https://doi.org/10.1056/NEJMc2022236.
[58] J.D. Goldman, D.C.B. Lye, D.S. Hui, K.M. Marks, R. Bruno, R. Montejano, C. D. Spinner, M. Galli, M. Ahn, R.G. Nahass, Y. Chen, D. SenGupta, R.H. Hyland, A. O. Osinusi, H. Cao, C. Blair, X. Wei, A. Gaggar, D.M. Brainard, W.J. Towner, J. Muñoz, K.M. Mullane, F.M. Marty, K.T. Tashima, G. Diaz, A. Subramanian, Remdesivir for 5 or 10 Days in Patients with Severe Covid-19, New Engl J Med (2020), https://doi.org/10.1056/NEJMoa2015301.
[59] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F.G. Hayden, P.W. Horby, B. Cao, C. Wang, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, Lancet 395 (2020) 1569–1578, https://doi.org/10.1016/S0140-6736(20)31022-9.
[60] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19, New Engl J Med 382 (2020) 1787–1799, https://doi.org/10.1056/NEJMoa2001282.
[61] D. Antwi Amoabeng, Z. Kanji, B. Ford, B.D. Beutler, M.S. Riddle, F. Siddiqui, Clinical outcomes in COVID-19 patients treated with tocilizumab: An individual patient data systematic review, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.26038.
[62] W. Zhang, Y. Zhao, F. Zhang, Q. Wang, T. Li, Z. Liu, J. Wang, Y. Qin, X. Zhang, X. Yan, X. Zeng, S. Zhang, The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China, Clin. Immunol. 214 (2020) 108393, https://doi.org/10.1016/j.clim.2020.108393.
[63] S. Yeleswaram, P. Smith, T. Burn, M. Covington, A. Juvekar, Y. Li, P. Squier, P. Langmuir, Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment, Clin. Immunol. 218 (2020) 108517, https://doi.org/10.1016/j.clim.2020.108517.
[64] M. Kellner, S. Noonepalle, Q. Lu, A. Srivastava, E. Zemskov, S.M. Black, ROS Signaling in the pathogenesis of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), Adv. Exp. Med. Biol. 967 (2017) 105–137, https://doi.org/10.1007/978-3-319-63245-2_8.
[65] M. Kalbitz, M. Karbach, S. Braumueller, P. Kellermann, F. Gebhard, M. Huber-Lang, M. Perl, Role of complement C5 in experimental blunt chest trauma-induced septic acute lung injury (ALI), PLoS One 11 (2016), e0159417, https://doi.org/10.1371/journal.pone.0159417.
[66] H. Gu, Z. Xie, T. Li, S. Zhang, C. Lai, P. Zhu, K. Wang, L. Han, Y. Duan, Z. Zhao, X. Yang, L. Xing, P. Zhang, Z. Wang, R. Li, J.J. Yu, X. Wang, P. Yang, Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus, Sci. Rep. 6 (2016) 19840, https://doi.org/10.1038/srep19840.
[67] B. Selvakumar, J. Wilhelm, D. Wolff, W. Seeger, J. Lohmeyer, S. Herold, Functional phenotype and role of resident and recruited bone marrow derived exudate

macrophages in influenza virus-induced lung injury and repair, Int. J. Infect. Dis. 73 (2018) 44, https://doi.org/10.1016/j.ijid.2018.04.3522.
[68] J. Yang, M. Azat, P. Peng, Y. Chang, R. Gao, W. Li, J. Li, Y. Chai, Dandan, serum levels of TNF-α, IL-1β, IL-9, and IL-15 in acute respiratory distress syndrome, Int. J. Clin. Exp. Pathol. 10 (2017) 781–788.
[69] Yumiko Imai, Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome, Jama 289 (2003) 2104.
[70] M.M. Levy, M.P. Fink, J.C. Marshall, E. Abraham, D. Angus, D. Cook, J. Cohen, S. M. Opal, J. Vincent, G. Ramsay, 2001 SCCM/ESICM/ACCP/ATS/SIS international Sepsis definitions conference, Intensive Care Med. 29 (2003) 530–538, https://doi.org/10.1007/s00134-003-1662-x.
[71] M.C.W. Chan, D.I.T. Kuok, C.Y.H. Leung, K.P.Y. Hui, S.A. Valkenburg, E.H.Y. Lau, J.M. Nicholls, X. Fang, Y. Guan, J.W. Lee, R.W.Y. Chan, R.G. Webster, M. A. Matthay, J.S.M. Peiris, Human mesenchymal stromal cells reduce influenza a H5N1-associated acute lung injury in vitro and in vivo, Proc. Natl. Acad. Sci. 113 (2016) 3621–3626, https://doi.org/10.1073/pnas.1601911113.
[72] P. Yang, H. Gu, Z. Zhao, W. Wang, B. Cao, C. Lai, X. Yang, L. Zhang, Y. Duan, S. Zhang, W. Chen, W. Zhen, M. Cai, J.M. Penninger, C. Jiang, X. Wang, Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury, Sci Rep-UK 4 (2015) 7027, https://doi.org/10.1038/srep07027.
[73] T.T.B. Phung, T. Suzuki, P.H. Phan, S. Kawachi, H. Furuya, H.T. Do, T. Kageyama, T.A. Ta, N.H. Dao, H. Nunoi, D.M. Tran, H.T. Le, N. Nakajima, Pathogen screening and prognostic factors in children with severe ARDS of pulmonary origin, Pediatr. Pulmonol. 52 (2017) 1469–1477, https://doi.org/10.1002/ppul.23694.
[74] R. Channappanavar, A.R. Fehr, R. Vijay, M. Mack, J. Zhao, D.K. Meyerholz, S. Perlman, Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice, Cell Host Microbe 19 (2016) 181–193, https://doi.org/10.1016/j.chom.2016.01.007.
[75] M. Koyama, G.R. Hill, The primacy of gastrointestinal tract antigen-presenting cells in lethal graft-versus-host disease, Blood 134 (2019) 2139–2148, https://doi.org/10.1182/blood.2019000823.
[76] J. Song, J. Yu, G.W. Prayogo, W. Cao, Y. Wu, Z. Jia, A. Zhang, Understanding kidney injury molecule 1: a novel immune factor in kidney pathophysiology, Am. J. Transl. Res. 11 (2019) 1219–1229.
[77] M. Shimizu, Clinical Features of Cytokine Storm Syndrome, 2019, pp. 31–41, https://doi.org/10.1007/978-3-030-22094-5_3.
[78] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet (London, England) 395 (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.
[79] Y. Jiang, X. Wei, J. Guan, S. Qin, Z. Wang, H. Lu, J. Qian, L. Wu, Y. Chen, Y. Chen, X. Lin, COVID-19 pneumonia: CD8+ T and NK cells are decreased in number but compensatory increased in cytotoxic potential, Clin. Immunol. 218 (2020) 108516, https://doi.org/10.1016/j.clim.2020.108516.
[80] J.M. Urra, C.M. Cabrera, L. Porras, I. Ródenas, Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients, Clin. Immunol. (Orlando, Fla.) 217 (2020) 108486, https://doi.org/10.1016/j.clim.2020.108486.
[81] W.S. Choi, C. Kang, Y. Kim, J. Choi, J.S. Joh, H. Shin, G. Kim, K.R. Peck, D. R. Chung, H.O. Kim, S.H. Song, Y.R. Kim, K.M. Sohn, Y. Jung, J.H. Bang, N.J. Kim, K.S. Lee, H.W. Jeong, J. Rhee, E.S. Kim, H. Woo, W.S. Oh, K. Huh, Y.H. Lee, J. Y. Song, J. Lee, C. Lee, B. Kim, Y.H. Choi, S.J. Jeong, J. Lee, J.H. Yoon, Y.M. Wi, M. K. Joung, S.Y. Park, S.H. Lee, S. Jung, S. Kim, J.H. Lee, H. Lee, H.K. Ki, Y. Kim, Clinical presentation and outcomes of middle east respiratory syndrome in the Republic of Korea, Infection & Chemother 48 (2016) 118, https://doi.org/10.3947/ic.2016.48.2.118.
[82] D.S.C. Hui, A. Zumla, Severe acute respiratory syndrome, Infect. Dis. Clin. N. Am. 33 (2019) 869–889, https://doi.org/10.1016/j.idc.2019.07.001.
[83] B.T. Bradley, A. Bryan, Emerging respiratory infections: the infectious disease pathology of SARS, MERS, pandemic influenza, and Legionella, Semin. Diagn. Pathol. 36 (2019) 152–159, https://doi.org/10.1053/j.semdp.2019.04.006.
[84] J.Y. Siegers, M.W.G. van de Bildt, Z. Lin, L.M. Leijten, R.A.M. Lavrijssen, T. Bestebroer, M.I.J. Spronken, C.I. De Zeeuw, Z. Gao, E.J.A. Schrauwen, T. Kuiken, D. van Riel, Viral Factors Important for Efficient Replication of Influenza A Viruses in Cells of the Central Nervous System, J. Virol. 93 (2019), https://doi.org/10.1128/JVI.02273-18.
[85] L. Ebdrup, K. Druey, T.H. Mogensen, Severe capillary leak syndrome with cardiac arrest triggered by influenza virus infection, BMJ Case Reports 2018 (2018), https://doi.org/10.1136/bcr-2018-226108 bcr-2018-226108.