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Hot Topic

Severe Type of COVID-19: Pathogenesis, Warning Indicators and Treatment

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ABSTRACT Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, is a major public health issue. The epidemic is unlikely to be contained until the global launch of safe and effective vaccines that could prevent serious illnesses and provide herd immunity. Although most patients have mild flu-like symptoms, some develop severe illnesses accompanied by multiple organ dysfunction. The identification of pathophysiology and early warning biomarkers of a severe type of COVID-19 contribute to the treatment and prevention of serious complications. Here, we review the pathophysiology, early warning indicators, and effective treatment of Chinese and Western Medicine for patients with a severe type of COVID-19.

KEYWORDS coronavirus disease 2019, pathogenesis, indicators, treatment, Chinese medicine

The coronavirus disease 2019 (COVID-19) pandemic is a major public health event in the world, which poses a great threat to people health and the economy. Clinical manifestations of patients with COVID-19 include fever, cough, fatigue, acute respiratory distress syndrome (ARDS), sepsis, and even death.[1,2] China has contained spread of the epidemic attributing to the intervention strategies of early detection, isolation, and treatment. The vaccine is a key weapon against COVID-19 because it can prevent hospitalization and severe diseases, and may provide herd immunity.[3,4] With the understanding of the protein constituents and genomic sequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several vaccines have been used for humans.[4,5] More than 60 vaccines are in the stage of clinical development.[4]

Although most patients with COVID-19 present with mild and moderate syndrome, severe infection can cause rapid progression, ARDS, coagulation dysfunction, and multiple organ failure.[6,7] Severe type of COVID-19 often occurs in elderly patients with comorbidities,[8] which bring burden to medical resources and medical staff. Early identification and effective management strategy are of great significance to reasonable resource allocation and reduction of mortality.[9,10] Thus, how to prevent occurrence of severe type of COVID-19 is a noteworthy problem. This paper summarizes the potential pathogenesis and early warning indicators of severe type of COVID-19. Besides, we highlight efficient therapeutic approaches of Western medicine and Chinese medicine (CM).

Pathogenesis

Pathophysiology

Severe type of COVID-19 might manifest as substantial damage to multiple organs (Figure 1). The pathophysiology of severe SARS-CoV-2 infection includes virus damage, endotheliopathy, and thrombosis, immune-inflammatory response, and renin–angiotensin–aldosterone (RAAS) system disorder (Figure 2).

Direct Viral Damage

Through the S protein, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor.[11,12] The cleavage of S protein by transmembrane protease serine 2 (TMPRSS2) makes coronavirus gain access to host cells.[11,12] ACE2 and TMPRSS2 are abundantly expressed in pneumocytes, cardiac myocytes, small intestineepithelial cells, and renal proximal tubules, and direct viral injury is a possible mechanism in severe COVID-19.[12-15]

Viral replication occurs chiefly in type Ⅱ pneumocytes, leading to continued destruction of the alveolar wall.[16] In

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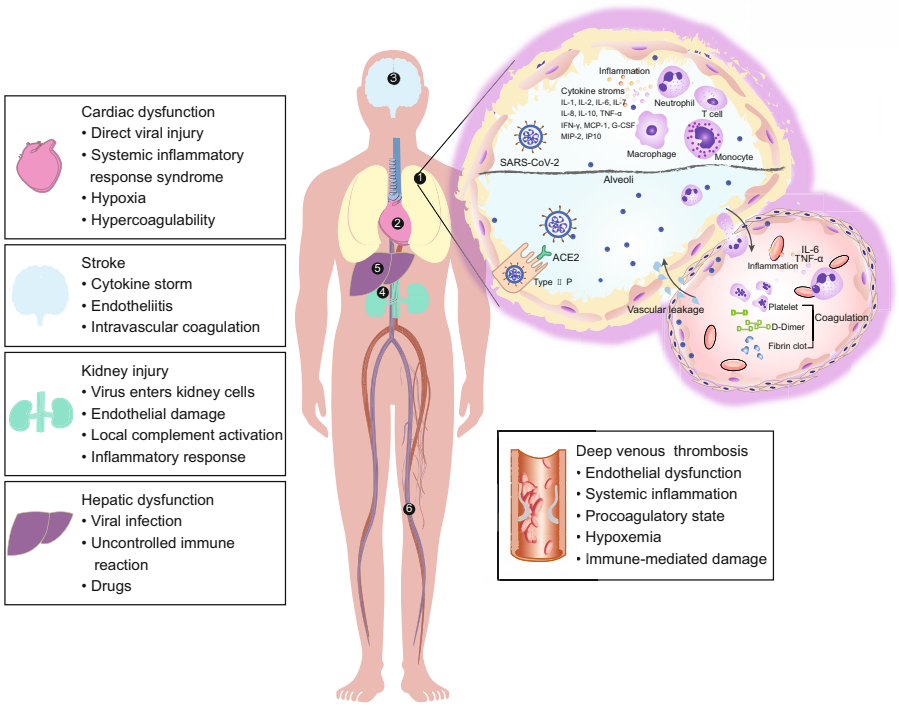

Figure 1. Potential Mechanisms of Multiple Organ Dysfunction Induced by Severe Type of COVID-19

Notes: Pathophysiological characteristics of lung: endothelial injury, inflammation, and thrombosis. Other organ dysfunction, including heart, brain, kidney, liver, and deep vein, are also summarized. IL: interleukin; TNF-α: tumor necrosis factor-alpha; IFN γ: interferon gamma; MCP: monocyte chemoattractant protein; G-CSF: granulocyte-colony stimulating factor; MIP: macrophage inflammatory protein; IP10: IFN γ-inducible protein 10; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; Type Ⅱ P: type Ⅱ pneumocyte; ACE2: angiotensin-converting enzyme 2

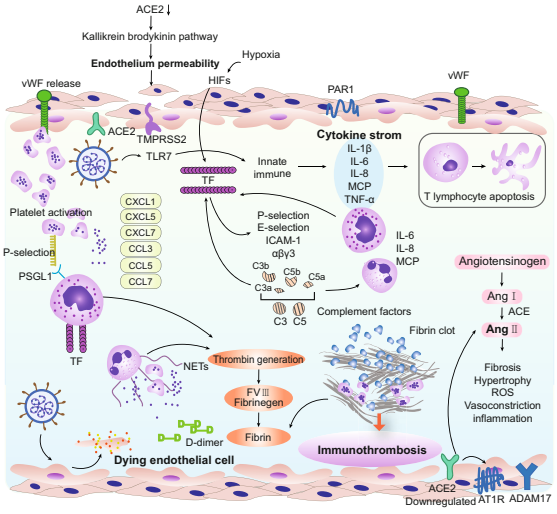

Figure 2. Pathophysiology for Patients with Severe Type of COVID-19

Notes: ACE2: angiotensin-converting enzyme 2; Ang: angiotensin; ADAM-17: a disintegrin and metalloproteinase 17; AT1R: angiotensin 1 receptors; COVID-19: coronavirus disease 2019; CXCL: CXC-chemokine ligand; CCL: chemokine ligand; IL: interleukin; ICAM: intercellular adhesion molecule; HIF: hypoxia-inducible factor; MCP: monocyte chemoattractant protein; NETs: neutrophil extracellular traps; PSGL1: P-selectin glycoprotein ligand 1; PAR1: proteinase activated receptor 1; RAAS: renin–angiotensin–aldosterone system; ROS: reactive oxygen species; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; TMPRSS2: transmembrane protease serine 2; TLR: toll-like receptor; TNF-α: tumor necrosis factor-alpha; TF: tissue factor; vWF: von Willebrand factor multimers

the late stage of disease, SARS-CoV-2 is mainly replicated in the lower respiratory tract, accompanied by ARDS in severe cases.[17,18] Numerous studies have indicated that SARS-CoV-2 is located in endothelial cells (ECs) in sections of the lungs, kidneys, and intestine.[12,19]

Endotheliopathy and Thrombosis

The key points of thrombosis are endothelial dysfunction, complement activation, immune response initiation, cytokine infiltration, platelet-leukocyte aggregation, hypoxia, and thrombin generation.[20,21]

Indeed, complement is an important component of innate immunity to SARS-CoV-2.[20] The recognition of the virus by toll-like receptor 7 (TLR7) may lead to innate immune hyperactivation.[22] Unrestrained activation of the complement increases endothelial permeability, facilitates the recruitment of monocytes and neutrophils, and mediates generalized microvascular injury, which culminates in immunothrombosis in severe COVID-19 cases.[23,24]

The activation of platelets releases chemokines, including CXC-chemokine ligand 1 (CXCL1), CXCL5, chemokine ligand 3 (CCL3), and CCL5,[25] which facilitate

leukocyte recruitment to sites of vascular injury.[26] Activated platelets promote neutrophils to discharge eneutrophil extracellular traps (NETs).[27,28] Although NETs are beneficial inensnaring pathogens, excessive NETs correlate with proinflammatory cytokine production, activation of the coagulation pathway, and multiple organ damage and death.[29] Platelet degranulation, leukocyte-platelet interactions, and platelet C3 release in turn stimulate NETs.[30,31]

Patients with severe type of COVID-19 have been demonstrated to have increased interleukin (IL)-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), interferon gamma (IFNγ), IFNγ-inducible protein 10 (IP10), macrophage inflammatory protein 1α (MIP-1α), and tumor necrosis factor (TNF)-α.[32-34] These inflammatory cytokines facilitate vascular endotheliopathy, leading to the release of von Willebrand factor and overexpression of tissue factor (TF) and fibrinogen.[35-37] These factors contribute substantially to increased mortality due to COVID-19 and affect other organs, leading to ischemic stroke, pulmonary embolisms, cardiac injury, acute kidney injury, and deep vein thrombosis (DVT).[18,20,37-40]

Inflammation-induced endothelial injury can lead to abundant plasminogen activator infiltration.[23,41] Thrombin, via proteinase activated receptor 1, promotes platelet activation, enhances the release of inflammatory factors, and activates the coagulation pathway.[42] In addition, hypoxia induces upregulation of hypoxia-inducible factor 1 signaling pathway, contributing to TF expression, vasoconstriction, inflammation, and thrombosis.[43,44]

Immune Inflammatory Response

Overactivation of innate immunity-induced cytokine storm is a feature of severe COVID-19.[45] Activated macrophages and neutrophils play a prominent role in the hyperinflammatory response and release cytokines and chemokines, including IL-1β, IL-6, IL-7, granulocyte-colony stimulating factor (G-CSF), IFN-γ, MCP-1, MIP-1α, IP10, TNF-α, and C-reactive protein (CRP).[2,45-48] Furthermore, a prominent feature of severe SARS-CoV-2 infection is lymphocytopenia, which is associated with adverse outcomes.[49,50] Because of massive T-cell lymphodepletion and dysregulation of the immune response, a number of cytokines are released. Excessive IL-6 can induce TF expression on mononuclear cells, upregulation of adhesion molecules including P- and E-selectin and integrin α and β3, and subsequently act to enhance coagulation and thrombin generation.[51,52]

Disorders of RAAS

Dysregulation of the RAAS is involved in the pathophysiological mechanism of severe COVID-19-associated tissue damage.[53] ACE2 serves a counterbalancing role in the RAAS, including blood-pressure regulation, fibrosis, and inflammation.[54,55] ACE promotes the conversion of angiotensin Ⅰ (Ang Ⅰ) to Ang Ⅱ.[56] SARS-CoV-2 impairs the activity of ACE2, resulting in an increase in Ang Ⅱ with increased angiotensin 1 receptor (AT1R) activation.[55,57-59] Subsequently, the activation of a disintegrin and metalloproteinase 17 resulted in ACE2 membrane shedding, RAAS overactivation, and a proinflammatory cascade.[60] Additionally, downregulation of ACE2 expression by SARS-CoV-2 infection reduced ACE2 and activated kallikrein–bradykinin pathway, increasing risk of vascular leakage, leading to further pulmonary edema.[41] Abnormal activation of ACE/Ang Ⅱ axis leads to pulmonary vasoconstriction, inflammation, fibrosis, hypertrophy, and accumulation of reactive oxygen species.[12,58]

Pathogenesis of CM

COVID-19 belongs to the category of "plague" in CM theory, which is caused by the cold-dampness epidemic virus.[61,62] This disease is located in Fei (Lung) and can affect Xin (Heart), Pi (Spleen), Gan (Liver), Shen (Kidney), and other organs.[62,63] The basic pathogenesis is characterized by dampness, toxin, blood stasis, and closure.[64]

Early Warning Indicators

A pattern of general features, comorbidities, hematologic, biochemical, coagulation, immune, and inflammatory biomarkers have been identified in patients with severe type of COVID-19 that included factors predicting disease progression (Figure 3).

General Features and Comorbidities

Compared to patients with non-severe COVID-19, those with severe COVID-19 were older, male, and had more comorbidities.[65-68] Regarding the underlying diseases associated with severe disease, the most recorded one was hypertension, followed by diabetes mellitus, cardiac diseases, kidney disease, chronic obstructive pulmonary disease (COPD), and malignant tumors[69-72] Downregulated PaO_2:FiO_2 and SpO_2/FiO_2, and upregulated sepsis-related organ failure assessment are risk factors for death.[32,33,70]

Hematologic Biomarkers

The higher the white blood cell (WBC), neutrophil

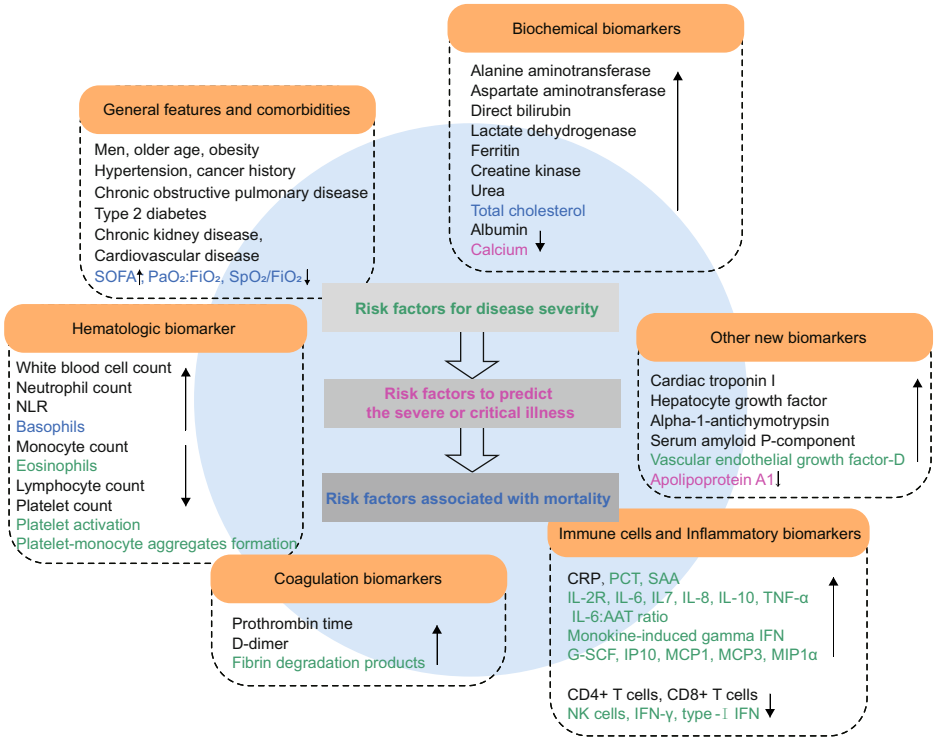

Figure 3. Early Warning Indicators in Severe Type of COVID-19 Progression

Notes: The text colors correspond to warning indicators for disease severity. Green text: severe illness; purple text: severe or critical illness; blue text: mortality; black text: possible predictive factors for severe, critical illness, and mortality. SOFA: sepsis-related organ failure assessment; PaO_2: partial pressure of oxygen; FiO_2: fraction of inspired O_2; SpO_2: pulse oxygen saturation; NLR: netrophil–lymphocty ratio; CRP: C-reactive protein; PCT: procalcitonin; SAA: serum amyloid protein A; IL: interleukin; TNF-α: tumor necrosis factor-α; AAT: alpha-1 antitrypsin; IFN: interferon; G-SCF: granulocyte colony-stimulating factor; IP10: IFN-γ-induced protein 10; MCP: monocyte chemotactic protein; MIP1α: macrophage inflammatory protein 1α; NK cells: natural killer cells

count, neutrophil–lymphocyte ratio (NLR), and basophils, and the lower the platelet, lymphocyte (especially $CD4^+$ and $CD8^+$T cells), and monocyte count, the higher the mortality.[73]

Biochemical Biomarkers

Patients with severe illness more frequently showed increased alanine aminotransferase, aspartate aminotransferase, ferritin, and lactate dehydrogenase levels and lower levels of albumin.[74] Lactate dehydrogenase (LDH), direct bilirubin, creatine kinase, urea, and calcium may serve as clinical predictors of severe or critical illness.[66,75,76] Independent risk factors associated with mortality included hypercholesterolemia, liver dysfunction, kidney dysfunction, increased lactate dehydrogenase and ferritin, and low albumin levels.[77]

Coagulation Biomarkers

Patients with severe type of COVID-19 had higher D-dimer, fibrin degradation products, and prothrombin time than those with non-severe disease. Elevated D-dimer at initial presentation was predictive of coagulation-associated complications during hospitalization, critical illness, and death.[78]

Immune and Inflammatory Biomarkers

The inflammatory factors, mainly IL-6, increase substantially, which results indisease progression approximately 7–14 days after onset.[79] CRP is related to disease progression and is a clinical predictor of severity and mortality.[80] Other relevated inflammatory biomarkers include procalcitonin, serum amyloid protein A, TNF-α, IL-7, IL-9, IL-10, IL-6: alpha-1 antitrypsin ratio, monokine-induced IFN-γ, granulocyte-colony stimulating factor, IP10, MCP-1, MCP-3, and MIP-1α.[66,81-85] Patients with severe disease had a lower natural killer cell count, IFN-γ, and type-Ⅰ IFNs than those with non-severe COVID-19.[86,87]

Other New Biomarkers

Markers of cardiac and muscle injury were elevated in patients with both severe and fatal COVID-19. Initial cardiac troponin Ⅰ, hepatocyte growth factor, alpha-1-antichymotrypsin, vascular endothelial growth factor-D, and serum amyloid P-component were substantially higher in patients with critical illness.[84,88]

Treatment

Remdesivir

Remdesivir, a nucleoside analog prodrug that impedes viral RNA synthesis, has been routinely used in the treatment of viral infections.[89,90] In a randomized study conducted by Wang, et al,[91] researchers found no statistically significant benefit of remdesivir when comparing placebo group with remdesivir group. Although not statistical significance was found, patients receiving remdesivir showed reduced duration of clinical symptoms compared to the control group within 10 days of symptom duration. Of note, a study by Siemieniuk, et al[92] verified the effectiveness of remdesivir in shortening both the time to recovery and the duration of mechanical ventilation; however, the mortality benefit is uncertain. In view of the clinical effectiveness of remdesivir, the United States Food and Drug Administration (FDA) has authorized remdesivir for emergency use in the treatment of patients with severe disease.[93] Moreover, the drug has been recommended by the European Union.[94]

Corticosteroids

The National Institutes of Health COVID-19 Treatment Panel Guidelines recommended dexamethasone at a dose of 6 mg once daily for up to 10 days for patients on mechanical ventilation and oxygen.[95] Available evidence suggests that corticosteroids have been identified as the only drugs that reduce mortality and mechanical ventilation compared to standard treatment.[96]

A trial from the United Kingdom found that low-dose dexamethasone was associated with a 33% lower mortality rate in patients receiving invasive ventilation and 20% in those needing oxygen compared to the usual care group.[97] In a multicenter study in hospitalized patients with ARDS patients administered dexamethasone had a 60-day mortality rate that was 15% lower than that of the control group.[98] A cohort study from China showed that methylprednisolone may reduce the mortality rate and has a significant clinical benefit in patients with COVID-19 with ARDS.[33] Thus, the appropriate dosage of corticosteroids may maximize benefits and minimizing adverse effects.

Anticoagulants

Given that thrombotic complications confer a high death rate in patients with COVID-19, prophylactic or therapeutic anticoagulation (AC) is of critical importance and established in advance.[99] Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in hospitalized patients should be administered unless they have contraindications (active bleeding or severe thrombocytopenia).[100-102]

A retrospective analysis by Tang, et al[103] found that patients administered heparin had a reduction in 28-day mortality. The use of AC mainly with LMWH markedly decreased the 28-day mortality in patients with severe COVID-19 with a sepsis-induced coagulopathy score of ⩾4 points or substantially increased D-dimer. Nevertheless, even with the use of LMWH or UFH, thrombotic events still occur.[7] In a multicenter study, many patients with ARDS still experienced thrombotic events despite AC treatment, in which D-dimer and fibrinogen levels increased markedly.[104] Thus, AC treatment needs to take into account the dose and coagulation characteristics of patients.

Convalescent Plasma

Convalescent plasma (CP) therapy has been applied in the treatment of SARS, Middle East Respiratory Syndrome, and H1N1 influenza, and has demonstrated efficacy.[105-107] Shen, et al[108] reported that 5 patients with COVID-19 with ARDS were successfully treated with CP, as evidenced by improved clinical symptoms, and treatment contributed to the clearance of the virus. Another study reported that in 10 patients with severe illness, 200 mL CP could increase or maintain a high level of neutralizing antibodies without severe adverse effects.[109] Moreover, clinical conditions rapidly improved within 3 days with increases in oxyhemoglobin saturation and lymphocyte counts. CP therapy offers a promising treatment option, and the United States FDA has authorized the use of plasma from convalescent patients to treat patients with severe COVID-19.[110]

CM

In the severe type of COVID-19 patients, the common syndrome types include epidemic virus blocking the Lung, blazing of both qi and nutrient, and internal block and external collapse syndrome.[111] The National Health Commission (NHC) of China has declared a combination of CM and Western medicine as a therapeutic regimen for COVID-19 and has published 8 versions of Diagnosis and Treatment Protocol. Several clinical studies showed that the combination of CM and Western medicine can improve the curative rate, shorten the average hospital stay, and reduce the number of cases from mild to severe.[112-114] A propensity score-based analysis suggested that CM is effective in reducing the mortality rate in severe and critical illnesses.[115] CM combined with conventional treatment has a protective effect on patients with severe COVID-19, and can reduce fever time and mortality.[116] A meta-analysis demonstrated that CM can

effectively reduce severe cases, improve lung imaging manifestations, and shorten the length of hospital stay.[1]

Qingfei Paidu Decoction (清肺排毒汤, QFPD), a prescription optimized from Maxing Shigan Decoction (麻杏石甘汤, MXSG), Shegan Mahuang Decoction (射干麻黄汤), Xiaochaihu Decoction (小柴胡汤), and Wuling Powder (五苓散), has been listed in the 6th edition of the protocol as a recommended prescription. QFPD is suitable for patients of COVID-19 at all stages, with the total effective rate 92.09%.[117,118] A multicenter cohort study manifested that early application of QFPD can improve nucleic acid negative conversion rate, reduce hospitalization time and mortality rate of patients.[119]

Huashi Baidu Decoction (化湿败毒方, HGBD) is applied to treat the epidemic virus blocking Lung syndrome. A result reported by Wuhan Jinyintan Hospital showed that compared with the Western medicine group, there was significantly better effect in pulmonary inflammation absorption, the mean duration of viral clearance, CRP level and serum iron in the severe patients treated with HGBD, Xuebijing Injection (血必净注射液, XBJ), Xiyanping Injection (喜炎平注射液, XYP), and Shengmai Injection (参麦注射液, SM).[120]

Yindan Jiedu Granules (银丹解毒颗粒, YDJDG), an in-hospital prescription from Beijing Ditan Hospital, has showed good clinical effects in the treatment of mild, moderate, severe and critical patients with COVID-19. YDJDG is a combination and innovation based on MXSG, Qingwen Baidu Decoction (清瘟败毒方), and Tingli Dazao Xiefei Decoction (葶苈大枣泻肺汤). In the YDJDG group, the proportion of recovered patients was remarkably higher than the lopinavir-ritonavir group. Compared with the control group, the average course of fever and pulmonary exudative lesions in the YDJDG group was remarkably shorter.[121]

Among the "Three CM and three formulas" recommended by the NHC, XBJ is the only injection form. XBJ, XYP, Xingnaojing Injection (醒脑静注射液, XNJ), Reduning Injection (热毒宁注射液, RDN), Tanreqing Injection (痰热清注射液, TRQ), Shenfu Injection (参附注射液, SF), and SM have been recommended for treating severe type of COVID-19 in the 6th and 7th edition of protocol. XBJ, XNJ, XYP, RDN, and TRQ indications are pattern of dual blaze of qi and nutrient. The indications of SF and SM are patients with pattern of internal block and external collapse. A case-control study showed that the body temperature and IL-6 level of the patients treated with XBJ combined with Western medicine were significantly lower than the control group (P<0.05).[122] The details of CMs and injections for severe type of COVID-19 including compositions, function, indication, and on-going clinical researches are summarized in Appendix 1.

CM, with multi-targets and multi-pathways, has potential advantages in human body regulation. We analyzed the mechanism of CM in the treatment of severe type of COVID-19: (1) Direct inhibition of viruses. Emerging evidence suggested that CM rich in flavonoid compounds has an antiviral effect.[123] *Radix Scutellariae* and *Radix Glycyrrhizae* in MXSG exhibit potential antiviral effects by binding to ACE2 and 3CL hydrolase.[124] (2) Inhibition of inflammatory storm and regulation immune function. RDN possesses the effect of regulating the activation of IL-6, IL-8, and TNF-α, which protects COVID-19 patients from lung injury.[125] XBJ plays a prominent role in anti-inflammation and has good immunostimulatory activity.[126] (3) Inhibition of thrombosis. Some studies have shown that MXSG exerts the effect in increasing the solubility of ephedrine, which can inhibit platelet adhesion and aggregation in Ephedra.[124,127] (4) Inhibition of oxidative stress. Emerging evidence indicated that glycyrrhizic acid has a good effect on anti-oxidative stress, inhibition of inflammatory reaction, and immunoregulation.[128]

Conclusions and Prospects

Owing to direct viral injury, endothelial damage and thrombosis, immune dysregulation, and RAAS overactivation, patients with severe COVID-19 might experience multiple organ complications or even die. Therefore, early identification is crucial to decrease the severity of disease and mortality of patients. The combination of CM and Western medicine is an efficient therapeutic strategy in the fight against COVID-19, which can improve clinical efficacy, delay progression of mild and moderate to severe and critical, and reduce the mortality rate. CM has won valuable time for the rehabilitation of severe types of patients. Currently, studies on CM mainly focus on the theory of CM and network pharmacology. In the future, large-scale, multicenter clinical studies, as well as pharmacological researches, should be carried out to systematically elaborate the efficacy of CM.

To date, the mortality rate of COVID-19 patients has been greatly reduced. In the severe pandemic, scientists have recognized the molecular biological,

and genetic of coronavirus, however, there are some unknowns about the coronavirus. With the continuously increasing understanding of pathogenesis, the maturity of treatment methods, and the popularization of vaccines, we hope to bring COVID-19 under control.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Wang XB was responsible for the design of this paper. Shi K and Liu Y drafted the manuscript and contributed equally to this work. Zhang Q, Ran CP, Hou J, and Zhang Y were responsible for collecting information. Wang XB revised and commented on the manuscript. All authors read and approved the final version for publication.

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