

The Pathogenesis of COVID-19 Indicates Therapeutic Strategies

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COVID-19 is another major pandemic of viral infectious disease in the 21st century. Since the first case was reported in Wuhan, China, in December 2019, COVID-19 has resulted in more than 100 million confirmed cases and more than 2 million deaths. COVID-19 has been considered to be a systemic inflammatory response syndrome caused by SARS-CoV-2 infection, mainly with pulmonary lesions. Most patients have mild symptoms and a good prognosis, but severe or critical cases can lead to death. Otherwise, there is no effective antiviral drug to treat COVID-19.

In addition to the basic elements such as pathogen and route of transmission, it is also very important to explore the pathogenesis of a novel infectious disease. Through reviewing the literature and observing the clinical patients, we first proposed the potential pathogenesis of COVID-19 in March 2020.^[1] The virus first passes through the nasal mucosa and throat mucosa, and then enters the lungs through the respiratory tract. The most common symptoms are fever and cough in the early infection. Subsequently, the virus may enter the peripheral blood from the lungs, causing viremia. Then, the virus attacks the target organs that express angiotensin-converting enzyme 2, such as lungs, hearts, kidneys, and gastrointestinal tract. In this way, the virus starts a second attack, leading to the aggravation of the patient's condition 7 to 14 days after the onset. Accordingly, we divided the course of COVID-19 into three phases (Fig. 1): viremia phase, acute (pneumonia) phase, recovery phase, and some patients entered severe phase from acute (pneumonia) phase. Lymphocytes in COVID-19 patients decreased gradually with the progression of the disease, and the expression of inflammatory factors increased, resulting in the formation of inflammatory factor storms. Besides, ischemic changes on the end of limbs were observed in severe patients. Combined with abnormal coagulation factors in the laboratory, it was clear that some severe patients had coagulation dysfunction. Based on the potential pathogenesis of COVID-19 and the clinical manifestations of the patients, immune intervention in the earlier stage of the disease may provide patients with more opportunities

for the cure. Then we propose that the combined intravenous immunoglobulin (IVIG) and low molecular weight heparin (LMWH) treatment strategy for severe COVID-19 patients in the early stage may be effective.

Gamma globulin contains various antibodies in the serum of healthy people, so it can enhance the body resistance to prevent infection. Our team proposed IVIG as a treatment strategy for severe COVID-19 patients at the end of January 2020, and reported for the first time that the use of high-dose of IVIG as immunomodulators for severe COVID-19 patients at an appropriate time could prevent disease progression and improve the prognosis in March of the same year.^[2,3] This year, we retrospectively studied the efficacy of high-dose IVIG combined with standard treatment compared to standard treatment in severe COVID-19 patients. The results showed that high-dose IVIG within 14 days after the onset of severe COVID-19 patients could reduce the 28-day mortality, which was more prominent in patients without complications or initial treatment earlier.^[4] During this period, Iranian scholars also reported that high-dose IVIG had a similar effect on 5 patients with severe COVID-19 who failed standard treatment.^[5] A retrospective study in China found that IVIG within 48 hours of ICU stay was associated with reduced mechanical ventilation, shorter hospital stay, and reduced 28-day mortality.^[6] In addition, 3 randomized controlled trials for IVIG treatment of COVID-19 were carried out. The existing results are controversial, but it is considered to be related to the timing and dosage of IVIG treatment. We recommend that IVIG be administered to severe COVID-19 patients at a dose of 0.3 to 0.5 g/Kg/day for 5 days, and that intervention is initiated preferably within 14 days of onset. Combined with the potential pathogenesis of COVID-19 mentioned above, IVIG intervention is more effective in the early acute (pneumonia) phase.

Severe COVID-19 patients not only suffered from inflammatory factor storms but also coagulation dysfunction. Specifically, D-dimer increased, prothrombin time prolonged, fibrinogen and platelets gradually decreased, and ischemic changes such as purple at the end of fingers and toes, and even blisters appeared. It was considered that SARS-CoV-2 can activate coagulation waterfall through various mechanisms, leading to severe hypercoagulability. Early anticoagulation may block coagulation waterfall, reduce microthrombosis, and further reduce the risk of other organ damage. Since then, the International Society for Thrombosis and Hemostasis and the American Society of Hematology recommend that all hospitalized patients with COVID-19 should receive venous thromboembolic prophylaxis. If the patient is clinically predisposed to a thrombotic event, the

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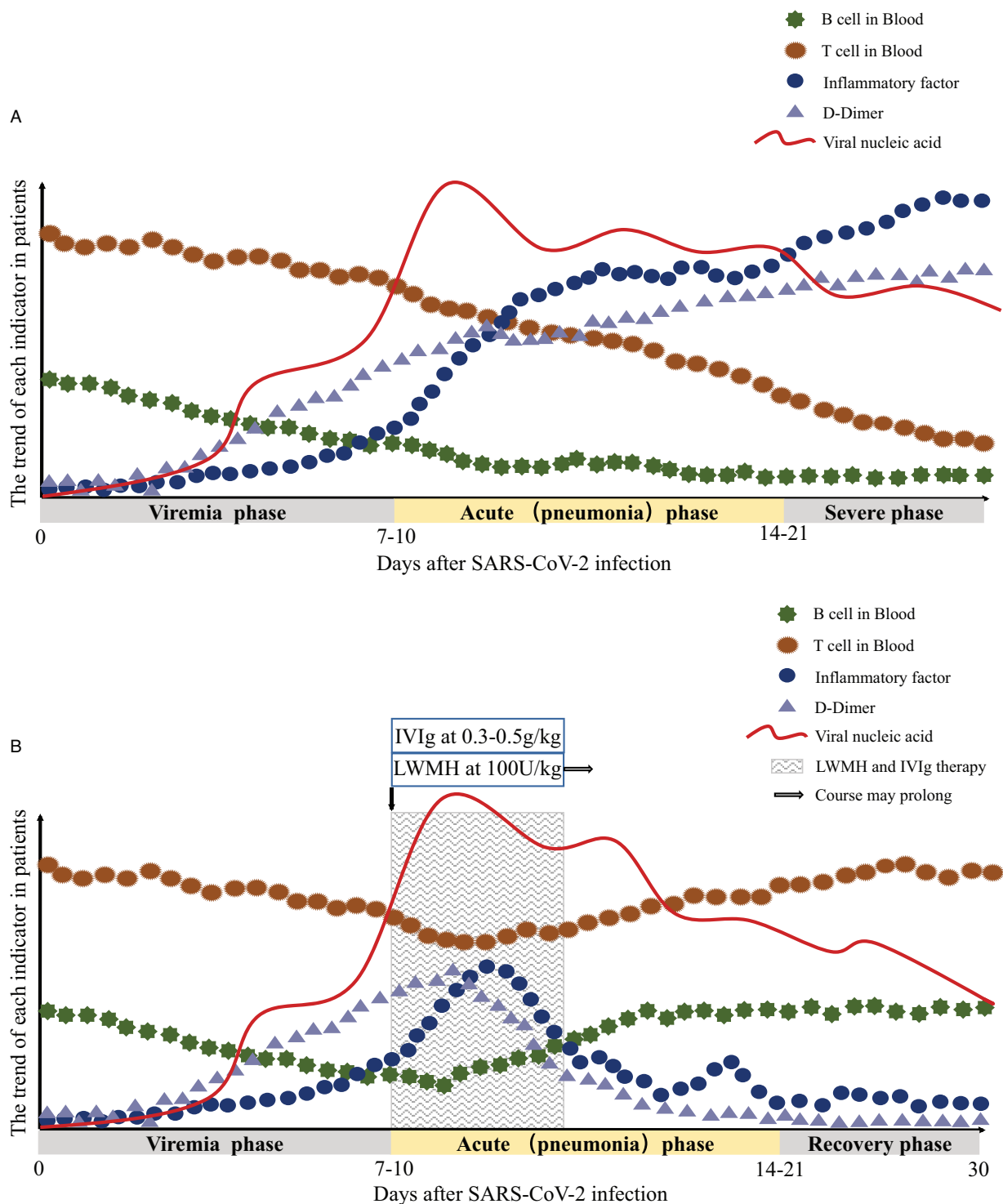


Figure 1: Hypothetical pathogenesis of COVID-19. The X-axis is the number of days after SARS-CoV-2 infection, and it is divided into three phases according to the above conjecture. The Y-axis is the trend of T cells, B cells, inflammatory factors, d-dimer and viral load in patients. (A) The trend of each indicator in COVID-19 patients with severe type. (B) The trend of each indicator in COVID-19 patients with severe type after LWMH and IVIG therapy. The shaded areas represent the recommended intervention times for LMWH and IVIG treatment.^[1] IVIG: intravenous immunoglobulin; LMWH: low molecular weight heparin.

anticoagulant dose should be increased. Mount Sinai Hospital performed the world's largest COVID-19 autopsy, the results showed that most of the 67 COVID-19 patients who underwent autopsy had clotting dysfunction and continued elevated levels of

d-dimer and fibrinogen. It is also confirmed that anticoagulation is an important strategy for the treatment of COVID-19 patients. The application dose of LMWH in severe COVID-19 patients was recommended to be 4000 U to 6000 U, subcutaneously

injected, once every 12 hours, at least 3 to 5 days. Then, according to the clinical symptoms and laboratory indexes to evaluate the need for further anticoagulant therapy.

COVID-19 is still prevalent worldwide, wane and wax, with the duration of the pandemic, SARS-CoV-2 is also constantly mutating. A novel pathogen needs to reduce its lethality and improve its ability to spread if it is to remain prevalent among the population. The three basic elements of controlling infectious diseases are controlling the source of infection, cutting off the transmission route, and protecting the susceptible population. Although there are no effective antiviral drugs that can attack and inhibit the replication of SARS-CoV-2, symptomatic treatment can help most mild to moderate patients improve their prognosis. We suggest that the combination of IVIG and LMWH in the early stage of severe type patients may lead to better clinical outcomes. The main transmission route of COVID-19 is droplet transmission. However, sporadic cases in some regions of China recently suggest that SARS-CoV-2 may be passed on to people through objects. That is, the survival time of the virus on the surface of the object in a cold environment may be prolonged. In the process of cutting off the transmission path, it is necessary to improve attention to surface monitoring, especially impermeable materials. Now, China, America, England, and other countries have begun to vaccinate. The effectiveness of the COVID-19 vaccine developed by each company is slightly different but generally can reach 75%–80%. Large-scale data are still needed to verify how long the COVID-19 vaccine can provide protection. We still need to wear masks in public places, maintain appropriate social distance, pay attention to hand hygiene and keep indoor air circulation. The road before us is long and winding, keep moving and we shall be arriving.

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Author Contributions

Ling Lin drafted the manuscript, Tai-Sheng Li revised the manuscript.

Conflicts of Interest

None.

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