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SARS-COV-2 Induce Pulmonary Injury from Basic to Clinical Research

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Abstract

The SARS-CoV-2 has infected over 194,909,000 cases and over 4,170,000 deaths in the world before the end of July 2021. The virus attacks human alveoli and induces severe lung injury (COVID-19 disease) and spreads rapidly. The mechanisms of COVID-19 disease are unclear. To better understand this disease, This review analyzes the SARS-CoV-2 biological characteristics, insights the effect of alveolar epithelium and its adjacent microvascular endothelium, investigates human host cells immune response and immunothrombosis. Explains clinical manifestations of COVID-19 associated lung injury. It may be helpful for development management strategies for COVID-19 associated pulmonary damage.

Keywords

COVID-19, SARS-CoV-2, Pulmonary Injury, Clinical Manifestation, Treatment Strategies

1. Introduction

The respiratory system comprises different epithelial cell layers and vascular beds. Because of constant exposure to the outside environment, lung infection is a risk factor for human. It can also develop into life-threatening conditions, when they induce excessive recruitment and activation of inflammatory cells [1] [2] [3] [4]. World Health Organization reports that the SARS-CoV-2 has infected over 194,909,000 cases and over 4,170,000 deaths in the world before the end of July 2021. SARS-CoV-2 primarily attacks lung of human, causes severe injury, inflammatory activation and immune response. The virus attacks human alveoli and induces severe lung injury (COVID-19 disease) and spreads rapidly [5] [6] [7] [8]. Pulmonary mainly includes epithelial layer, extracellular matrix and

pulmonary capillaries. The extracellular matrix between alveolar epithelium and pulmonary microvascular endothelium forms an alveolar-capillary barrier. The alveolar surface covers type I (95%) and type II (5%) epithelial cells. These cells are tightly connected to prevent the fluid accumulation within the alveoli. Type II cells are very important for repairing and regulating the alveoli epithelial cells, their secreted active substances can regulate the surface tension of the alveolar. When SARS-CoV-2 enters alveolar and attacks the type II cells, it changes the surfactant lining of the alveolus making alveolar collapse. Pulmonary infection caused inflammatory cytokine excessive expression and leaded to SIRS, activated and damaged vascular endothelial cells, induced strong immune response and cytokine storm formation intravascular coagulation and thrombus. The patients with COVID-19 present hypoxia, respiratory failure and ARDS. Damaged vascular endothelial cells may help to develop ARDS, The sustained inflammation, immune response and thrombi formation lead to patients with COVID-19 septic shock, multi-organ failure and death [9] [10] [11] [12] [13]. This review researches on SARS-COV-2 induced pulmonary injury from molecular mechanism to clinical manifestations. Investigate SARS-COV-2 attack pulmonary and host defence relationship. Find the diversity of pulmonary damage mechanism and clinical evidences. It may be helpful for development treatment strategies for COVID-19 associated pulmonary damage [14] [15] [16] [17] [18].

1.1. SARS-CoV-2 Infected Pulmonary Epithelial Cells

SARS-CoV-2 virus enters the human lungs, its spike glycoprotein connects ACE-2 on host cell and gets into it **Figure 1(A)** [19]. The life recycle of SARS-CoV-2 is shown in **Figures 1(B)-(D)** [20]. Type II cells were attacked by SARS-CoV-2 virus, which cause inflammatory cytokine excessive expression, chemokines and interferons release. These inflammatory factors made large numbers of macrophages, neutrophils recruit and T cells activation. Activated macrophages secrete inflammatory mediators such as IL-1, IL-6 and TNF-α. These inflammatory mediators cause capillary permeability increase, which make plasma to leak into the pulmonary interstitial and the alveolus space [21] [22] [23] [24] [25]. Activated neutrophils secrete proteinases and release reactive oxygen species, these inflammatory mediators cause infected cell destroy into debris. The plasma and cell debris combine to form a protein-rich fluid. This protein-rich fluid leaks into the pulmonary interstitial and the alveolus space cause dyspnoea and pneumonia **Figures 2(A)-(C)** [26]. It also dilutes the alveolar surfactant, decreases the surface tension of the alveolar and makes alveolar collapse, which leads to hypoxaemia and ARDS in COVID-19 patients [27]-[32]. The sustained severe inflammation response leads to SIRS, septic shock, MOF and death **Figures 2(D)-(I)** [33].

1.2. SARS-CoV-2 Associated Pulmonary Endotheliopathy

SARS-CoV-2 infected pulmonary vascular endothelial cells through ACE-2

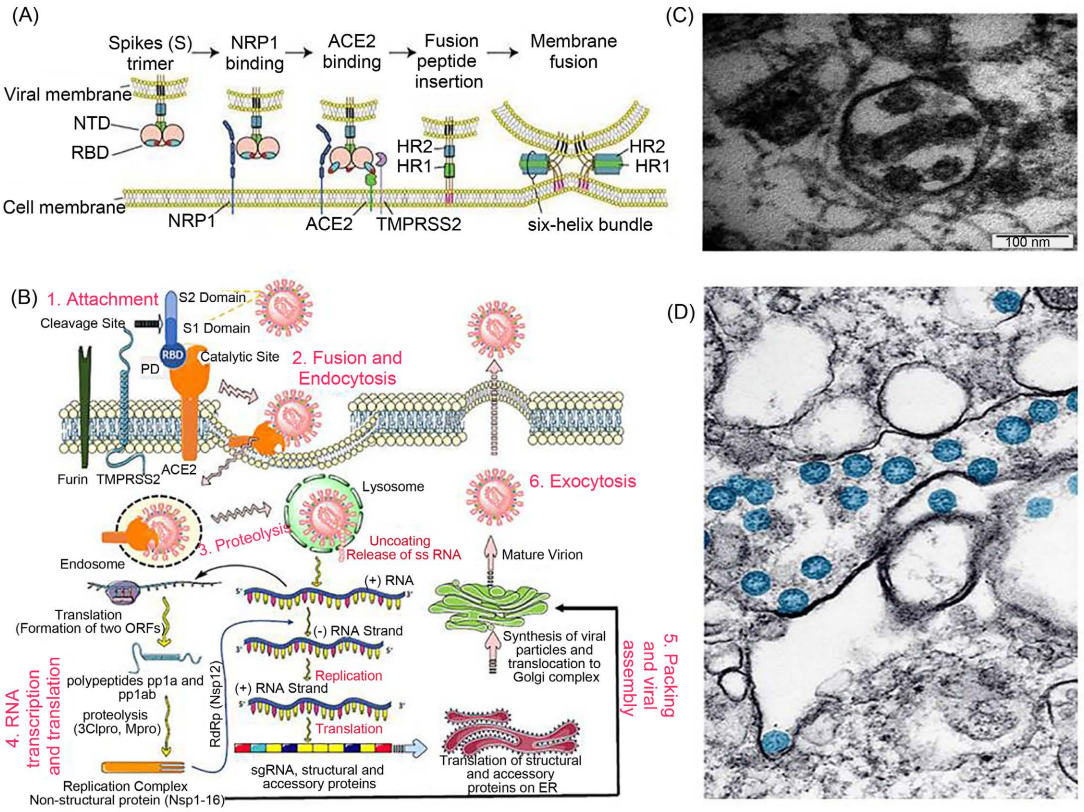

Figure 1. SARS-CoV-2 lifecycle in virus susceptible host cell. (A)-(B): Schematic representation of SARS-CoV-2 virus enters host cell and replication. (C)-(D): A transmission electron microscope image of SARS-CoV-2 spherical viral particles in cell, The virus is colorized in blue.

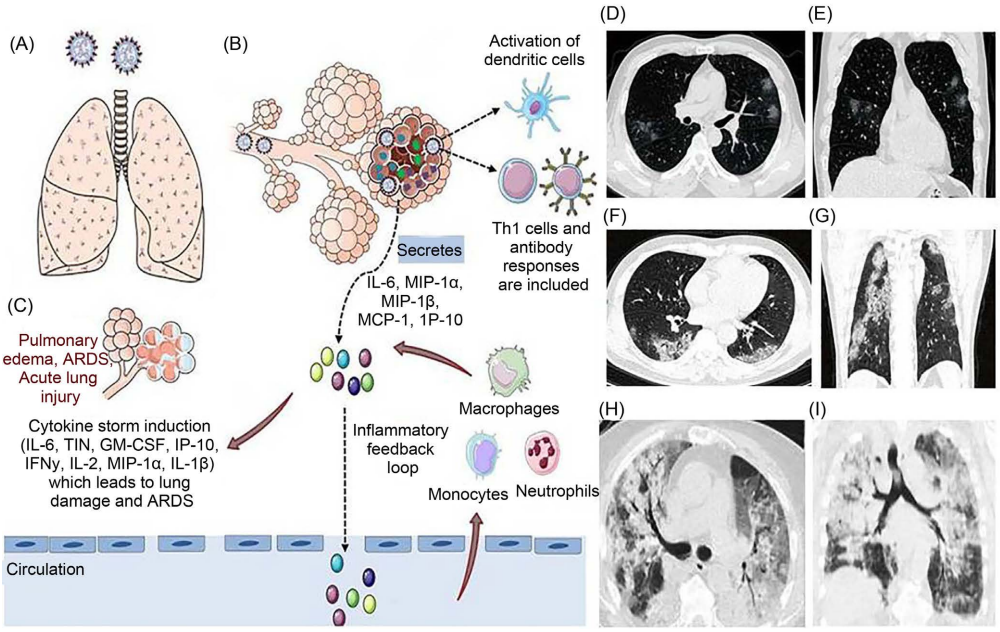

Figure 2. SARS-CoV-2 infected epithelial cells and human host inflammation response. (A)-(B): SARS-CoV-2 infected respectory tract and alveolar epithelial cells. (C): SARS-CoV-2 induced inflammation response mechanism. (D)-(E): The Images representative mild pulmonary infection. (F)-(G): The Images representative moderate pulmonary infection. (H)-(I): The Images representative severe pulmonary infection.

receptor. The pulmonary endothelial cells injury was caused directly and indirectly by the virus. The mechanisms were shown in **Figure 3(A)** and **Figure 3(B)** [34]. Damaged pulmonary vascular endothelial induce inflammatory cells further activation, inflammatory cytokine further expression, inflammatory mediators further release [35] [36] [37] [38]. Which increased pulmonary vascular endothelial cells and pulmonary interstitial and the alveolus damage. This process leads to endothelial damage, endothelial dysfunction, Alveolar damage, vascular wall edema, microhemorrhage, thrombocytopathy, thromboinflammation, hyaline thrombi, diffuse thrombosis (peripheral or central vasculars) [39]-[43]. The patients with COVID-19 present Hypoxia, respiratory failure, ARDS, septic shock, MOF and death. According to Harry Karmouty-Quintana and Lisa Allnoch's reports [44] [45], if covid-19 patients got better or recovered, the damaged blood vessels are repaired and remodeled by themselves. The mechanisms and experimental results were shown in **Figures 3(C)-(G)**.

1.3. SARS-CoV-2 Associated Pulmonary Coagulopathy

Severe COVID-19 associated with coagulation dysfunction. PT, fibrin and D-dimer are the important coagulation markers that may imply the progression of COVID-19. The pathomechanisms of pulmonary coagulopathy were shown in **Figure 4** [46]. SARS-CoV-2 viral attacked pulmonary alveolar epithelial and

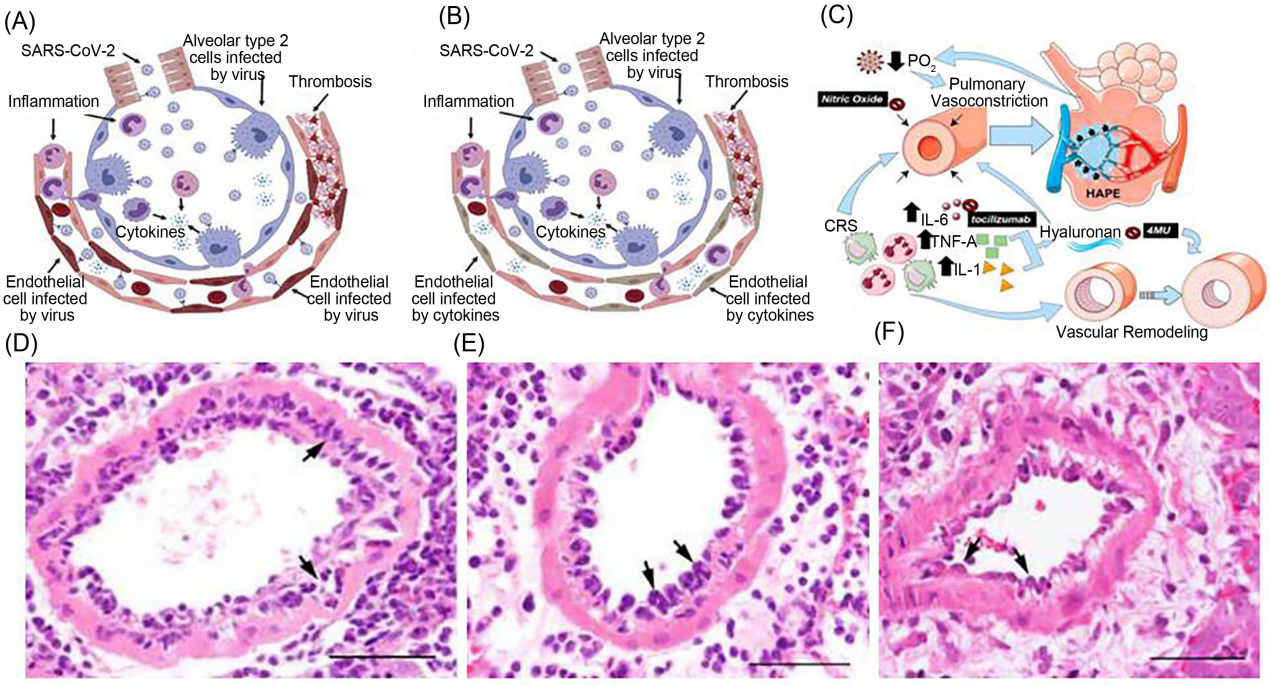

Figure 3. SARS-CoV-2 induced pulmonary vascular endothelial injury and remodeling. (A): pulmonary vascular endothelial cell direct injury mechanism. (B): pulmonary vascular endothelial cell indirect injury mechanism. (C): pulmonary vascular remodeling mechanism. (D): The Images representative pulmonary vasculitis in infection SARS-CoV-2 hamster lungs (Hematoxylin & eosin, ×200). (E): The Images representative pulmonary vascular endothelialitis in infection SARS-CoV-2 hamster lungs (Hematoxylin & eosin, ×200). (F): The Images representative pulmonary vascular endothelial hypertrophy in infection SARS-CoV-2 hamster lungs (Hematoxylin & eosin, ×200).

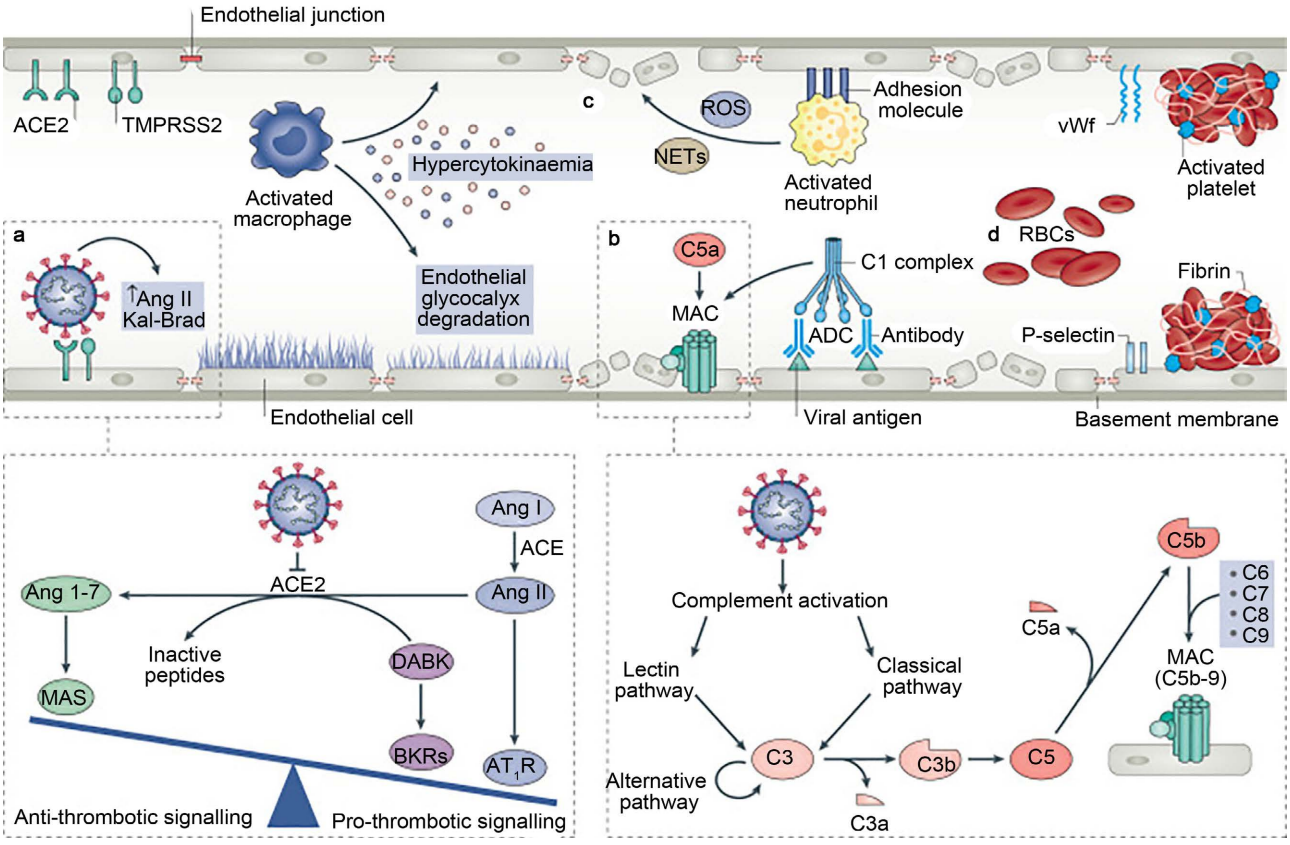

Figure 4. Mechanisms of coagulopathy and thrombosis.

vascular endothelial cells, induced thromboplasm inflammation, systemic inflammation, immune microthrombi formation, activated macrophages, neutrophils, T cells, complements, platelets, coagulation system and fibrinolysis system, which leads to peripheral or central vascular embolization, organ dysfunction, bleeding, and poor outcome [47]-[52]. Severe pulmonary infection making alveolar collapse and VA/Q mismatch leads to pulmonary elastance decrease, pulmonary edema, hypoxemia, respiratory failure, ARDS.

The patients with COVID-19 who have these clinical characteristics called pulmonary intravascular coagulation [53] [54]. If the SARS-CoV-2 viral is overload, SARS-CoV-2 viral induced SIRS, DIC, thrombosis disseminates to the systemic circulation, diffuse thrombosis of peripheral and centra lvessels embolization, diffuse alveolar damage **Figure 5** [55]. All of these lead to septic shock, ARDS, multi-organ failure and death.

1.4. SARS-CoV-2 Associated Pulmonary Immunopathy

The natural history of COVID-19 includes an initial stage of viral replication that can be followed by a second stage of immunopathology driven by a hyperinflammatory response to SARS-CoV-2 infection. This disease is due not only to the virus but also to the result of an excessive and detrimental host immune response [56] [57] [58]. Immune response to SARS-CoV-2 involves both the innate and adaptive immunity **Figure 6** [59]. Activated innate immune cells

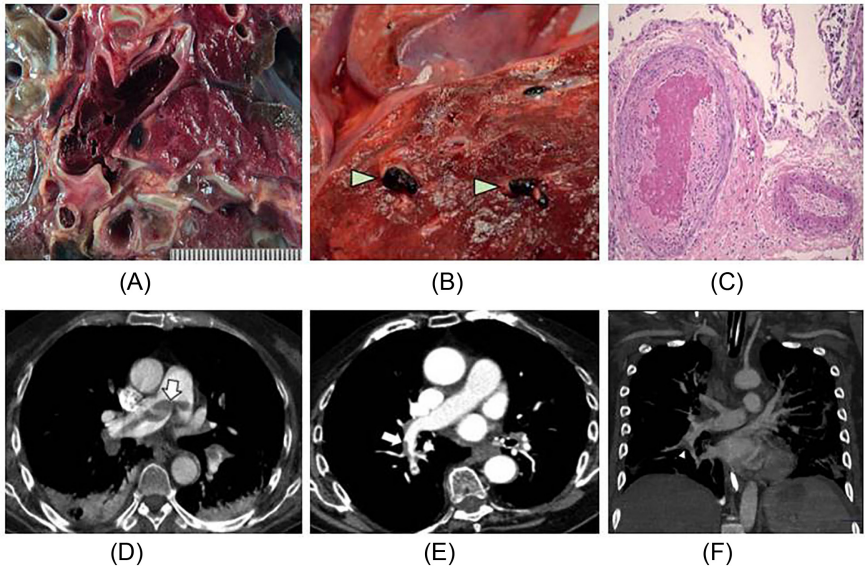

Figure 5. Thrombosis of pulmonary in COVID-19 patients. (A)-(B): The Images of COVID-19 patients' lung with pulmonary embolism. (C): COVID-19 patients' lung with with thrombosis (HE, stain, ×200). (D)-(F): peripheral and centra lvessels pulmonary thrombosis of COVID-19 patients.

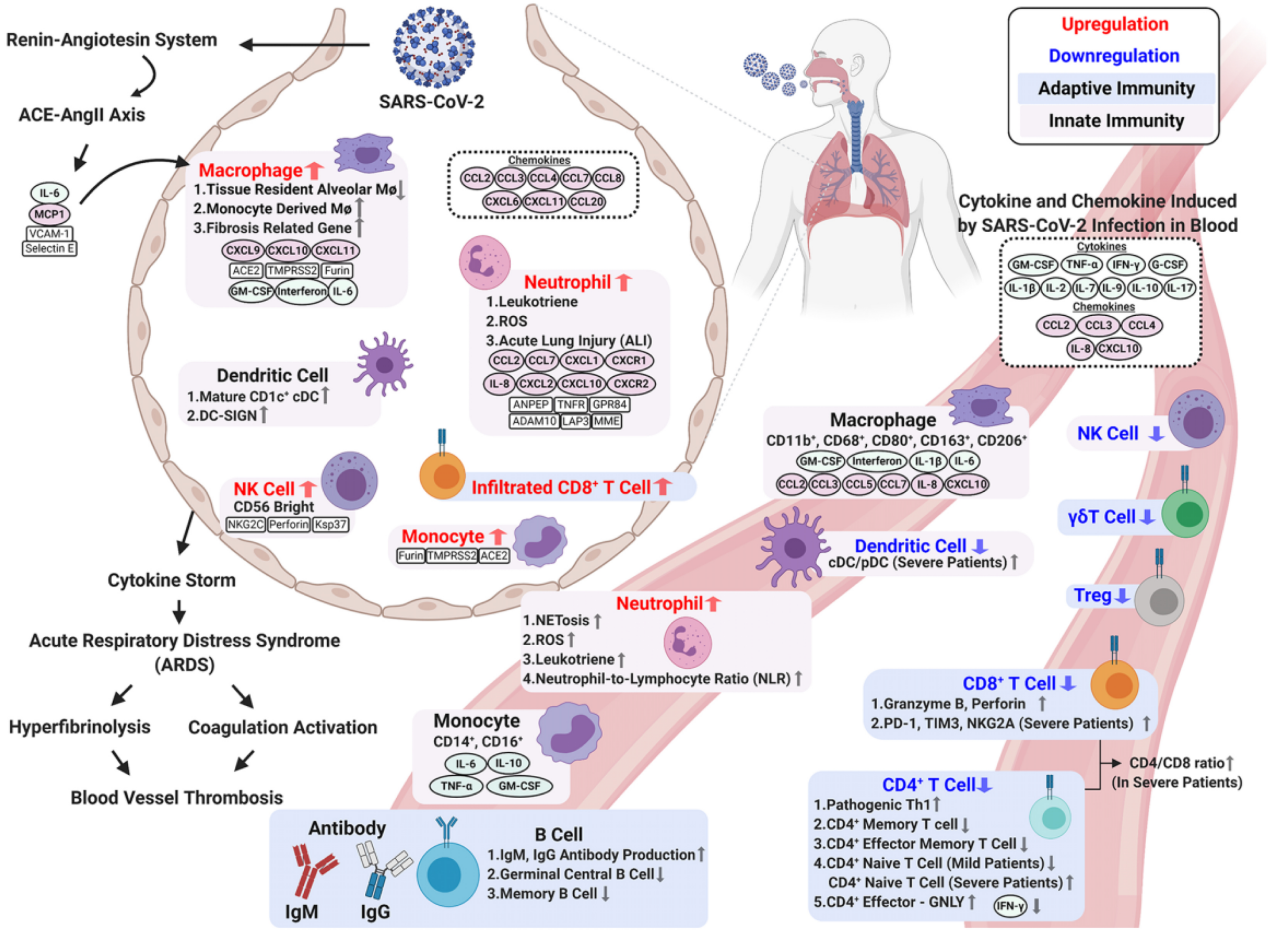

Figure 6. SARS-CoV-2 induced the immune microenvironment Change and immunopathy (Figure created with BioRender).

trigger a strong immune response to secrete cytokines, which cause a cytokine storm and ARDS, which induces intravascular coagulation and hyperfibrinolysis and causes high thrombus burden in COVID-19 patients. SARS-CoV-2 infection significantly decreases total adaptive immunity lymphocytes and impairs their ability to defend against the virus. Upon infection, CD4+ T cells differentiate less frequently into Th1 cells, and this is associated with the decreased IFN-g production for antiviral response [60] [61]. Severe COVID-19 patients exhibit the exhausted phenotype CD8+T cell with high PD-1 and Tim-3 expression. Interestingly, compared to mild cases, severe COVID-19 patients have higher counts of activated CD8+ T cells in circulation to produce cytotoxic granzyme B and perforin [62]-[67]. The humoral response is less affected by the virus. The increase in activated B cells gives greater antibody production and better protection to eliminate the virus. The immune response is a double-edged sword and then the host appear immunopathy **Figure 7** [55]. Immunothrombosis is mainly triggered by neutrophils and monocytes and formated microthrombi in small vessels. Immunothrombosis was originally described to refer to an intrinsic effector pathway of innate immunity triggered by pathogens and injured cells to reduce the spread and survival of the invading pathogens. Immunothrombosis can be considered a beneficial mechanism of intravascular immunity [68] [69] [70] [71] [72]. However, when immunothrombosis is uncontrolled, it causes dysregulated activation of the coagulation cascade, leading to microthrombus

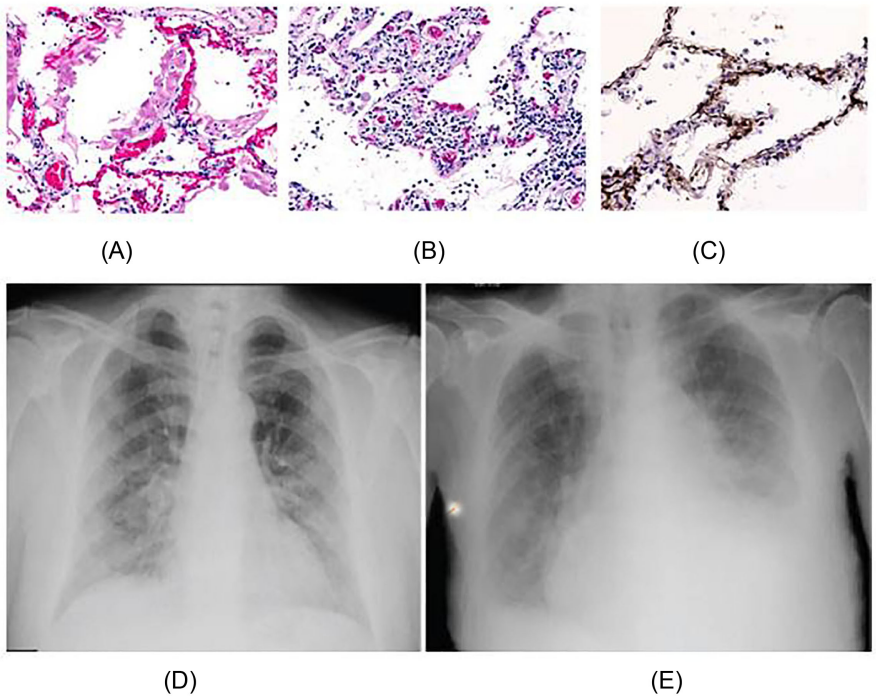

Figure 7. SARS-CoV-2 induced immunopathy in patients. (A): Diffuse alveolar damage and hyaline membranes formation in COVID-19 patient (HE stain, ×200). (B): Diffuse Interstitial inflammation cells infiltration in COVID-19 patient (HE stain, ×200). (C): Microthombi formation in capillaries of the alveoli in COVID-19 patient (Fibrin stain, ×200). (D)-(E): The Images representative pulmonary edema in COVID-19 patients.

formation and inflammation, which in turn enhance each other and may, ultimately, develop into thrombosis and DIC [73] [74] [75] [76].

1.5. SARS-CoV-2 Associated Pulmonary Fibrosis

Severe COVID-19 patients suffer from pulmonary dysfunction even months after diagnosis and may possibly never fully recover. SARS-CoV-2 attack alveolar epithelial cells and an imbalanced inflammatory response result in diffuse alveolar damage and trigger a fibrotic response to regenerate the epithelial barrier and lung function [77]-[82]. It is unclear whether fibrosis will develop and consequently resolve or progress. The alveolar epithelial cell injury triggers a cascade of reactions, which includes the release of pro-inflammatory cytokines, activates immune responses and promotes fibroblast proliferation as well as interstitial fibrogenesis [83] [84] [85] [86] [87]. This would be primary wound healing mechanisms for pulmonary recovery. These effects will be reconstituted by recovery of the basal lamina, re-epithelialization of the alveolar epithelium and pulmonary fibrosis **Figure 8** [88] [89]. A precise and

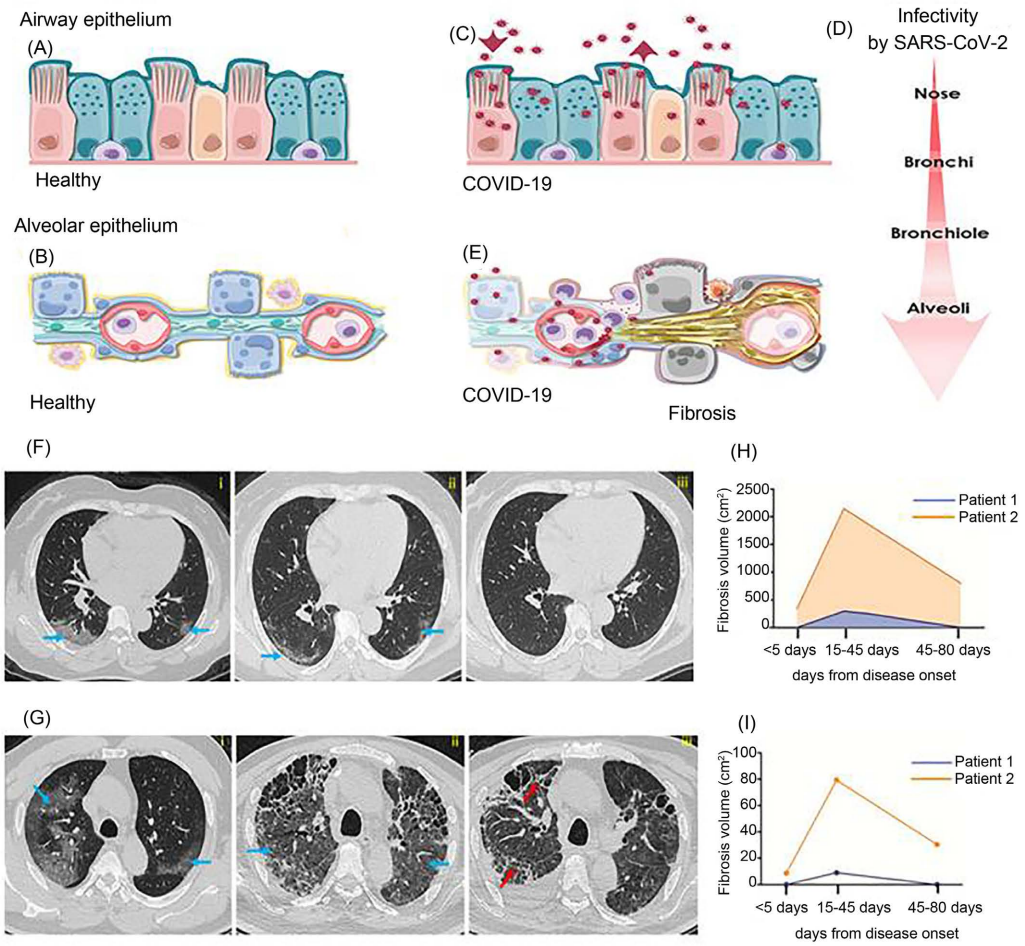

Figure 8. Pulmonary fibrosis mechanism and manifestation. (A)-(E): SARS-CoV-2 induce Pulmonary fibrosis evolution process. (F): Patient-1 Pulmonary fibrosis evolution process. (G): Patient-2 Pulmonary fibrosis evolution process. (H)-(I): Fibrosis volume evaluate Pulmonary fibrosis for the two patients.

controlled recovery mechanism following alveolar damage is crucial to terminate progression of the lung remodeling toward pulmonary fibrosis [90] [91] [92] [93] [94]. A progressive phase is characterized by fibrin deposition and infiltration of inflammatory cells and fibroblasts. Pulmonary fibrosis consolidates with collagen deposition and fibroblast proliferation in the interstitial spaces.

1.6. Clinical Manifestations and Treatment Strategies for SARS-CoV-2 Pulmonary Infection

Natural history of SARS-CoV-2 pulmonary infection, from incubation to critical disease is shown in **Figure 9** [95].

Phase 0: Asymptomatic infection is reported as different time between 0 - 14 days.

Phase I: The patients have mild clinical symptoms, such as upper respiratory tract infection (rhinitis, anosmia and agueusia) and/or lower respiratory tract infection (cough, fever, thoracic pain).

Phase II: This phase is characterised by persistent lower respiratory tract infection with abnormal blood parameters involved in the severity of the disease can be detected.

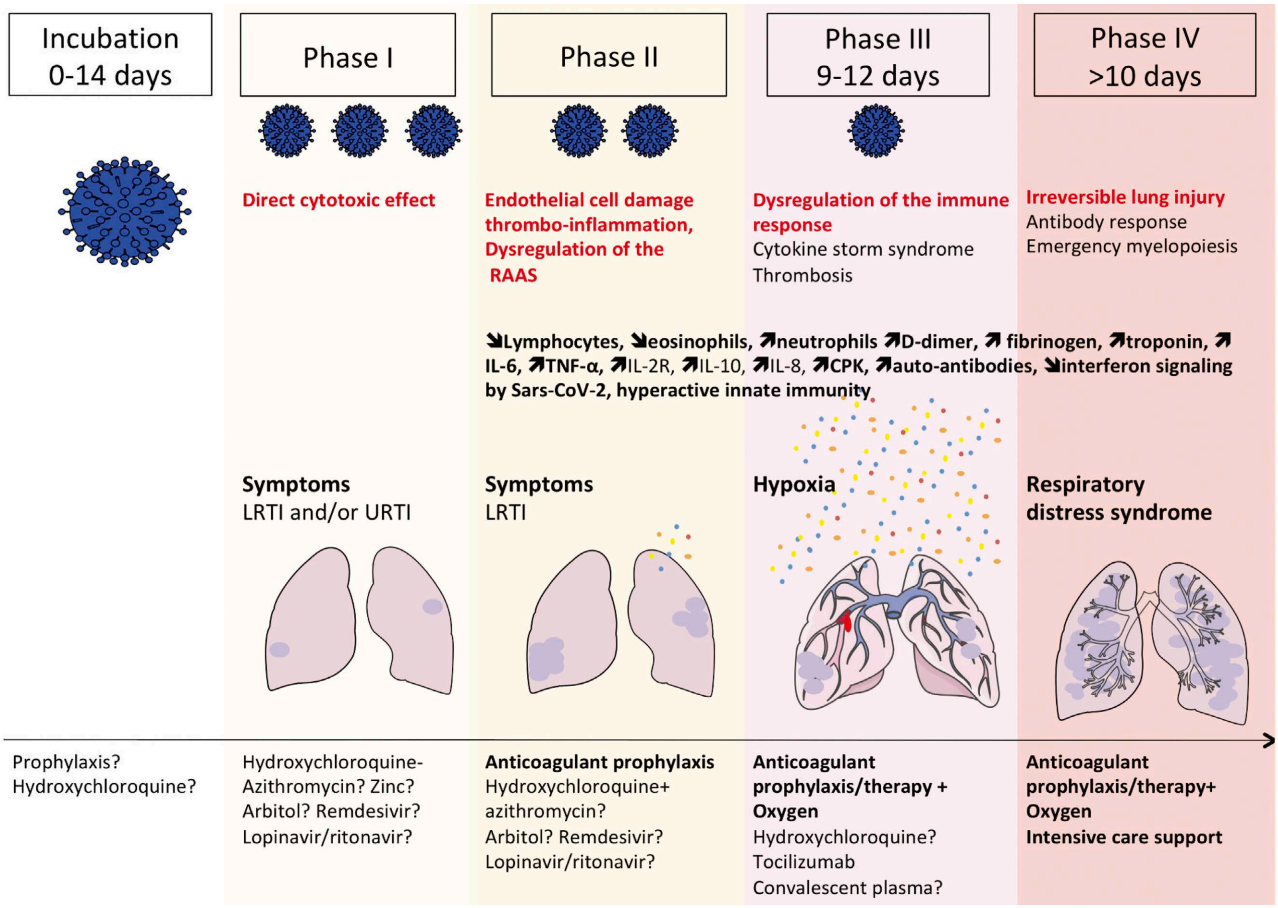

Figure 9. Different stages clinical manifestations of SARS-CoV-2 infection and pulmonary injury.

Phase III: After the onset of symptoms, sudden deterioration caused by the cytokine storm syndrome and pulmonary embolism can lead to hypoxia and ARDS. Oxygen and intensive care therapy are used in these patients [96] [97] [98] [99].

Phase IV: patients are involved critical state. 30% patients required non-invasive mechanical ventilation, Mechanical ventilation is implemented in 12.3% of cases and less than 3% required invasive mechanical ventilation with ECMO [100] [101] [102].

To date, COVID-19 treatment methods include fluid and nutritional therapies **Figure 10** [103], supportive treatments such as hypoxia and respiratory failure therapy **Figure 11** [104], antiviral managements & network-based drug target

- Start EN early within 24¬36 hours ICU admission, or within 12 hours of intubation and placement on mechanical ventilation.
- Infuse EN into the stomach via a 10¬12 Fr tube. A large-bore orogastric or nasogastric tube placed at time of intubation is appropriate to use if that is the only enteral access device available.
- If EN delivery is limited due to intolerance, add a prokinetic agent before attempting post-pyloric tube placement into the small bowel.
- Use of a feeding tube placed by bedside electromagnetic guidance or integrated imaging is recommended over one placed by endoscopic or fluoroscopic guidance (which often requires transport out of the ICU).
- Any abdominal films required to confirm tube placement should be clustered with attainment of chest x-rays requested by the primary team.
- Use of continuous EN infusion is recommended over bolus infusion to decrease exposure to the healthcare provider. In case of pump shortages, infusion by gravity drain is preferred over bolus infusion.
- Initiate trophic low-dose EN and advance slowly over 1 week to:
  - Energy goal of 70¬80% of caloric requirements (15¬20 kcal/kg ABW/day)
  - Protein goal of 1.2¬2.0 g/kg ABW/day
- In obesity, calculate goals by:
  - Energy at 11¬14 kcal/kg ABW per day for BMI 30¬50, 22¬25 kcal/kg IBW/day for BMI >50
  - Protein at 2.0 (Class I, II) or 2.5 (Class III) g/kg IBW/day
- Use a standard isosmotic polymeric formula.
- Consider supplementation with soluble prebiotic fiber and probiotics and switching to a mixed fiber formula once tolerance of the EN regimen is established.
- Withhold EN if there is a rising lactate level, or hemodynamic instability with the need for escalating vasopressor support.
- Switch from EN to PN if there is significant EN intolerance, as evidenced by unexplained abdominal pain, vomiting, diarrhea, abdominal distention, pneumatosis intestinalis, or dilated loops of bowel with air/fluid levels.
- Initiation of PN should be considered as soon as possible in the following patients for whom gastric feeding is contraindicated or not feasible:
  - High nutrition risk
  - Malnourished, poor nutrition status
  - Expected prolonged intensive care unit length of stay
  - Gastrointestinal involvement of COVID-19 with significant intolerance
- Delay initiation of PN in the low-risk patient for 5¬7 days.
  - Limit use of ω-6 soy-based intravenous lipid emulsion (ILE) for the first week, either by restricting use of an ILE altogether or switching to a mixture of lipids such as SMOF (soy, medium-chain triglycerides, olive oil, fish oil).
- Monitor serum triglyceride levels closely if propofol or soy-based ILE are used.

Figure 10. Nutrition recommendations for enteral and parenteral nutrition in patients with COVID-19.

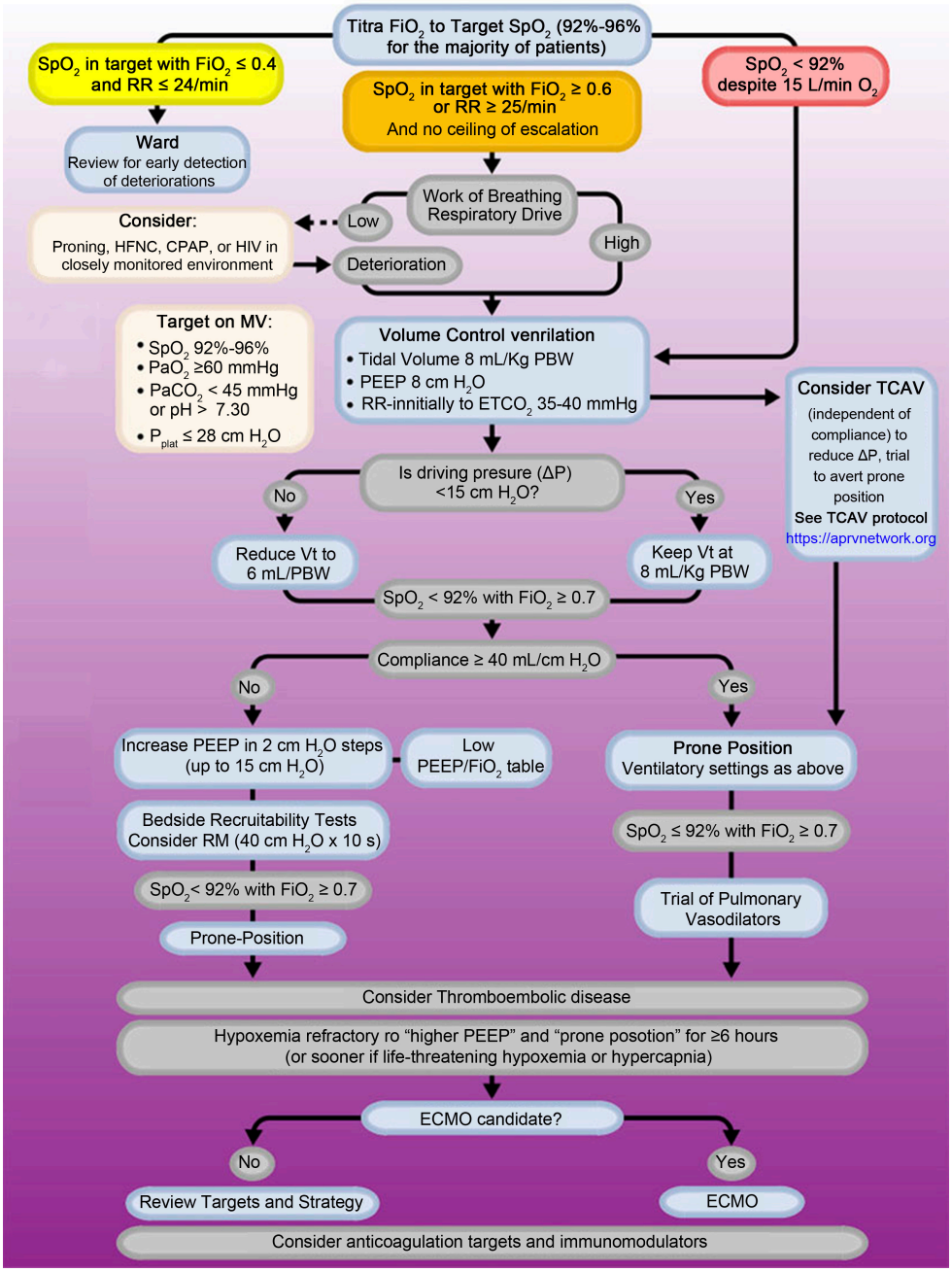

Figure 11. Illustrative flowchart for the management of hypoxia and respiratory failure in SARS-CoV-2 infection patients.

strategies **Figure 12** [105], immune therapies **Figure 13** [106], and anticoagulation therapies, *et al.* However, we have no safe, effective and specific antiviral therapies or vaccines for COVID-19 patients. The researchers tried their best to develope vaccines **Figure 14** [107] or antiviral therapies **Figure 15** [108] to control or prevent COVID-19 disease. More than 10 vaccines have already applicated in clinic to prevent SARS-CoV-2 infection and achieved a certain protection affection [109] [110] [111]. These results need to further evaluation and research.

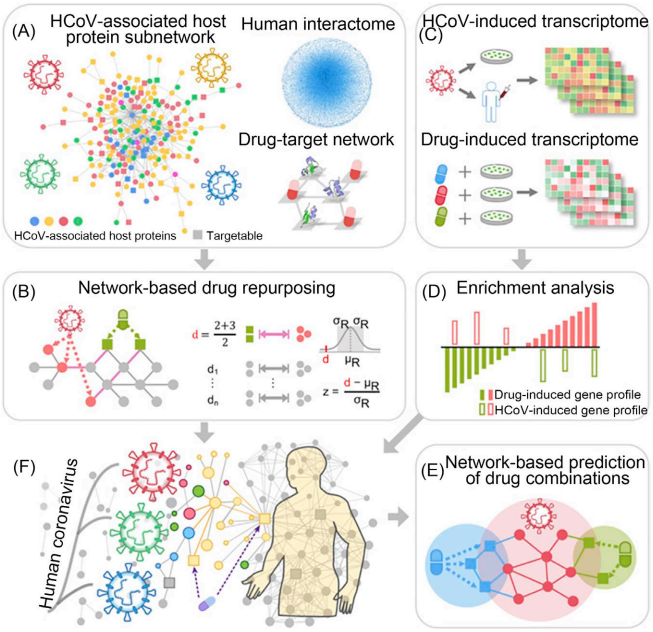

Figure 12. Network-based methodology combining pharmacology-based network medicine platform to quantify the interplay between the virus-host interactome and drug targets in the human protein-protein interactions network.

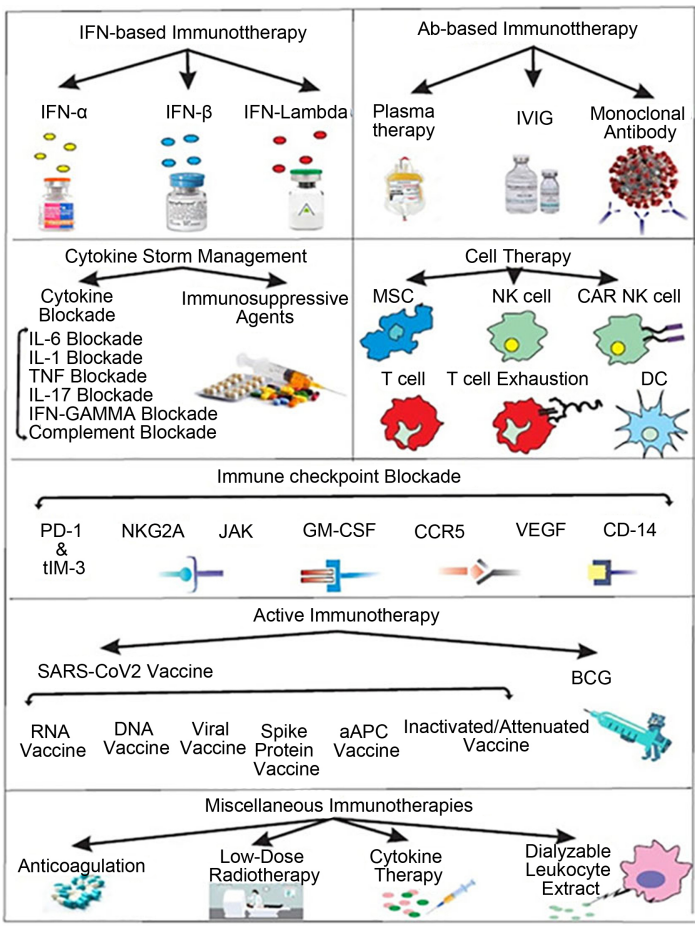

Figure 13. Immunotherapeutic approaches for COVID-19.

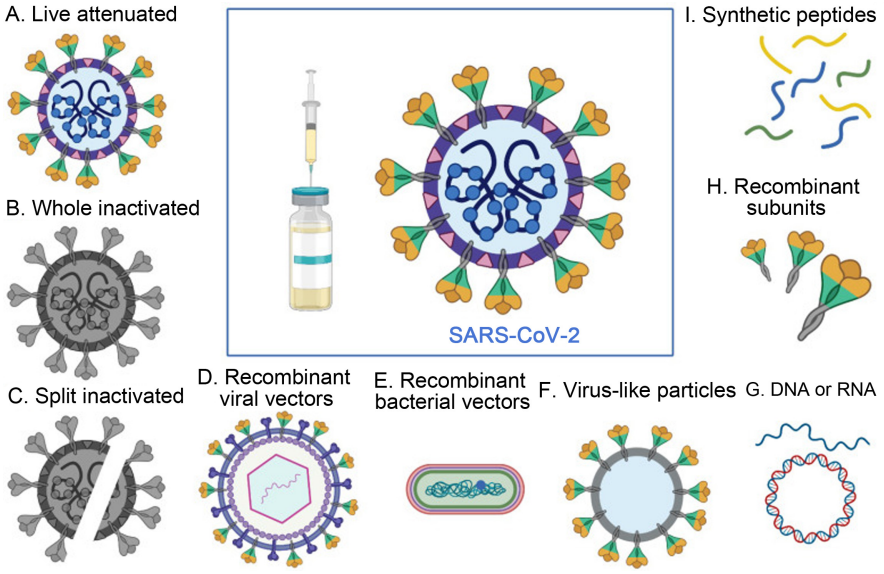

Figure 14. Approaches to SARS-CoV-2 vaccine development.

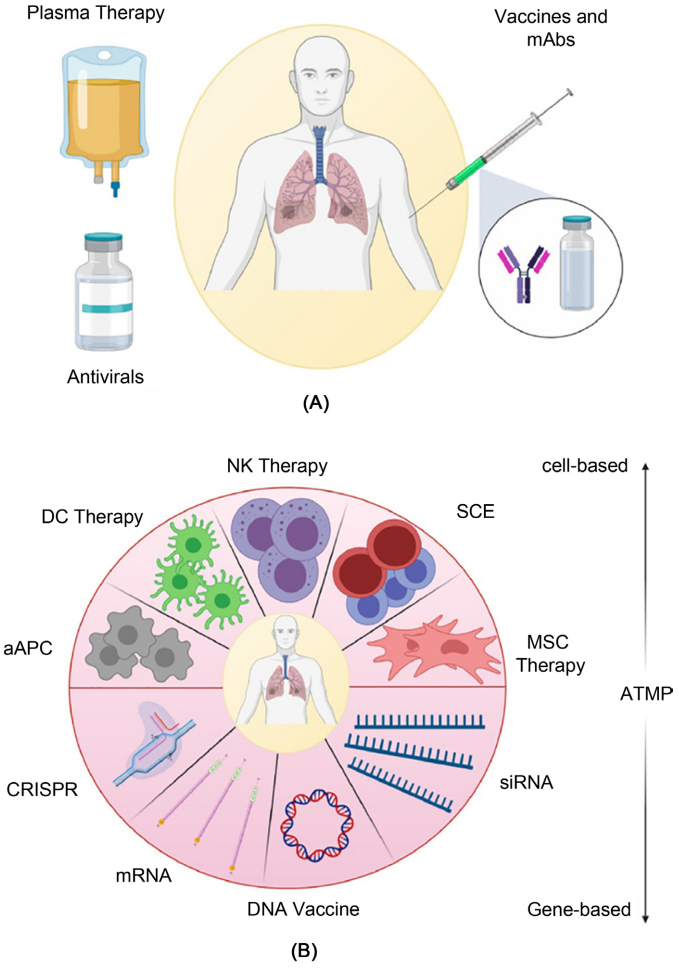

Figure 15. Treatment strategies. (A) Current therapeutics used to treat patients with COVID-19. (B) Advanced therapeutic medicinal products with cell-and gene-based candidate therapies (created by Biorender.com).

2. Conclusion

SARS-CoV-2-induced pulmonary injury is a critic health crisis in the world. SARS-CoV-2 attacks human lung and causes alveolar collapse, inflammation response, cytokine storm, endothelial dysfunction, coagulopathy and thrombus formation are its typical characteristics. The patients developed hypoxia, difficulty breathing, ARDS, infectious shock, multiple organ failure, and death. These review researches on SARS-COV-2 induced pulmonary injury from molecular mechanism to clinical manifestations and treatment strategies. Investigate SARS-COV-2 attack pulmonary and host defense relationship. Find the diversity of pulmonary damage mechanism and clinical evidences. It may be helpful for development treatment strategies for SARS-COV-2 associated pulmonary damage.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviations

COVID-19: Coronavirus disease 2019;
SARS: Severe acute respiratory syndrome;
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2;
ACE2: Angiotensin-converting enzyme 2;
ARDS: Acute respiratory distress syndrome;
aAPC: artificial antigen-presenting cell;
BCG: Bacille Calmette–Guérin;
CAR NK cell: Chimeric antigen receptor natural killer cell;
CCR5: CC Chemokine receptor 5;
CD14: Cluster ofdifferentiation 14;
DC: Dendritic cell;
DNA: Deoxyribonucleic acid;
GM-CS: Granulocyte-macrophage colony-stimulating factor;
IFN-γ: Interferon-γ;
IL: Interleukin;
IVIG: Intravenous immunoglobulin;
JAK: Jasus kinase;
MSC: Mesenchymal stem cell;
PD-1: Programmed death-1;
RNA: Ribonucleic acid;
Tim-3: T-cell immunoglobulin and mucin-domain containing-3;
TNF: Tumor necrosis factor;
VEGF: Vascular endothelial growth factor
ALI: Acute lung injury;
DIC: Disseminated intravascular coagulation;
mAbs: monoclonal antibodies;
aAPC: artificial antigen-presenting cell;
SCE: Stem cell educator;
MSC: Mesenchymal stem/stromal cell.
ABW: Actual body weight;
BMI: Body mass index;
EN: Enteral nutrition;
IBW: Ideal body weight;
ICU: Intensive care unit;
PN: Parenteral nutrition.