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Successful Treatment of White Lung in Elderly Patients with COVID-19

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Abstract: Novel coronavirus (SARS-CoV-2, hereby known as COVID-19) has the characteristics of rapid variation and multiple variants, which has caused a huge impact on human health worldwide. At the end of 2022, the Omicron variant was widely spread in China, and the patients infected with COVID-19 were mainly concentrated in the elderly over 80 years old and people with serious basic diseases. Pathologically, diffuse lung injury can be seen in the advanced stage of severe and critical diseases, with a large number of inflammatory cells and fibrous mucus exudation, alveolar epithelial cells shedding and necrosis, severe pulmonary edema, hyaline membrane formation, and diffuse ground-glass shadow or consolidation on imaging, which is manifested as "white lung" [1], and its mortality rate has significantly increased. This study reported two cases of elderly patients admitted to the Affiliated Hospital of Hebei University for the treatment of COVID-19.

Keywords: Advanced age; COVID-19; White lung; Treatment; Experience

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1. Case reports

1.1. Case 1

Zhang XX, female, 87 years old, had a chief complaint of coughing, wheezing, and discomfort for 7 days. Her past medical history showed that she had chronic bronchitis and a history of right artificial knee resurfacing. Seven days before admission, she coughed and wheezed. She had a chest CT scan at a local hospital, which showed that there were infectious lesions and interstitial lesions in both lungs. She was treated with doxofylline, cefoperazone/sulbactam, ambroxol, and other drugs, but the symptoms were not relieved, so she came to the Department of Infectious Diseases of our hospital for further diagnosis and treatment. The COVID-19 nucleic acid test showed negative on admission. Lung auscultation showed coarse breath sounds in both lungs and scattered moist rales, but no wheeze. Diagnosis of lung infection, chronic bronchitis, right artificial knee resurfacing, abnormal liver function, and hypoproteinemia was recorded.

The following are the extracts from her progress notes:

(1) December 22, 2022: The patient coughed and wheezed; under the condition of oxygen inhalation 2 L/min, blood gas: partial pressure of oxygen (PO_2) 69 mmHg, partial pressure of carbon dioxide (PCO_2) 29 mmHg; blood routine: white blood cell count (WBC) 13.72×10^9/L, neutrophil % (N%) 81.6%, lymphocyte % (L%) 10.9%, C-reactive protein count (CRP) 11.08 mg/L, serum amyloid A (SAA) 110.0 mg/L. Azvudine was given for antiviral function, ambroxol + eucalyptus and limonene for reducing phlegm, prophylline for asthma, ceftazidime for anti-infection, nebulized inhalation of

salbutamol sulfate and budesonide, as well as the intermittent prone position, was encouraged for oxygen concentration increase.

(2) December 23, 2022: Due to her critical condition in addition to coughing and wheezing, the oxygenation index ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2 ratio) 237%, the patient was changed to nasal high-flow oxygen inhalation 40 L/min, fractional inspired oxygen (FiO_2) 60%. An injection of Chinese medicine Xuebijing for antagonizing endotoxin *in vitro* and methylprednisolone for anti-inflammatory were given.

(3) December 24, 2022: Considering that COVID-19 can cause hypercoagulation, and the patient had low O_2 and CO_2, pulmonary embolism was not excluded, and low molecular weight heparin calcium was added for anticoagulation; meanwhile, oral probiotics and whole protein enteral nutrition (EN) powder were given.

(4) December 25, 2022: Under the conditions of high flow oxygen inhalation 40 L/min, FiO_2 60%, blood gas analysis PO_2 84 mmHg, PCO_2 34 mmHg.

(5) December 26, 2022: Blood gas analysis PO_2 131 mmHg, PCO_2 35 mmHg, gradually adjusted the high flow parameters according to the oxygenation situation, adjusted to 30 L/min, under the condition of FiO_2 40%, finger pulse oxygen can reach more than 96%.

(6) December 27, 2022: Continued to reduce the high-flow parameters, and gradually transition to nasal cannula oxygen inhalation at 2 L/min, finger pulse oxygen can reach more than 95%. Chest CT scan showed infectious lesions in both lungs (see **Figure 1a**), and blood gas analysis the next morning showed PO_2 90 mmHg and PCO_2 36 mmHg.

(7) December 29, 2022: Blood routine WBC 9.84×10^9/L, N% 74.5%, L% 13.9%, CRP 1.51 mg/L, SAA 6.8 mg/L, infection index improved significantly, albumin was as low as 26 g/L, hence albumin was given 10 g intravenous infusion, four times a day, for 6 days.

(8) December 31, 2022: Under the condition of nasal cannula oxygen inhalation at 2 L/min, blood gas analysis showed PO_2 113 mmHg and PCO_2 39 mmHg.

(9) January 1, 2023: Re-examination of chest CT scan showed the density of bilateral lung lesions is higher than before (see **Figure 1b**). Considering that imaging studies have entered the consolidation stage, thymosin enteric-coated tablets are added to improve immunity. The patient has an obvious cough, and Suhuang Zhike Capsules are added.

(10) January 5, 2023: Nasal cannula oxygen inhalation 2 L/min, blood gas analysis PO_2 76 mmHg, PCO_2 42 mmHg.

(11) January 7, 2023: Chest CT re-examination showed the lesions in the lower lobes of both lungs are slightly absorbed (see **Figure 1c**).

(12) From January 9 to 11, 2023: Under the condition of nasal cannula oxygen inhalation 2 L/min, finger pulse oxygen fluctuation was 96%–100%.

(13) January 11, 2023: The patient is discharged from the hospital.

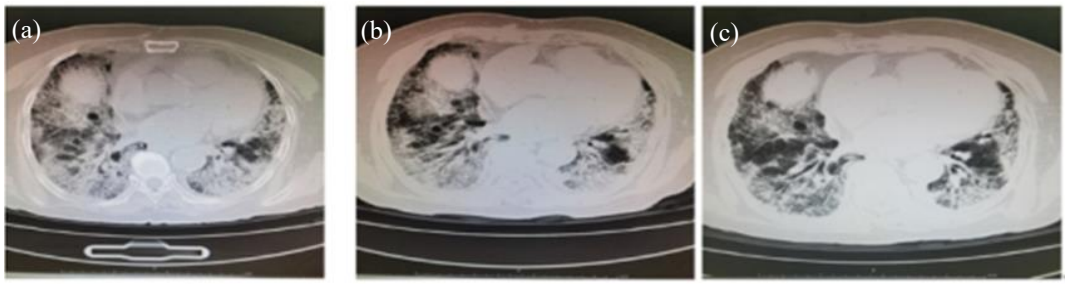

Figure 1. Chest CT scans of the patient in Case 1. (a) Scan on December 27, 2022; (b) Scan on January 1, 2023; (c) Scan on January 7, 2023

1.2. Case 2

Sun XX, male, 89 years old, was admitted to the hospital mainly due to cough, choking, and fever for 8 days. His past medical history consisted of coronary heart disease, coronary stent implantation, and prostatic hyperplasia. The patient developed a cough, suffocation, and fever 8 days before admission, with a body temperature of 38.5°C and coughed white sticky sputum. A chest CT scan was performed in a local hospital 1 day before admission, and showed that there were multiple ground-glass changes in both lungs, and interstitial inflammation was considered. He came to our hospital for further diagnosis and treatment.

The following are the extracts from her progress notes:

(1) December 16, 2022: The patient coughed and suffocated. Under the condition of oxygen inhalation 2 L/min, the blood gas PO_2 57 mmHg, PCO_2 32 mmHg, the comprehensive assessment considers that the patient has severe pneumonia; timely application of nasal high-flow oxygen inhalation 40 L/min, FiO_2 60%; blood routine: WBC 2.2×10^9/L, N% 74.5%, L% 17.3%, CRP 72.6 mg/L, SAA 251.8 mg/L. Bromhexine was given to reduce phlegm, nebulized inhalation of salbutamol sulfate and budesonide, as well as the intermittent prone position, was encouraged to improve oxygenation, oral azvudine for antiviral, low molecular weight heparin calcium as anticoagulant, bicyclol for liver protection as the patient had a poor liver function.

(2) December 18, 2022: High flow as before, blood gas PO_2 43 mmHg, PCO_2 32 mmHg, adjusted high flow to 40 L/min, FiO_2 70%; blood routine: WBC 7.36×10^9/L, N% 88%, L% 6.9%, CRP 97.52 mg/L, SAA 584.1 mg/L. The index of infection was higher than before, and the chest CT scan showed two pneumonia lesions (see **Figure 2a**) leading to obvious wheezing, and the patient was critically ill. Considering that the patient was thin and poor in nutritional status with severe pneumonia, intravenous moxifloxacin was added for anti-infection and oral doxofylline for anti-asthma, in addition to whole protein EN powder nutritional support treatment.

(3) December 20, 2022: High flow as before; blood gas PO_2 88 mmHg, PCO_2 26 mmHg; blood routine: WBC 5.25×10^9/L, N% 83.3%, L% 10.7%, CRP 125 mg/L, SAA 702.2 mg/L. On the next day, the chest CT scan showed an increase in both pneumonia lesions, and a small amount of pleural effusion is found on the right side. Considering that the patient had severe pneumonia and the disease progressed, an intravenous infusion of 40 g methylprednisolone, four times a day for four days was given. The nutritional status was poor, the protein level was low, and lower extremity edema was observed, hence an intravenous infusion of 10 g albumin, four times a day for three days was given, followed by furosemide for diuresis.

(4) December 24, 2022: High flow as before; blood gas PO_2 72 mmHg, PCO_2 37 mmHg; blood routine: WBC 5.76×10^9/L, N% 83.3%, L% 7.5%, lymphocyte ratio progressively decreased, intravenous injection of 5 g human immunoglobulin, four times a day for seven days was given, and oral administration of thymosin enteric-coated tablets was applied.

(5) December 28, 2022: The chest CT scan showed slightly more inflammation in the basal segment of the left lower lobe compared to the scan on December 23, 2022. The patient's condition progressed, and Xuebijing traditional Chinese medicine is added for anti-inflammation, hormones are added again, and the prone position is continued to be encouraged.

(6) January 4, 2023: Re-examination of chest CT compared with December 28, 2022, the range of multiple inflammations in both lungs was slightly smaller than before, bilateral pleural effusion was slightly increased (see **Figure 2b**), blood gas improved to PO_2 80 mmHg and PCO_2 42 mmHg.

(7) January 11, 2023: The patient's condition fluctuated again, and the wheezing worsens. The high-flow oxygen inhalation through the nose is adjusted to 50 L/min, FiO_2 80%; a small amount of sphere-shaped and rod-shaped gram-negative bacteria, sphere-shaped gram-positive bacteria, fungal spores, and bacteria with hypha were found in the sputum smear; the chest CT scan showed a slight increase

in left apical inflammation, left pleural effusion, and a slight decrease in right pleural effusion as compared to the scan on January 4, 2023. Blood routine: WBC 7.31×10^9/L, N% 89.8%, L% 5.6%, CRP 140.56 mg/L, SAA 693.6 mg/L. The patient had viral pneumonia complicated with bacterial and fungal infections, hence piperacillin-tazobactam (total 15 d) and voriconazole (15 d) were given. Doxofylline (13 d), albumin (6 d), and furosemide (16 d) were re-applied.

(8) January 14, 2023: The patient's general condition was poor, with suffocation, sweating, constipation, and phlegm in the throat. After consultation with the Department of Traditional Chinese Medicine, a Chinese herbal decoction was given. Sputum culture included *Acinetobacter baumannii* complex +++. Due to the patient being critically ill and cannot leave the high-flow oxygen inhalation, a chest CT re-examination was not performed, and it was replaced by a bedside chest X-ray: infectious lesions in both lungs, a small amount of pleural effusion. Treatment of piperacillin-tazobactam combined with drug-sensitive antibiotic levofloxacin was given intravenously for 14 days.

(9) January 17, 2023: Sputum culture included *Acinetobacter baumannii* complex +.

(10) January 20, 2023: Under the conditions of nasal high-flow oxygen inhalation 50 L/min, FiO_2 80%, blood gas PO_2 147 mmHg, PCO_2 53 mmHg, oxygenation improved as compared to before, and the high-flow parameters are lowered in time: 40 L/min, FiO_2 70%; blood routine: WBC 8.23×10^9/L, N% 73%, L% 11.9%, CRP 61.05 mg/L, SAA 86.3mg/L; infection indicators improved.

(11) January 21, 2023: The sputum culture was normal, and the fungal spores and hyphae on the sputum smear were positive.

(12) January 25, 2023: The chest X-ray showed a smaller range and less density than the X-rays in both lungs from January 1 to January 17, 2023.

(13) January 26, 2023: Blood routine: WBC 8.28×10^9/L, N% 67.6%, L% 19.7%, CRP 28.24 mg/L; sputum smear showed a small amount of rod-shaped gram-negative bacteria, sphere-shaped gram-positive bacteria, fungal spores and hyphae, as well as normal sputum culture; pulse oxygen fluctuation above 95%, gradually reduced the high flow parameter to 30 L/min, FiO_2 40%, breathing gradually improved.

(14) January 28, 2023: Gradually changed to face mask oxygen inhalation 5 L/min, blood gas PO_2 69 mmHg, PCO_2 44 mmHg.

(15) January 29, 2023: Mask oxygen inhalation 5 L/min, blood gas PO_2 101 mmHg, PCO_2 49 mmHg.

(16) January 30, 2023: He got better and was discharged from the hospital.

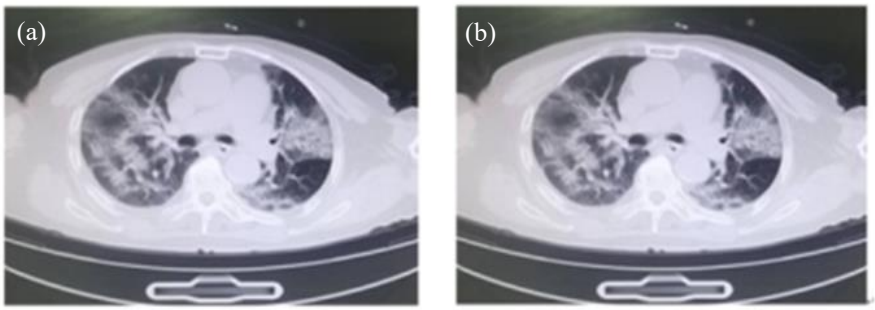

Figure 2. Chest CT scans of the patient in Case 2. (a) Scan on December 18, 2022; (b) Scan on January 4, 2023.

2. Treatment experience

2.1. Early application of antiviral drugs

Antiviral treatment is a key link, and the early and standardized use of antiviral drugs can significantly reduce the viral load in infected patients, reduce the body damage induced by high-load viruses, and especially reduce the hospitalization of groups with high-risk factors such as the elderly rate, severe disease rate and mortality rate [2].

2.1.1. Nematevir/ritonavir combination package (Paxlovid)

This drug acts on the main protease of COVID-19, inhibits the processing of protein precursors mediated by this enzyme, inhibits virus replication, reduces patients' disease progress from severe to mild or moderate, and greatly reduces the mortality rate [3]. It is suitable for infected adult patients with mild to moderate infection within 5 days of onset and with high-risk factors that may progress to severe disease. Due to its multiple interactions with many drugs, it is essential to carefully read the instructions before use.

2.1.2. Azvudine

Azvudine tablet is the first domestically produced oral small-molecule antiviral drug in China. It has the characteristics of a significant curative effect, strong accessibility, and is available for home use. People infected with COVID-19 should use it as soon as possible, with its best time of 5 days before the onset of infection symptoms, and recommended to be taken for ≤ 14 days. It is not recommended to stop the drug without a doctor's authorization if it is tolerable. Patients with mild hepatic and renal insufficiency should monitor liver and kidney function during the consumption of medication, and patients with moderate to severe hepatic and renal insufficiency should use it with caution. Azvudine is a P-glycoprotein (P-gp) substrate and a weak P-gp inducer [4], hence it is required to read the instructions carefully before use.

2.2. Importance of improvement in oxygenation

For COVID-19, patients with underlying diseases and elderly patients are likely to develop severe and critical conditions. If the patient's respiratory rate is ≥ 30 times/min, and the oxygen saturation is ≤ 93% at rest, this indicates that the clinical classification is severe [5]. Patients with PaO_2/FiO_2 < 300 mmHg should be given oxygen therapy immediately. For critically ill patients who receive nasal cannula and mask oxygen inhalation, if respiratory distress and/or hypoxemia do not improve in a short time (1–2 hours), nasal high-flow oxygen therapy (HFNC) or non-invasive ventilation (NIV) should be used.

2.2.1. Use of high flow rate

If it meets the diagnostic criteria for severe new coronary pneumonia [6], HFNC can be considered. For patients with type I respiratory failure, the recommended initial flow rate is 30–40 L/min. The acceptance rate should be adjusted to the highest flow rate that can be tolerated, and the blood oxygen saturation (SpO_2) is maintained at 92%~96%. For patients with type II respiratory failure, the recommended initial flow rate is 20–30 L/min. If the patient has significant PCO_2 retention, it can be increased to 45–55 L/min to the highest flow rate that the patient can tolerate and maintain SpO_2 at 88%~92% [5].

2.2.2. Prone position ventilation

Prone position ventilation is currently one of the most effective adjuvant treatments. Early prone position mechanical ventilation can improve clinical efficacy and significantly reduce mortality in patients with severe acute respiratory distress syndrome (ARDS). It has high application value and is worthy of promotion [7]. Moderate, severe, and critical cases with a high risk of severe disease and rapid disease progression should be treated in the prone position, and it is recommended not less than 12 hours a day [8]. However, it is unacceptable for many frail elderly people. Therefore, individualized body positions are formulated for different patients to ensure both patient tolerance and blood oxygen improvement.

2.3. Precaution to combined bacterial, fungal, and atypical pathogenic bacteria infections

Studies have shown that the abundance of bacteria in throat swabs of patients infected with COVID-19 increased significantly, and these bacteria can stimulate the expression of COVID-19 ACE2 receptor to

promote virus infection, suggesting that the pharyngeal bacteria of patients with new coronary pneumonia play a role in COVID-19 infection. COVID-19 infection is involved in the interaction between the virus and the host [9]. Due to the decline of immunity after the COVID-19 infection, it is necessary to be vigilant against the combination of mycoplasma, chlamydia, influenza A, influenza B, and other pathogen infections, the resurgence of tuberculosis, and fungal infections. As the patients are elderly and critically ill, their clinical manifestations are often atypical. Therefore, it is essential to closely monitor infection indicators, sputum etiology, and chest imaging for viral pneumonia.

2.4. Traditional Chinese medicine treatment

Traditional Chinese medicine (TCM) has played a unique advantage in the treatment of COVID-19. Several studies have shown that heat-clearing and detoxifying TCM treatments have clear clinical effects in anti-COVID-19, especially in clinical aspects such as anti-infection, fever reduction, shortening hospital stay, and improving curative effect [10-14]. On the one hand, it helps the body to quickly clear the virus and improve the state of immunosuppression. On the other, it also regulates the balance of the immune system, prevents the occurrence of cytokine storms and the potential damage of the body's immune system to normal cells, and reduces the mortality rate [15].

2.5. Immunotherapy

Experience in the treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) has shown that high viral titers and subsequent strong inflammatory and chemokine responses are associated with high morbidity and mortality during coronavirus infection. Reducing the viral load through early intervention and controlling the inflammatory response through immunomodulators are effective measures to improve the prognosis of patients [16,17].

Intravenous immune globulin (IVIG) can block Fc receptors, reduce cytokine storm [18], and can be used to enhance the immunity of severe and critically ill patients. A meta-analysis showed that IVIG has a good clinical effect on critically ill patients with the new coronavirus pneumonia [19]. The clinical efficacy of IVIG may be positively correlated with the severity of COVID-19.

Tocilizumab (TCZ) can prevent the binding of IL-6 to its receptor and exert the immunosuppressive effect promoted by IL-6. Michot et al reported a 42-year-old man with respiratory failure due to COVID-19 infection [20]. After 4 days of TCZ treatment, CRP decreased from 225 mg/L to 33 mg/L and he finally recovered completely clinically. Likewise, some case reports have shown that TCZ is an effective and safe approach for the treatment of COVID-19 [21-23].

Thymus preparations can induce the production of macrophages, interferon, interleukin, and other factors, thereby improving the suppressed immune function of the body, and can affect peripheral immune organs to enhance immunity. Fang et al used the thymus method as a neoadjuvant therapy for elderly patients with severe pneumonia, and the results showed that the thymus method can increase the proportion of CD4 and T lymphocyte subsets *in vivo* [24]. Commonly used thymus preparations are thymosin, thymofaxin, and so on.

2.6. Glucocorticoids

The “double-edged sword” effect of glucocorticoids should be fully utilized. For severe and critical cases with progressive deterioration of oxygenation indicators, rapid disease progression shown in imaging, and excessive activation of the body's inflammatory response, glucocorticoids should be used appropriately, and it is recommended not to exceed 10 days. Commonly used glucocorticoids included dexamethasone 5 mg/d or methylprednisolone 40 mg/d, where large doses and long-term use of glucocorticoids are avoided in order to reduce the occurrence of side effects [8].

2.7. Nutritional support

Before patients receive any nutritional support, hypovolemia and water, electrolyte, and acid-base imbalances should be corrected first. According to age, nutritional risk, oral intake, whether accompanied by heart, lung, kidney diseases, etc., the appropriate nutritional support route, energy, and nutritional components are chosen, and an individualized nutritional support plan is then formulated. In the process of nutritional support, the functional status of important organs and the effect of nutritional support should be addressed, and the nutritional plan should be evaluated and adjusted promptly. Enteral nutrition is the first choice for elderly patients with normal gastrointestinal function, and parenteral nutrition should be considered only when the intestines cannot tolerate enteral nutrition, or when enteral nutrition is far from enough for the body's needs [25,26].

2.8. Anticoagulant therapy

Like most patients with severe infection accompanied by disseminated intravascular coagulation, some patients with severe COVID-19 have abnormal coagulation function, manifested by a significant increase in D-dimer and fibrinogen degradation products [28]. Unfractionated or low-molecular-weight heparin can be given to moderate cases with high-risk factors for severe disease and rapid disease progression, as well as severe and critical cases without contraindications.

2.9. Care of functions of other important organs and maintaining the internal environment

People infected with COVID-19 are often accompanied by water and electrolyte disorders, protein and energy imbalances, which all cannot be ignored. Some patients with COVID-19 infection may have elevated liver enzymes, muscle enzymes, lactate dehydrogenase, myoglobin, troponin, ferritin, and other indicators [8]. Therefore, it is necessary to closely monitor the biochemical indicators of patients and intervene in time.

3. Conclusion

For patients with severe or critical pneumonia, especially for high-risk elderly people, strengthening monitoring of vital signs, giving effective oxygen inhalation methods promptly, improving oxygenation, and strengthening airway management are the initial steps, followed by early application of antiviral drugs, as well as close monitoring of blood infection indicators, sputum etiology detection, and chest CT to guard against concurrent bacterial, fungal, and other viral infections. Reasonable anticoagulant therapy, immune support, and comprehensive nutritional support are equally important. Meanwhile, it is also indispensable to take care of the functions of other organs. When the COVID-19 epidemic occurs on a large scale, we must make rational use of medical resources and strive to improve the success rate of treatment.

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Disclosure statement

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