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Narrative review

Severe acute respiratory syndrome coronavirus 2 causes lung inflammation and injury

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ABSTRACT

Background: As of 14 October 2021, coronavirus disease 2019 (COVID-19) has affected more than 246 million individuals and caused more than 4.9 million deaths worldwide. COVID-19 has caused significant damage to the health, economy and lives of people worldwide. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not as lethal as SARS coronavirus or Middle East respiratory syndrome coronavirus, its high transmissibility has had disastrous consequences for public health and health-care systems worldwide given the lack of effective treatment at present.

Objectives: To clarify the mechanisms by which SARS-CoV-2 caused lung inflammation and injury, from the molecular mechanism to lung damage and tissue repair, from research to clinical practice, and then presented clinical requirements.

Sources: References for this review were identified through searches '(COVID-19 [Title]) OR (SARS-CoV-2 [Title])' on PubMed, and focused on the pathological damage and clinical practice of COVID-19.

Content: We comprehensively reviewed the process of lung inflammation and injury during SARS-CoV-2 infection, including pyroptosis of alveolar epithelial cells, cytokine storm and thrombotic inflammatory mechanisms.

Implications: This review describes SARS-CoV-2 in comparison to SARS and explores why most people have mild inflammatory responses, even asymptomatic infections, and only a few develop severe disease. It suggests that future therapeutic strategies may be targeted antiviral therapy, the pathogenic pathways in the lung inflammatory response, and enhancing repair and regeneration in lung injury. **Le-Le Wang, Clin Microbiol Infect 2022;28:513**

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Introduction

In December 2019, Li et al. first confirmed the human-to-human transmission of a novel coronavirus among close contacts [1]. On 17 February 2020, the disease was termed coronavirus disease 2019 (COVID-19) by the WHO [2]. The International Committee on Taxonomy of Viruses renamed 2019-nCoV as acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in May 2020 [3]. There are nearly one million new cases of COVID-19 every day worldwide. In addition, there have been frequent mutations to this novel

coronavirus. Although the virulence has been decreasing, transmission has increased, especially with the Delta (Lineage B.1.617.2) mutation [4]. Mutations not only bring about challenges to epidemic control, but also greatly reduce the effectiveness of vaccines [5]. SARS-CoV-2 has had a devastating impact on human lives and prompted global efforts to develop countermeasures. Social prevention and control measures include traffic restrictions, increasing social distancing, personal protection, environmental hygiene, social mobilization, publicity and education. Confirmed cases, suspected cases and close contacts will be treated or put under medical observation in a standardized manner and the population is encouraged to be vaccinated. This review started with the pathogenesis of SARS-CoV-2 and provides some strategies and bases for clinical treatment and management of COVID-19.

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Structures of SARS-CoV-2 and of angiotensin-converting enzyme 2

The Coronaviridae are a family of enveloped viruses with a single-strand, positive-sense RNA genome of 26–32 kilobases [6] that consists of four structural proteins: the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins [6], which are encoded in the order S-E-M-N (Fig. 1). The S protein, a type I glycoprotein, forms peplomers on the virion surface; the small membrane protein E, a highly hydrophobic protein, has a short ectodomain, a transmembrane domain and a cytoplasmic tail [7]; the M protein, spans the membrane three times and has a short N-terminal ectodomain and a cytoplasmic tail; and the N protein, forms a helical capsid [8]. SARS-CoV-2 has a receptor-binding domain (RBD) similar in structure to the S protein to SARS-CoV (nearly 80%) [9]. The RBD directly binds to the peptidase domain of angiotensin-converting enzyme 2 (ACE2), mainly expressed in type II alveolar cells of the lung, to gain entry into host cells (Fig. 1) [10].

Infection with SARS-CoV-2 is initiated when the RBD binds to ACE2, for which the affinity is ten times higher than that of SARS-CoV [11,12]. The binding triggers the cleavage of ACE2, which is highly upregulated by type 2 inflammation through interleukin-13 (IL-13) and interferons (IFNs) [13]. Transmembrane protease serine 2 (TMPRSS2) helps ACE2 bind to the S protein for easy entry into host cells [14]. The upregulation of ACE2 increases the levels of functional cytokines involved in COVID-19, such as IL-1, IL-10, IL-6 and IL-8 [15]. Overexpression of ACE2 increases the rates of viral infection and replication during SARS-CoV infection [16]; however, for patients with SARS-CoV-2, especially the elderly or those with type 2 diabetes, lower expression of ACE2 results in COVID-19-related death [17]. This difference may be the result of an overexpression of mitochondria-localized NADH4, which is known to produce reactive oxygen species [18]. Clinical outcomes of patients with COVID-19 were improved by transplantation with ACE2-negative mesenchymal stem cells due to decreased tumour necrosis factor- α (TNF- α) and increased IL-10 [19].

In conclusion, the virus is prevented from entering alveolar epithelial cells by antagonizing ACE2 or blocking its downstream signal TMPRSS2.

Lung inflammation

Innate immune response to SARS-CoV-2

Human innate immunity is of great importance during SARS-CoV-2 infection. The single-stranded RNA virus is detected by

Toll-like receptor 3 (TLR3), TLR7 or TLR8, and potentially Retinoic acid-inducible gene I (RIG-I) and Protein kinase receptor (PKR). Next, SARS-CoV-2 non-structural protein 13 (NSP13) interacts with signalling intermediate TANK-binding kinase 1 (TBK1) [20], and NSP15 associates with NSP15, an activator of TBK1 and interferon regulatory factor [21]. NSP9 and NSP10 induce IL-6 and IL-8 production, potentially by inhibition of NKRF, an endogenous nuclear factor- κ B (NF- κ B) repressor factor [22]. Moreover, to prevent signalling downstream of IFN release, SARS-CoV-2 proteins inhibit the IFN receptor subunits (IFNAR1 and IFNAR2) to transduce signals and activate transcription [23]. Compared with patients with asymptomatic or mild disease, those with severe disease have significantly impaired type I IFN (IFN- β) signatures, and higher IL-12 and IL-2 levels [24,25]. The most common deteriorations in patients with COVID-19 are increases in IL-2, IL-6, TNF, IFN- γ -induced CXCL10, granulocyte colony-stimulating factor, CCL3 α , CCL2 and CCL7 [26] (Fig. 2).

During the COVID-19 pandemic, macrophage activation appears to facilitate the initiation and propagation of the hyper-inflammatory response [27]. In contrast to human coronavirus 229E and influenza virus infections, in SARS-CoV-2 infections macrophages cannot induce the expression of IFN- β [28]. Single-cell sequencing of bronchoalveolar lavage fluid from patients with COVID-19 has demonstrated an increase in pro-inflammatory monocytes and ficolin-positive monocyte-derived macrophages, which was paralleled by a decrease in tissue-resident reparative alveolar macrophages in patients with severe disease compared with moderate cases [29]. Merad et al. summarize possible therapeutic targets linked to macrophage activation in COVID-19, including the anti-IL-6 receptor, anti-IL-6, anti-TNF, anti-granulocyte-macrophage colony-stimulating factor, and Janus tyrosine kinase 1 (JAK1)/JAK2 inhibitors [30] (Fig. 2). These drugs are in clinical trials, and there is currently insufficient evidence for their effectiveness in treating COVID-19.

Neutrophils are key components of innate immunity and function to resist harmful microorganisms. However, they also produce cytotoxic factors and aggravate lung inflammation through degranulation, lysis and the expression of chemokines, such as CXCR2 and IL-8, during severe pneumonia [31]. SARS-CoV-2 infection causes more neutrophil infiltration than other forms of pneumonia [32]. The neutrophil/lymphocyte ratio is an independent risk factor for in-hospital mortality for patients with COVID-19, and it increases significantly in severe cases [33]. Patients also overexpress complement 3 (C3) and the receptor for the C3a anaphylatoxin [34]. However, other studies found that the neutrophil/lymphocyte ratio does not reflect the severity of COVID-19 [35].

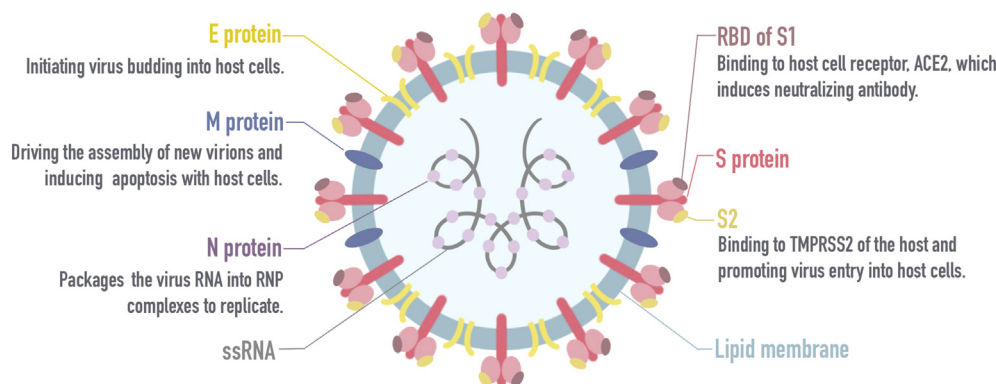


Fig. 1. The structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the function of components. The SARS-CoV-2 virion has a diameter of approximately 100–200 nm; its four structural proteins are spike (S), envelope (E), membrane (M) and nucleocapsid (N). The S protein is comprised S1 and S2. The receptor-binding domain (RBD) of S1 binds to angiotensin-converting enzyme 2 (ACE2). Subsequently, S2 binds to transmembrane protease serine 2 (TMPRSS2) of the host and promotes virus entry into the host cells.

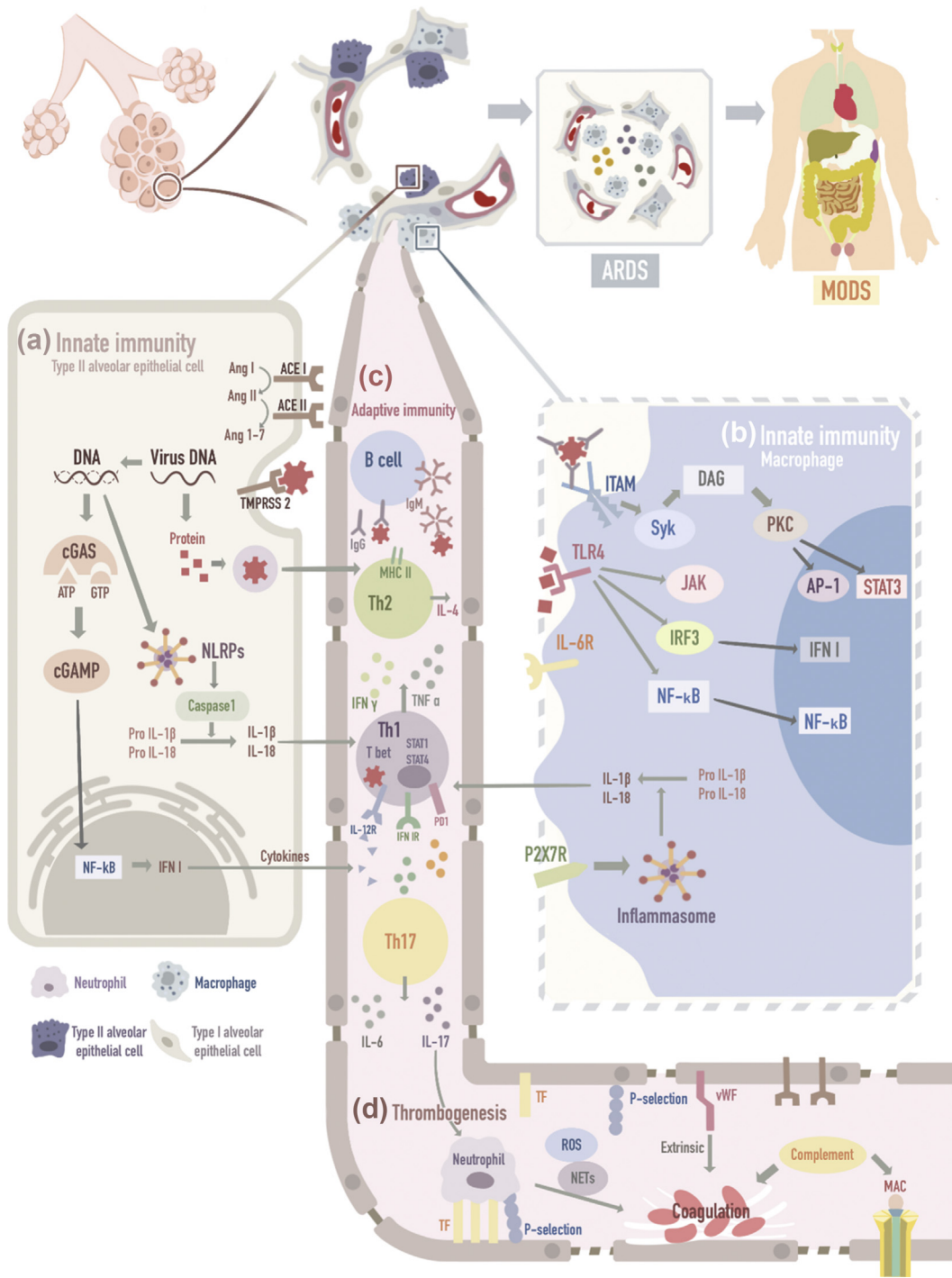


Fig. 2. Immune and inflammatory damage caused by coronavirus disease 2019 (COVID-19). (a) The virus invades the cells and proliferates through the receptors on the surface of alveolar epithelial cells, which activates the immune response in the epithelial cells. As pathogen-associated molecular patterns (PAMPs), the virus directly activates the innate immune response in the body. (b) Macrophages release a large number of cytokines while phagocytes are phagocytes. (c) Activated acquired immunity produces antibodies and memory cells. If the immune response is appropriate, the virus infection can be controlled. If not, the alveolar epithelial cells will undergo pyroptosis, which together with the immune cells causes cytokine storm, leading to acute respiratory distress syndrome (ARDS). (d) Under the role of endothelial cells, complement system, neutrophils and platelets, the coagulation system is activated and forms thromboses; severe cases further develop systemic inflammatory response syndrome (SIRS), or even multiple organ dysfunction syndrome (MODS), and eventually die. Abbreviations: ACEI, angiotensin-converting enzyme I; AngI, Angiotensin I; AP-1, Activator protein-1; cGAMP, 2'3'-cyclic GMP-AMP monophosphate; cGAS, cyclic GMP-AMP synthase; DAG, diacyl glycerol; IFN-I, interferon I; IFN- γ , interferon γ ; IL-1 β , interleukin-1 β ; IRF3, interferon regulatory factor; ITAM, immunoreceptor tyrosine-based activation motif; JAK, Janus tyrosine kinase; NETs, neutrophil extracellular traps; NF- κ B, nuclear factor κ B; PD1, programmed death receptor 1; PKC, protein kinase C; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; Syk, tyrosine kinase; TF, tissue factor; TLR4, Toll-like receptors 4; TMPRSS2, transmembrane protease serine 2; TNF- α , tumour necrosis factor- α .

More interestingly, the autopsy pathology of two patients with COVID-19 revealed that secreted cytokines and chemokines attract immune cells, notably monocytes and T lymphocytes, but not neutrophils [36]. Neutrophils may play important roles in the late stage of this disease.

Adaptive immune response to SARS-CoV-2

T cells in COVID-19

The most common feature of severe COVID-19 is lymphopenia, particularly a drastic reduction in CD8⁺ T cells [37–39]. Persistent viral stimulation contributes to T-cell exhaustion, leading to loss of cytokine production and reduced function [40]. IFN- γ -producing T cells contribute to faster viral clearance and milder SARS-CoV-2 infection [41]. The counts of total T cells of patients in intensive care units, CD4⁺ T cells and CD8⁺ T cells are reduced and negatively associated with patient survival [42]. Autopsies of the spleen and lymph nodes have identified high levels of T-cell apoptosis via the P53 signalling pathway and increased expression of the death receptor Fas, the receptor for FasL, which suggests that activation-induced cell death is probably responsible for T-cell depletion in patients with severe disease [43]. Cytokines such as IFN-I and TNF- α facilitate the retention of T cells in lymphoid organs and their attachment to the endothelium rather than recirculation in the blood [44] (Fig. 2). The higher the serum IL-6, IL-10 and TNF- α concentration, the lower the T-cell numbers [42]. In addition, recruitment of T cells to infection sites decreases T cells in the peripheral blood compartment [37,45]. Extensive lymphocyte infiltration has been observed in lungs [46], but another study found only neutrophilic infiltration in post-mortem biopsies [47]. Therefore, further studies are needed to determine the reason for the lymphopenia in patients with COVID-19.

Interestingly, lymphocytes from 20%–50% of unexposed donors displayed significant reactivity to SARS-CoV-2 antigen peptide pools [48]. Pre-existing cross-reactivity against COVID-19 is presumably a reflection of T-cell memory to circulating “common cold” coronaviruses. Pre-existing T-cell immunity to SARS-CoV-2 is relevant to the severity of COVID-19 because it is plausible that people with a high level of pre-existing memory CD4⁺ T cells to SARS-CoV-2 activates a faster and stronger immune response to better limit disease severity. Memory CD4⁺ T cells accelerate increasingly and generate rapid neutralizing antibody responses against SARS-CoV-2. Memory T cells also facilitate direct antiviral immunity soon after exposure [49]. Furthermore, a negative correlation between age and lymphocyte count indicates heavier clinical manifestations, greater severity and longer disease courses [50]. Therefore, closer monitoring and more medical interventions are needed when treating elderly patients with COVID-19.

B cells in COVID-19

The effects of SARS-CoV-2 on B cells have mainly focused on the generation of specific neutralizing antibodies. RBD-binding antibodies are found within 4–8 days after symptom onset, and most patients develop neutralizing antibodies by 3 weeks [51]. Although the protective duration of antibodies against the disease remains unknown, 40% of asymptomatic patients and 13% of symptomatic patients become negative for anti-spike IgG in the early convalescent phase, which implies that the host response to SARS-CoV-2 is transient [52]. Recent studies have inferred that neutralizing antibody is maintained over 1 year with higher antibody titres and longer duration of detectable antibody in those with severe disease [53]. However, antibodies are not always protective, and previous studies in animals infected with SARS-CoV-2 showed that neutralizing antibodies against S protein amplify severe lung injury by exacerbating inflammatory responses [51]. Besides, 80% of

patients with acute respiratory distress syndrome (ARDS) coincided with antiviral IgG seroconversion. Patients who died of infection took an average of 14.7 days to reach the peak level of neutralizing antibody activity, compared with 20 days for those who continued to recover. Surprisingly, convalescent plasma, used to treat moderate COVID-19, did not improve severe disease progression or all-cause mortality [54]. This may be due to the presence of more than 100 substances in the plasma, most of which are pro-coagulant factors, which aggravate thrombosis [55]. Moreover, the antibody-mediated binding of CoV-Fc receptors increases the uptake of the virus by macrophages and reduces the function of macrophages through virus-mediated immunosuppression [56]. Memory B cells express neutralizing antibodies to SARS-CoV-2, and increase with length of infection [57]. Neutralizing antibodies have entered phase 2 and 3 clinical trials and are expected to be used in the treatment and prevention of COVID-19 [58,59].

Lung injury in COVID-19

The reason for the shift from mild to severe disease in COVID-19 is largely unknown. More than 40% of individuals hospitalized for severe and critical COVID-19 develop ARDS, more than 50% of whom die from the disease [60]. The main pathological features of ARDS are increased pulmonary microvascular permeability and exudation of protein-rich fluid from alveoli, leading to pulmonary oedema and hyaline membrane formation, which are accompanied by pulmonary interstitial fibrosis [61]. The pathophysiological changes mainly result in decreased lung volume, decreased lung compliance and severe ventilation/blood flow imbalance. The clinical manifestations include respiratory distress and refractory hypoxaemia, whereas the lung imaging findings show heterogeneously exudative lesions [62]. The principal characteristics of ARDS in COVID-19 include alveolar epithelial cell damage, cytokine storm, microvasculature endothelial damage and thrombosis.

Alveolar epithelial cell pyroptosis

In pyroptosis of COVID-19, damage-associated molecular patterns activate intracellular sensors, leading to activation of the inflammasome, such as caspase 1, which cleaves and activates the precursor forms of IL-1 β and IL-18. Interleukin-1 β causes acute lung injury via $\alpha_v\beta_5$ and $\alpha_v\beta_6$ integrin-dependent mechanisms [62]. Viral infection and replication in airway epithelial cells cause high levels of virus-associated pyroptosis with vascular leakage [63]. The mechanism of pyroptosis is associated with calcium ion leakage, potassium ion leakage, and the NOD-like receptor family pyrin domain-containing 3 inflammasome–caspase-1–gasdermin-D signal pathway [64,65].

Cytokine storm

Cytokines play a vital role against viruses, but excessive and dysregulated immune responses cause immune damage. Compared with patients with mild disease, those with severe disease present with lymphopenia, neutrophilia, lower levels of antiviral factors and IFNs, and higher serum concentrations of IL-6, TNF and transforming growth factor- β [66] (Table 1). These inflammatory cytokines activate the T helper type 1 cell response, which is the trigger for adaptive immunity [37,67]. However, in contrast to patients with SARS, patients with COVID-19 also have elevated levels of cytokines from T helper type 2 cells (such as IL-4 and IL-10), which function to inhibit the inflammatory response.

Reports on COVID-19 have shown mean IL-6 levels of 25 pg/mL [68], which is far less than the 282 pg/mL in ‘hypoinflammatory’ ARDS [69] and the 1618 pg/mL in ‘hyper-inflammatory’ ARDS [70]. The onset

Table 1
Significance of laboratory indicators in COVID-19

Research	Object	Indicators	Significance
Chaolin Huang et al. [34]	Total (n = 41) ICU (n = 13) Non-ICU (n = 28)	Higher amounts of IL-1 β , IFN- γ , IP10, MCP1 Higher concentrations of G-CSF, IP10, MCP1, MIP1A, TNF- α	Infected people compared with uninfected people Requiring ICU admission
Fei Zhou et al. [79]	Total (n = 191) Died (n = 54) Discharged (n = 137)	Older age, D-dimer levels greater than 1 μ g/mL, and higher SOFA score Higher IL-6, high-sensitivity cardiac troponin I, and LDH and lymphopenia	Higher odds of in-hospital death In severe COVID-19 illness
Dawei Wang et al. [29]	Total (n = 138) ICU (n = 36) Non-ICU (n = 102)	Lymphopenia, prolonged prothrombin time, higher LDH	Infected people compared with uninfected people
Qirong Ruan et al. [80]	Total (n = 150) Died (n = 68) Discharged (n = 82)	WBC counts, absolute values of lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, blood creatinine, myoglobin, cardiac troponin, CRP, IL-6	Predictors of a fatal outcome
Chaomin Wu et al. [53]	Total (n = 201) ARDS (n = 84) Without ARDS (n = 117)	Older age Neutrophilia Higher LDH Higher D-dimer High fever (>39°C)	Develop to ARDS HR3.26 (2.08-5.11) Death HR6.17 (3.26-11.67) Develop to ARDS HR1.14 (1.09-1.19) Death HR1.08 (1.01-1.17) Develop to ARDS HR1.61 (1.44-1.79) Death HR1.30 (1.11-1.52) Develop to ARDS HR1.03 (1.01-1.04) Death HR1.02 (1.01-1.04) Develop to ARDS HR1.77 (1.11-2.84) Death HR0.41 (0.21-0.82) Develop to severe cases
Guang Chen et al. [35]	Total (n = 21) Severe (n = 11) Moderate (n = 10)	Higher alanine aminotransferase, lactate dehydrogenase, CRP, ferritin, D-dimer, IL-2R, IL-6, IL-10, and TNF- α . Lower absolute numbers of T lymphocytes, CD4 ⁺ T cells, CD8 ⁺ T cells, IFN- γ by CD4 ⁺ T cells	Develop to severe cases
Xiaochen Li et al. [81]	Total (n = 548) Severe (n = 269) Non-severe (n = 279)	Older age, underlying hypertension, high cytokine levels (IL-2R, IL-6, IL-10 and TNF- α), and higher LDH Male sex, older age, leucocytosis, higher LDH, cardiac injury, hyperglycaemia	Develop to severe cases Higher risk of death
Zhongliang Wang et al. [82]	Total (n = 69) SpO ₂ <90% (n = 14) SpO ₂ \geq 90% (n = 55)	Higher IL-6, IL-10, LDH, CRP Older age and with underlying comorbidities	Induced a mortality rate of 7.5%. Higher risk of death
Chuan Qin et al. [61]	Total (n = 452) Severe (n = 286) Non-severe (n = 166)	Lower T lymphocytes NLR and lymphocyte subsets Lower lymphocyte counts, T cells, helper T cells, memory helper T cells, regulatory T cells, percentages of monocytes, eosinophils and basophils. Higher leucocyte counts and NLR, naive helper T cells, infection-related biomarkers and inflammatory cytokines.	Pathological process Screening of critical illness, diagnosis and treatment Develop to severe cases
Suxin Wan et al. [83]	Total (n = 123) Severe (n = 21) Mild (n = 102)	Lower CD4 ⁺ T, CD8 ⁺ T, IL-6, IL-10 and PII Lower PII	Indicators of disease evolution An independent indicator for disease progression
Bo Xu et al. [84]	Total (n = 187) Died (n = 28) Discharge (n = 117)	Lower T lymphocyte subsets counts Higher SAA, CRP Higher IL-6, and IL-10 Lower median lymphocyte, CD3 ⁺ T cell, CD4 ⁺ T cell, CD8 ⁺ T cell and B cell	Develop to severe cases Higher risks of in-hospital death

Abbreviations: CRP, C-reactive protein; G-CSF, granulocyte colony-stimulating factor; IFN- γ , interferon γ ; IL-1 β , interleukin 1 β ; IP10, interferon-inducible protein-10; LDH, lactate dehydrogenase; MCP1, mitochondrial pyruvate carrier 1; MIP1a, macrophage inflammatory protein 1 α ; NLR, neutrophil to lymphocyte ratio; PII, pulmonary inflammation index; SAA, serum amyloid a protein; TNF- α , tumour necrosis factor α .

time of COVID-19-related ARDS is 8–12 days, which is inconsistent with the ARDS Berlin criteria, which defines a 1-week onset limit. Lung compliance might be relatively normal in some patients with COVID-19 and ARDS who meet ARDS Berlin criteria [71]. Mechanically ventilated patients with ARDS infected with COVID-19 have been similar to other causes of ARDS with high compliance, and increasing mortality with the degree of ARDS severity [72]. Although early reports suggested that COVID-19-associated ARDS has distinctive features, emerging evidence indicates that COVID-19-associated ARDS is similar to historical ARDS [73].

Glucocorticoid is a broad-spectrum anti-inflammatory drug that can regulate immune function in many aspects, inhibit innate and adaptive immunity, inhibit the release of pneumonia-related cytokines and induce apoptosis of lymphocytes. Therefore, it may reduce the level of systemic inflammation in patients with COVID-

19. The RECOVERY study suggested that systemic glucocorticoids were associated with a lower risk of death within 28 days in patients receiving mechanical ventilation ($n = 3883$, relative risk 0.64; 95% CI 0.51–0.81) and oxygen therapy alone ($n = 1007$, relative risk 0.82; 95% CI 0.72–0.94) [74]. Another meta-analysis involving seven randomized controlled trials ($n = 1703$) suggested that systemic glucocorticoid treatment reduced the risk of 28-day all-cause death in critically ill COVID 19 patients (OR 0.66, 95% CI 0.53–0.82) [75]. Therefore, glucocorticoid therapy is recommended for critically ill COVID-19 patients.

Thrombotic inflammatory mechanisms

Abnormal coagulation parameters are associated with high mortality in patients with COVID-19 [76]. Thrombosis mechanisms

in COVID-19 include endothelial inflammation, disruption of intercellular junctions, microthrombus formation, increased cytokines and increased activation of platelets, endothelium and complement [77] (Fig. 2).

In the early phases of infection, ACE2 consumption by viral entry increases the concentration of angiotensin-II, which is mainly metabolized to the anti-inflammatory peptide angiotensin (1–7) by endothelial ACE2. Angiotensin-II has effects on endothelial activation, vasoconstriction, pro-inflammatory cytokine release, platelet activation and even accelerates lymphocyte recruitment and suppression [78]. Interestingly, the basal level of angiotensin-II increases microvascular permeability, but a higher level decreases permeability, which is attributed to the inflammation-induced shift from ACE1 to ACE2 [79].

Less ACE2 leads to reduced angiotensin 1–7 and reduced activation of the MAS receptor, which results in a pro-thrombotic endothelial cell phenotype [80]. Reduced expression of ACE2 indirectly activates the kallikrein–kinin system, which ultimately increases vascular permeability [8,18]. High levels of bradykinin might explain the majority of severe symptoms, ranging from blood vessel injury to neurological complications [81]. Therefore, it is important to regulate the thrombosis resistance of endothelial cells by balancing the kallikrein–kinin and renin–angiotensin systems [15,82,83]. The anti-C5 monoclonal antibody eculizumab may be a valuable tool for preventing complement activation in patients with COVID-19 [84].

Furthermore, neutrophil extracellular traps (NETs) play a prominent role in promoting severe cytokine release and exacerbate lung damage by directly killing epithelial and endothelial cells [85]. NET formation is initiated by hypoxia-induced release of von Willebrand factor and P-selectin from the endothelium, which recruits and activates neutrophil NETosis. Neutrophil accumulation is P-selectin-dependent and leads to the recruitment of platelets to promote thromboxane A2 production, which induces endothelial cell expression of intercellular adhesion molecule 1 to strengthen neutrophil interactions with the endothelium [86]. Post mortems of COVID-19 patients have demonstrated the presence of NETs in the airway compartment and neutrophil-rich inflammatory areas, whereas NET-prone primed neutrophils were present in arteriolar microthrombi [87]. Hence, more attention should be paid to neutrophils given their involvement in inflammation, the immune response and thrombosis.

Conclusion

COVID-19 has attracted attention around the world, and there are many clinical and fundamental research studies ongoing. Even though the current science and technology are highly developed, the underlying pathogenesis is still unclear. Because SARS-CoV-2 has been around for a limited time, long-term studies of the effectiveness and adverse effects of drugs and vaccines remain scarce. In general, when infected with COVID-19, the homeostasis of the human immune system, the normal anti-infection function of the innate immune and the adaptive immune systems, and the rapid and sustained effect of neutralizing antibodies are very important. The timely study of mutant strains and the uptake of the vaccines are imperative. The fight against COVID-19 requires the contribution of every country and every individual.

Author contributions

L-LW drafted the first and subsequent versions of the manuscript. J-WY and J-FX provided critical feedback and contributed to the manuscript. J-FX offered funding acquisition.

Transparency declaration

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