Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Integrated Chinese herbal medicine and Western medicine successfully resolves spontaneous subcutaneous emphysema and pneumomediastinum in a patient with severe COVID-19 in Taiwan: A case report

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ABSTRACT

Case: Serious complications of severe coronavirus disease 2019 (COVID-19) include subcutaneous emphysema (SE) and pneumomediastinum, which are complicated to treat with conventional Western medicine. We report how combining Chinese herbal medicine (CHM) with Western medicine quickly resolved a patient's COVID-19-associated pulmonary complications, shortened hospital stay and improved quality of life.
Clinical features and outcome: A 59-year-old male with a history of smoking and tumors was diagnosed with COVID-19 in May 2021. At hospitalization, his oxygen saturation (SpO_2) was 80%, he had a continuous severe cough, rapid shallow breathing, spontaneous SE and pneumomediastinum. By Day 4 of hospitalization, his condition was worsening despite standard care, so CHM was added. After 3–5 days, his coughing had lessened and supplementary oxygen therapy was de-escalated. Nine days after starting CHM, the SE had completely resolved and the patient avoided intubation. His WHO OS 10-point Scale score had fallen from 6 to 3 points and the modified Medical Research Council Dyspnea Scale score from 4 to 2 points. He was hospitalized for 19 days. At 1 week post-discharge, the patient could handle most of his daily activities and experienced minor shortness of breath only when performing labor-intensive tasks. At 1 month, his work output was restored to pre-COVID-19 levels.
Conclusion: CHM combined with standard Western medicine improved pulmonary function, respiratory rate, blood oxygen saturation and shortened the hospital stay of a patient with severe COVID-19 complicated by SE and pneumomediastinum.

Introduction

In December 2019, viral pneumonia with an unknown cause was detected in patients in Wuhan City, Hubei Province, China (Wu et al., 2020b).[1] By late October 2021, over 243 million confirmed cases of COVID-19 had been reported worldwide since the start of the pandemic.[2] COVID-19 is highly contagious and is classified by traditional Chinese medicine (TCM) theory as "pestilent Qi". The clinical presentation includes fever, dyspnea and pulmonary infiltrates observable in both lungs by a chest radiograph. Risk factors for death of patients with COVID-19 include age over 65 years, cardiovascular diseases (e.g., diabetes and hypertension), a history of cancer, and male sex.[3]

By the end of October 2021, the Central Epidemic Command Center (CECC) of Taiwan reported that infection with COVID-19 had been laboratory-confirmed in 16,412 cases and a cumulative total of 847 COVID-19 deaths had occurred since 2020. In July 2021, Taiwan's

Abbreviations: COVID-19, coronavirus disease 2019; 2019-nCoV, novel coronavirus; SE, subcutaneous emphysema; CHM, Chinese herbal medicine; SpO_2, Blood oxygen saturation; WHO, World Health Organization; ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mMRC, Modified Medical Research Council Dyspnea Scale

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Centers for Disease Control reported that amongst people who had died in Taiwan of COVID-19, 90% were aged 60 years or more. The development of acute respiratory distress syndrome (ARDS) in patients with COVID-19 is also a fatal complication.[4] Moreover, patients with ARDS and COVID-19 have a 7-fold risk of developing subcutaneous emphysema (SE) and pneumomediastinum.[5] SE is associated with worse outcome in critically ill COVID-19 ARDS patients.[6] The duration of hospital stay, a patient's survival, and therapeutic approaches that enable rapid hospital discharge to avoid collapse of the healthcare system are important topics worldwide.

We report a case study of a hospitalized patient initially administered standard therapy for COVID-19 consisting remdesivir,[7] dexamethasone and tocilizumab.[8] These drugs help to reduce the mortality rate, but have minimal impact on hospital stay and pulmonary complications after hospital discharge.[9,10] In this case, COVID-19 symptoms complicated by SE and pneumomediastinum worsened on standard treatment. CHM was added to the regimen in an attempt to ameliorate the clinical respiratory symptoms, shorten the hospital stay and improve quality of life.

Case presentation

Case

The patient was a 59-year-old male (body mass index 25.59) with prostate cancer who had undergone cryotherapy 10 years previously and he was a smoker (0.5 packs per day for 3 years). The patient was diagnosed with COVID-19 on May 20, 2021, with associated symptoms of fever, headache, and a rapid-shallow respiration pattern (33–36 breaths per minute). As the patient's condition continued to worsen, he was hospitalized on May 26, 2021 (Day 1) for further management in an isolation room of China Medical University Hospital (CMUH). The patient's blood oxygen saturation (SpO_2) was 80% under room air, with a respiratory rate of over 30 breaths per minute associated with respiratory distress, which necessitated oxygen therapy and satisfied the clinical definition of a severe illness.[11] During his hospitalization, the patient's fever subsided. However, his coughing was severe with blood-tinged sputum and his mouth was dry. The patient was diagnosed with acute respiratory failure and he was given oxygen via a non-rebreathing mask at 15 L/min. Medications including remdesivir, dexamethasone, tocilizumab, empirical antibiotics, and mesenchymal stem cell therapies[12] were prescribed. Other test findings were as follows: PCR cycle threshold (Ct) 32; D-Dimer levels 661.2 ng/mL (<0.4 μg/mL fibrinogen equivalent units); serum high-sensitivity C-reactive protein (hsCRP) 10.8 mg/dL; serum lactate dehydrogenase (LDH) 506 μ/L; serum myoglobulin 75 ng/mL; and fibrinogen 301.4 mg/dL. Chest radiography revealed severe infiltrates in both lungs. On Day 4, the patient experienced severe shortness of breath; the Chinese Medicine Outpatient Department was consulted for CHM treatment. Dyspnea was assessed with the Modified Medical Research Council (mMRC) Dyspnea Scale[13] and graded as 4. The patient scored 6 points on the World Health Organization Clinical Progression 10-point Scale,[14] necessitating continuous high-flow oxygen therapy. On Day 7, the patient had SE and pneumomediastinum in the lower neck and chest wall. The timeline of sequential changes in symptoms of the patient and the treatments administered during the CMUH stay are shown in Fig. 1. Chest X-ray results are presented in Fig. 2.

Treatment and intervention

Other symptoms included a dry mouth with a thick yellow coating on the tongue, a change in taste sensation, a bitter taste in the mouth, diarrhea, and loss of appetite. Within four days of hospitalization, the patient had lost over 3 kg of body weight (falling from 82 to 78.8 kg). A TCM prescription, mainly consisting of a modified Ganlu Xiaodu Decoction,[15] was administered to this patient until hospital discharge. The modified Ganlu Xiaodu Decoction contains *Pogostemon cablin, Scutellaria baicalensis, Artemisia capillaris, Houttuynia cordata,*[16] *Aconitum carmichaelii,*[17] *Plantago asiatica, Lepidium apetalum, Salvia miltiorrhiza, Carthamus tinctorius* L., *Prunus persica,*[18] *Atractylodes lancea, Rhodiola crenulata*, and *Codonopsis pilosula.*[19] The herbal materials were decocted with water. The patient ingested one pack three times a day.

During hospitalization, the WHO OS 10-point scale and the mMRC Dyspnea Scale determined the severity of clinical symptoms. The WHO OS 10-point scale assessed whether the patient needed to be hospitalized and measured oxygen use. The mMRC Dyspnea Scale

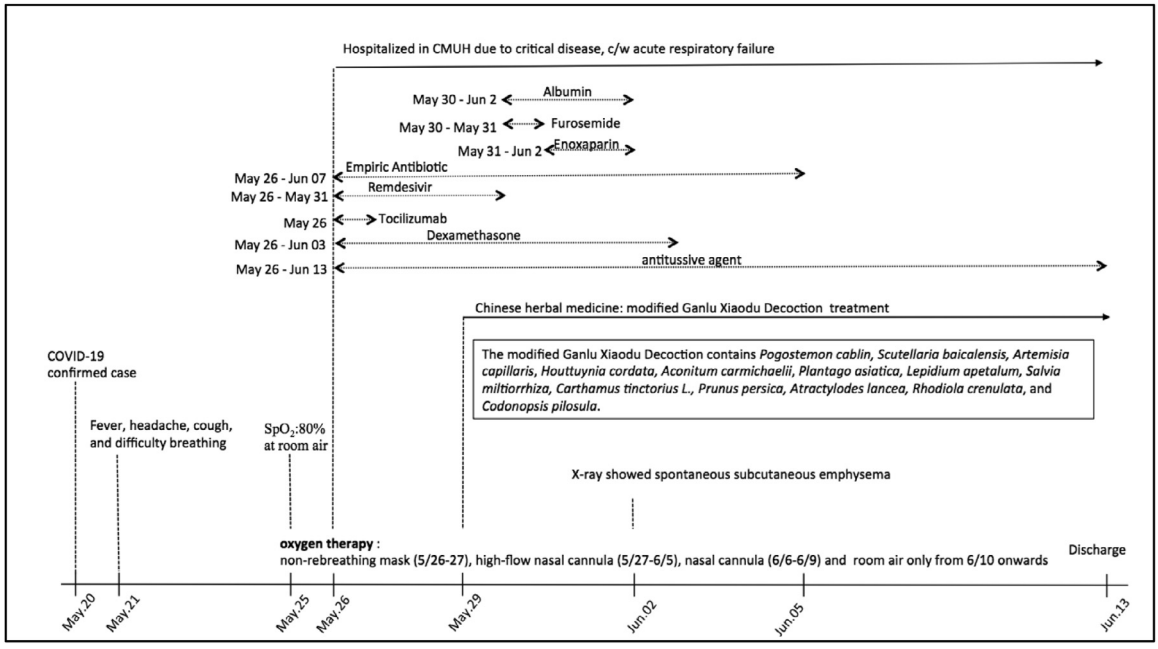


Fig. 1. The study timeline shows the sequential changes in symptoms and treatment of the patient during CMUH hospitalization.

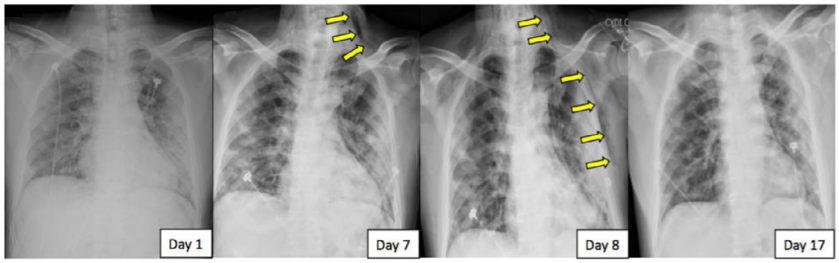


Fig. 2. Changes in chest radiographs during hospitalization. (a) Infiltration in the bilateral lung fields on Day 1. (b) Pneumomediastinum and emphysema in the left side of the neck on Day 7. (c) Pneumomediastinum and emphysema in the bilateral lower sides of the neck and bilateral chest walls on Day 8. (d) Pneumomediastinum and emphysema had disappeared gradually in the bilateral lower neck area and bilateral chest walls by Day 17.

assesses dyspnea severity during daily activities on a scale of 0 (no breathlessness) to 4 (breathless when dressing or not able to leave the house). Higher scores in both scales indicate higher severity of clinical symptoms.

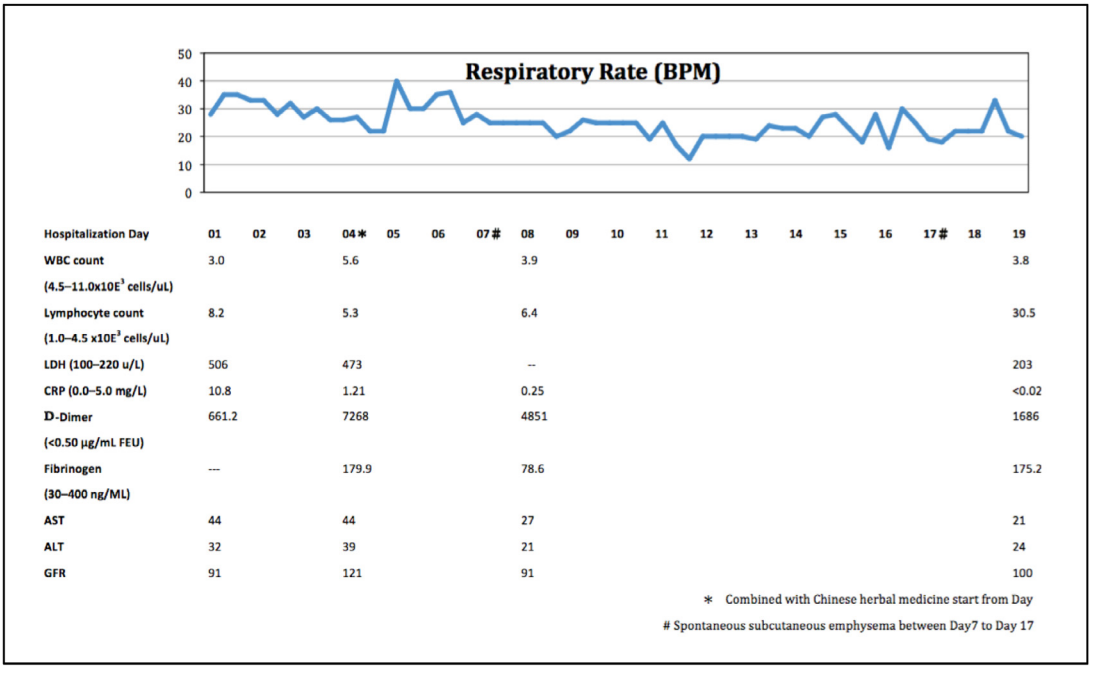
When CHM was combined with conventional medicine for the patient's treatment, his clinical symptoms began to improve. Respiratory rate was less than 24 breaths per minute and saturation of peripheral oxygen was stable for 3 consecutive days, as shown in Fig. 3. The crackling sensation on palpation of the affected area of subcutaneous emphysema improved gradually. The respiratory supportive system was de-escalated after 3–5 days of CHM treatment. After 9 days of combination treatment with CHM, the subcutaneous emphysema subsided completely; the WHO OS 10-point scale score was reduced from 6 to 3 points and the mMRC Dyspnea Scale score was reduced from 4 to 2 points. After a total hospitalization of 19 days, the patient was discharged on Day 25, with a score on the WHO OS 10-point scale of 1 and an mMRC Dyspnea Scale score of 1.

Post-discharge, the patient could independently manage most of his daily activities and experienced only mild shortness of breath when performing labor-intensive tasks. At 1 month of follow-up by telephone, he reported that he was able to work normally, at the same level of output as he had prior to COVID-19 infection. Laboratory data during hospitalization are shown in Fig. 3. Fig. 4 presents the patient's blood oxygen variations, oxygen therapy requirements, and clinical pulmonary function evaluations during hospitalization.

Discussion

This middle-aged patient was a smoker with a cancer history who suffered from COVID-19 with spontaneous SE. A previous study has reported that patients with COVID-19 complicated by SE have a poor prognosis, a higher likelihood of intubation and mortality.[6] In patients with severe acute respiratory syndrome (SARS) or COVID-19, those who develop spontaneous pneumomediastinum (SP) have a prolonged median length of ICU stay (11 days; interquartile range 6-21) and take longer to completely recover (18 days; interquartile range 12-28) compared with patients who do not develop SP.[5,20] The addition of CHM to the conventional treatment regimen of this patient was associated with a shorter hospitalization, better pulmonary function and improved quality of life after discharge, compared with conventional treatment alone.

Increasingly, people worldwide are seeking complementary and alternative medicine treatment modalities, due to more positive attitudes towards health and self-care.[21,22] An analysis of data from the 2017 Taiwan Survey of Family Income and Expenditure reported that approximately 78.4% of the general population used TCM in that



Hospitalization Day	01	02	03	04∗	05	06	07#	08	09	10	11	12	13	14	15	16	17#	18	19
WBC count (4.5–11.0x10E^3 cells/uL)	3.0			5.6				3.9											3.8
Lymphocyte count (1.0–4.5 x10E^3 cells/uL)	8.2			5.3				6.4											30.5
LDH (100–220 u/L)	506			473				--											203
CRP (0.0–5.0 mg/L)	10.8			1.21				0.25											<0.02
D-Dimer (<0.50 μg/mL FEU)	661.2			7268				4851											1686
Fibrinogen (30–400 ng/ML)	---			179.9				78.6											175.2
AST	44			44				27											21
ALT	32			39				21											24
GFR	91			121				91											100

∗ Combined with Chinese herbal medicine start from Day

Spontaneous subcutaneous emphysema between Day7 to Day 17

Fig. 3. Laboratory data during CMUH hospitalization.

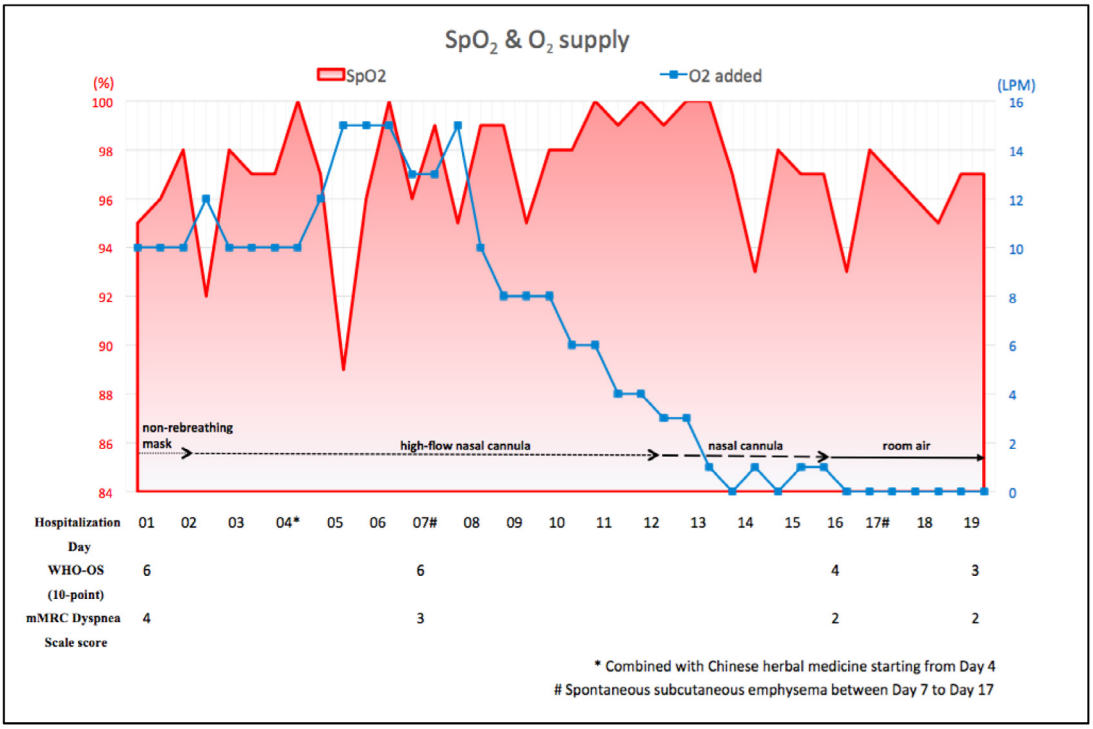


Fig. 4. Symptom assessments with the WHO OS 10-point scale and mMRC Dyspnea Scale, with details of oxygen therapy during CMUH hospitalization. LPM: liters per minute.

year.[23] Evidence also shows that the general population has turned to TCM during the COVID-19 pandemic, with one survey from Hong Kong conducted from November to December 2020 revealing that traditional, complementary and integrative medicine was commonly used there for COVID-19 prevention and treatment.[24] An animal study has indicated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes hyperinflammation in senescent cells, increases the expression of viral entry proteins and reduces antiviral gene expression,[25] which indirectly explains the high mortality rates of older adults with chronic disease who contract SARS-CoV-2 infection. Fisetin and quercetin are commonly consumed botanical antioxidants found in various herbs and used as food supplements. Fisetin may reverse age-related tissue damage, improve antibody production and reduce the inflammatory reaction that occurs after infection.[26,27] Quercetin has the potential to inhibit the extent of SARS-CoV-2 infection by binding with the active sites of 3CL and ACE2, the main proteases of SARS-CoV-2, and thus inhibit viral propagation.[28] Natural products may therefore have potential as food supplements to protect older adults with multiple chronic diseases against bodily harm caused by COVID-19 infection.

The Ganlu Xiaodu Decoction is amongst the top three most commonly prescribed prescriptions for patients with severe COVID-19.[29] The formula is well-known for its ability to clear heat and resolve toxins, based on TCM theory. A cytokine storm in a critically ill patient may be life-threatening and contribute to multiple organ failure. We therefore adopted a modified Ganlu Xiaodu Decoction to reduce extensive lung inflammation and inhibit viral replication. The mixture of herbal materials in the modified Ganlu Xiaodu Decoction is shown in Supplementary Table 1.

P. cablin, S. baicalensis and *A. capillaris* in the Ganlu Xiaodu Decoction are widely used herbal medicines for their antiviral effects.[30–32] *S. baicalensis* is commonly used for upper respiratory tract infections and in particular for its anti-influenza viral activities in H1N1 and H3N2 infections. Moreover, the derivative *S. barbata* D. Don inhibits the main proteases of SARS-CoV-2 infection (Mpro and TMPRSS2) and replication protease activity.[33] *A. lancea* and *C. pilosula* have been used in patients with diarrhea to improve gastrointestinal function and reduce the frequency of diarrhea.[19,34] *A. lancea* has a high affinity for ACE2 and has been shown to reduce viral reactions *in vivo*.[35] *A. lancea* can also attenuate virus-induced lung injury by downregulating the expression of proinflammatory cytokines interleukin (IL)−6, IL-1β and tumor necrosis factor alpha (TNF-α) and promoting the anti-inflammatory role of interferon beta (IFN-β) by upregulating IFN-β expression.[36] However, the underlying mechanisms of these Chinese herbal medicines remain unclear. It has been proposed that the active components of multiple herbs may act synergistically to inhibit SARS-CoV-2 infection.[37]

COVID-19 infection can result in long-term lung damage. Up to 80% of patients with severe or critical COVID-19 infection will experience physical complications or mental impairment after ICU discharge.[38] Most patients with severe COVID-19 infection have a persistent cough, shortness of breath and fatigue for some months after hospital discharge.[39,40] Advanced age, more severe illness, duration of ICU stay and smoking status are all risk factors for pulmonary fibrosis.[41] *P. asiatica* and L. *apetalum* have diuretic effects and can improve pulmonary edema.[42] *R. crenulata* might act as an immunoregulator and prevent the cytokine storm induced by COVID-19.[43] *S. miltiorrhiza* and *C. tinctorius* have anti-inflammatory, antioxidant and antiapoptotic properties; moreover, they slow the progress of irreversible pulmonary fibrosis.[44,45] *S. miltiorrhiza* combined with *R. crenulata* may have protective effects against pulmonary fibrosis.[46,47]

We report the details of a patient with SE and pneumomediastinum associated with severe COVID-19 infection that occurred 12 days following symptom onset in the absence of mechanical ventilation. The patient suffered from painful swelling and palpable crepitus that developed in the cheeks, neck and the chest wall, similar to symptoms described in a previous report.[48] SE is very rare in the general population, with fewer than 10 cases per 100,000 annually.[49] The prevalence of SE in COVID-19 is still unclear. One study noted that 13.6% of patients on mechanical ventilation with ARDS and COVID-19 suffered from SE.[5] It is interesting that up to 36% of patients with COVID-19 infection who were not on mechanical

ventilation or who were not intubated were observed to have SE in another study.[48] Generally, spontaneous SE without other complications improves within 3–5 days and completely subsides within 7–10 days. However, mortality is reported to be as high as 30% in patients with severe COVID-19 complicated by SE.[48,50] In our case, after receiving combination treatment with CHM and Western medicine, the patient's breathing and blood oxygen saturation improved and remained stable. Respiratory support was de-escalated from a non-rebreathing mask to a nasal cannula every 3–5 days. Serum LDH concentrations continued to fall. SE resolved completely after 9 days, which is much shorter than the time taken for it to completely subside among patients with comparably severe COVID-19 infection.[20,48] The total duration of hospitalization for the current case was 19 days, shorter than that in a previous retrospective cohort report.[51]

Conclusion

We have described the case of a patient with severe COVID-19 complicated with SE and pneumomediastinum treated with the modified Ganlu Xiaodu Decoction. During hospitalization, liver and kidney functions were normal. According to scores on the WHO OS 10-point scale and mMRC Dyspnea Scale and clinical symptoms under combination therapy continuously improved during hospitalization, with noted improvements in the patient's respiratory rate and blood oxygen saturation, the short hospital stay and improved quality of life after discharge.

Authors' Contributions

Shuo-Wen Hung and Yuan-Ching Liao wrote the manuscript and collected research data. I-Chang Chi, Ting-Yen Lin and Yu-Chuan Lin collected research data. Hung-Jen Lin provided administrative support and instructed on the TCM prescription. Sheng-Teng Huang organized the manuscript, provided technical assistance and edited the manuscript. All of the authors approved the final manuscript.

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Ethics statement

We obtained written informed consent from the patient for scientific purposes. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH110-REC2-127).

Availability of data and materials

The datasets used during this study are available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.explore.2021.12.005.

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