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The combined therapy of a traditional Chinese medicine formula and Western medicine for a critically ill case infected with COVID-19

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\textbf{ABSTRACT}

\textbf{Objective:} Presentation of a case illustrating the benefits of traditional Chinese medicine (TCM) for treatment of Coronavirus disease 2019 (COVID-19) in critically ill patients.

\textbf{Clinical features and outcome:} A 58-year-old woman presented with cough, fever, dizziness, chest tightness, polypleena and poor appetite. She was admitted to Guizhou Provincial People's hospital, and diagnosed with critically ill type of COVID-19 in February 2020. According to the patient's symptoms and signs, the TCM syndrome differentiation was qi deficiency, dampness-stasis and toxin accumulation. Then she received the combined therapy of a modified Chinese herbal formula and Western medicine. During a twelve-day period of treatment, her respiratory distress and appetite quickly improved. Abnormal laboratory indicators were resumed in time and lung lesions in CT scan largely absorbed. No side effects associated with this Chinese herbal formula were found. Before discharge, two consecutive nasopharyngeal swabs were shown to be negative for severe acute respiratory coronavirus 2 (SARS-CoV-2).

\textbf{Conclusions:} Our case report suggests that collaborative treatments with traditional Chinese medicine prove beneficial in the management of COVID-19 in critically ill patients. In order to give optimal care for this COVID-19 crisis for the whole world, Chinese medicine practitioners and Western medical doctors should work together in frontline.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) is a newly recognised illness that has spread rapidly throughout Wuhan (Hubei province) to other provinces in China and around the world. The clinical spectrum of COVID-19 ranges from mild to critically ill cases, and the mortality of critically ill patients with COVID-19 is very high. Until now, no specific treatment has been recommended for severe coronavirus infection except for meticulous supportive care. For Western medicine, the fundamental pathophysiology of this severe viral pneumonia is massive alveolar damage and severe acute respiratory distress syndrome (ARDS). From the perspective of traditional Chinese medicine (TCM), its pathogenesis is characterized by "dampness, heat, toxin, stasis, closure and prostration". Here, we report 1 critically ill case, who was infected by COVID-19, obtained good results after the combined therapy of our TCM formula and Western medicine. TCM syndrome differentiation, the detailed therapeutic formula and management were described through analysis of the patient's clinical course. We also introduced how the health care system in China has both Chinese medicine practitioners (CMP) and Western medical doctors to work together in frontline to give optimal care for this COVID-19 crisis for the whole world.

2. Case report

On February 6, 2020, a 58-year-old woman was admitted to Guizhou Provincial People's hospital, with a 7-day history of productive cough and subjective fever, and a 3-day history of dizziness, chest tightness, polypleena and poor appetite. She disclosed that she had returned to Guiyang, China on January 18 after traveling to visit family in Wuhan, China. Sputum specimen obtained from the patient tested positive for SARS-CoV-2 on real-time reverse transcription-polymerase-
lactate dehydrogenase, and electrolyte disturbance (Table 1). This pa-

surgically removed. After that, she has hypothyroidism, and has taken

Abnormal laboratory indicators on admission and their changes after treatment.

Table 1

| Measure                        | Reference Range | Illness Day 1 | Illness Day 2 | Illness Day 3 | Illness Day 4 | Illness Day 5 | Illness Day 6 | Illness Day 7 | Illness Day 8 | Illness Day 9 | Illness Day 10 |
|-------------------------------|-----------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Lymphocyte count (× 10^9/L)   | 1.1–3.2         | 0.53         | 0.36         | 0.42         | 0.71         | 1.13         | 1.21         |              |              |              |              |
| Lymphocyte ratio (%)          | 20–50           | 7.6          | 8.6          | 5.5          | 18.6         | 24.1         | 23.3         |              |              |              |              |
| C-reactive protein (mg/L)     | 0–5             | 139.1        | 130.8        | 46.7         | 10.6         | 8.6          | 4.7          |              |              |              |              |
| Interleukin 6 (pg/mL)         | 0–7             | 100.1        | 86.6         | 62.4         | 25.6         | 14.3         |              |              |              |              |              |
| Lactate dehydrogenase (U/L)  | 120–250         | 318          | –            | 260          | 193          | 188          | 205          |              |              |              |              |
| α Hydroxybutyrate dehydrogenase (U/L) | 44–148    | 223          | –            | 188          | 157          | 152          | 147          |              |              |              |              |
| Total bilirubin (mmol/L)      | 3.4–20.5        | 24.8         | 26.3         | 24.3         | 10.7         | 11.4         | 13.1         |              |              |              |              |
| Direct bilirubin (mmol/L)     | 0–8.6           | 11.8         | 16.9         | 16.1         | 6.0          | 5.4          | 5.4          |              |              |              |              |
| Fibrinogen (g/L)              | 1.8–3.5         | 6.61         | 8.85         | 5.44         | 3.32         | 2.8          | 3.9          |              |              |              |              |
| Albumin (g/L)                 | 40–55           | 33.7         | 33.8         | 30.3         | 32.5         | 37.8         | 39.7         |              |              |              |              |
| Potassium (mmol/L)            | 3.5–5.3         | 3.18         | 3.53         | 3.86         | 4.01         | 3.86         | 4.23         |              |              |              |              |
| Sodium (mmol/L)               | 137–147         | 130          | 131          | 134          | 134          | 137          |              |              |              |              |              |
| Chloride (mmol/L)             | 99–110          | 97.6         | 99           | 100.8        | 100.4        | 109.1        | 104.7        |              |              |              |              |
| Carbon dioxide (mmol/L)       | 22–29           | 18.6         | 18.3         | 23.5         | 27.2         | 23.7         | 24.2         |              |              |              |              |

levothyroxine sodium for a long time. Moreover, she has a history of sinus bradycardia with paroxysmal atrial premature (basic heart rate: 50–65 beats per minute) for more than one year and has been taking aspirin. According to the fifth version of guideline of the COVID-19 diagnosis and treatment in China, the patient was diagnosed as COVID-19 (critically ill type).

After admission, the patient was immediately given high flow oxygen by a noninvasive ventilator to correct respiratory failure. Moreover, vasoactive drug hydroxylamine was given to raise blood pressure. She was also treated empirically with non-specific antiviral Western medicines including Lopinavir/ritonavir and Arbidol. Moxifloxacin (0.4 g once daily, intravenously) was used to prevent secondary infection. Given the serious shortness of breath and hypoxemia, methylprednisolone (initial dose 80 mg once daily, intravenously) was administered to attenuate lung inflammation.1 Shenfu injection was discontinued due to the patient's anaphylaxis.

It has been known that COVID-19 belongs to yi bing (epidemic disease) in traditional Chinese medicine, and its lesions are mainly in the lung.2 Tongue diagnosis was carried out by a fixed senior Chinese medicine Practitioner (CMP). Due to wearing heavy protective equipments, CMP did not examine the patient's pulse and did not take the tongue photos. The pathogenesis of TCM is characterized by “dampness, heat, toxin, stasis, closure and prostration”. According to the patient's symptoms and signs, the TCM syndrome differentiation was qi deficiency, dampness-stasis and toxin accumulation. In addition to guideline-based COVID-19 management, this patient was in time treated with our TCM formula. The therapeutic principles were to strengthen the body resistance and eliminate pathogenic factors. The specific method is to supplement qi, remove dampness-stasis and toxin. The TCM formula included Sangbaipi (Cortex Mori) 20 g, Huaqiu (Exocarpium Citri Grandis) 15 g, Huangqi (Radix Astragali) 40 g, Taizishen (Radix Pseudostellariae) 30 g, Nanshanshen (Radix Adenophorae) 20 g, Huangqin (Scutellaria Baicalensis Georgi) 10 g, Doukou (Round Cardamom) 10 g, Gualoupi (Pericarpium Trichosanthis) 20 g, Danshen (Salvia Miltiorrhiza) 30 g, Baihu (Stemona Japonica) 20 g, Huoxiang (Agastache Rugosa) 10 g, Fuling (Poria cocos) 20 g, Baishu (Atractylodes Macrocephala) 15 g, Guizhi (Cinnamomum Cassia Presl) 5 g, Jinyinhu (Lonicera) 15 g, and Shengma (Rhizoma Cimicifugae) 6 g. This formula was decocted in water, one dose a day and 100 mL three times daily.

With the above combined therapy of Chinese herbs and Western medicine, the patient's dyspnea was gradually improved, and FiO₂ needed gradually decreased to 70 % on hospital day 2, 50 % on hospital day 3, 45 % on hospital day 4, 40 % on hospital day 5, and 30 % on hospital day 6. Her temperature returned to normal on hospital day 3. Methylprednisolone was reduced by 20 mg per day and discontinued on hospital day 4. From hospital day 7, the patient only needed...
supplemental oxygen through nasal cannula at 2–3 liters per minute, and her oxygen saturation values improved to 95–98%. From the morning of hospital day 11, the patient's blood pressure returned to normal (117/73 mmHg), and hydroxyamine was discontinued. Compared with chest computed tomographic (CT) scan on hospital day 6, a seconed chest CT scan on hospital day 10 showed patchy shadows and ground glass opacity were obviously absorbed (Fig. 2). The laboratory examinations on hospital day 11 showed all abnormal indicators had returned to normal (Table 1). Two consecutive nasopharyngeal swabs were found to be negative for SARS-CoV-2 on RT-PCR assays, Her appetite improved, and she was asymptomatic aside from occasional dry cough. According to the fifth version of guideline of the COVID-19 diagnosis and treatment in China, the patient had met discharge criteria, and was discharged on February 17, 2020 (illness day 18, hospital day 12).

3. Discussion

The SARS-CoV-2 infection can lead to acute resolved or fatal pneumonia. Currently, the main source of infection is COVID-19 patients. The route of human-to-human transmission of SARS-CoV-2 is mainly through respiratory droplets and contacts. Although the number of cases has increased rapidly around the world, information, especially treatment information about critically ill patients with SARS-CoV-2 infection is scarce. As previously reported, older patients with a history of underlying diseases are at increased risk of becoming critically ill or dying if they have SARS-CoV-2 infection. Since no specialised medication to treat COVID-19 has been identified at this time, the mainstay of treatment has been supportive care.

TCM has accumulated abundant clinical experiences and effective formulas on the prevention and treatment of epidemic diseases in the past thousands of years. TCM also worked very well clinically in the treatment of severe acute respiratory syndrome. Therefore, the Chinese government has highly valued TCM in this campaign to contain and eradicate SARS-CoV-2. Health Commissions in almost all provinces have officially declared that TCM should be used in combination with conventional medicine for the treatment of COVID-19 patients. During the treatment period of COVID-19, thousands of CMP were dispatched to Hubei province, and TCM scheme was included in the guideline on diagnosis and treatment of COVID-19, and CMP fully participated in the whole rescue process. The decoction, Chinese patent medicine, acupuncture and other characteristic therapy of TCM were comprehensively employed based on syndrome differentiation. Moreover, dozens of clinical trials aiming to evaluate the efficacy and safety of TCM treatments for COVID-19 patients have been launched in China. It's reported from Chinese official website that the cure rate of COVID-19 (about 94.3%) in China was significantly higher than that in many other countries, which might be due to the combined therapy of Chinese and Western medicine. Given the urgency of treating an increasing number of patients in some countries, experiences in TCM are well worth learning for the management of patients with COVID-19. The practical application of TCM should be seriously considered by the health care systems of other countries without prejudice, and all frontline health care workers should stick together to give optimal care for this COVID-19 crisis.

We report on a 58-year-old critically ill patient with confirmed COVID-19, characterised by type 1 acute respiratory failure and septic shock. In addition to Western medicine and symptomatic support, we found that timely administration of appropriate TCM formula might significantly improve the prognosis of critically ill patients, according to the specific TCM syndrome differentiation of the patients. Although our patient has endocrine and cardiac co-morbidities, her respiratory distress was quickly improved by the combined therapy of TCM formula and Western medicine. The need for invasive ventilator or even extracorporeal membrane oxygenation was avoided. Her abnormal laboratory indicators had been resumed in time and lung lesions in CT scan also been largely resolved. Compared with other studies of critically ill patients, both the dose and duration of methylprednisolone treatment were reduced. We did not use immunoglobulin in this patient. The patient's total hospital stay was 11 days, shorter than reported days. Moreover, TCM treatment did not cause any adverse event. Fei Zhou et al reported shortening of viral shedding duration after lopinavir/ritonavir treatment was not observed in their study. Young et al observed that the decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs appeared similar between those treated and not treated with lopinavir/ritonavir. But in our case, the combination of lopinavir/ritonavir and TCM treatment seemed to enhance the efficacy of each other and avoid side effects such as diarrhea.
Recently, a randomized controlled study showed no statistically significant benefits for remdesivir treatment beyond those of standard of care treatment. But this trial did not attain the predetermined sample size because the outbreak of COVID-19 was brought under control in China. Future studies of remdesivir, including in combination with TCM treatment in those with severe COVID-19 are needed to better understand their potential synergistic effectiveness.

It has been known that proper TCM formulae are quite effective for severe stroke, refractory Lichen Planus Pigmentosus-Inversus, and so on. Now, it seems that traditional Chinese medicine also has a good effect on severe COVID-19, at least in our case it is. In our TCM formula, Huangqi (Radix Astragali), Taizishen (Radix Pseudostellariae) and Nanshen (Radix Adenophorae) are principal drugs, playing the role of invigorating qi and replenishment of the lungs. Sangbaipi (Cortex Mori), Doukou (Round Cardamom), Gualoupi (Pericarpium Trichosanthis), Huoxiang (Agastache Rugosa), Fuling (Poria Cocos), Baishu (Atractylodes Macrophala) and Guizhi (Cinnamomum Cassia Presl) are considered as ministerial drugs. Sangbaipi (Cortex Mori) and Gualoupi (Pericarpium Trichosanthis) can improve lung function and remove dampness. Doukou (Round Cardamom) can invigorate the spleen and help it dissipate dampness, so that the spleen can’t be trapped by dampness. Fuling (Poria Cocos), Baishu (Atractylodes Macrophala) and Guizhi (Cinnamomum Cassia Presl) can promote the excretory function of kidney so that dampness can be removed through the bladder. All the three main pathways (lung, spleen, and kidney) have been properly applied to dispel dampness in our formula. Huoxiang (Agastache Rugosa) can dispel the dampness through the body surface and make Yang qi reach the body surface and limbs. Danshen (Salvia Miltiorrhiza), Huangqin (Scutellaria Baicalensis Georgi), Jinyinhua (Lonicer a), Huajuhong (Exocarpium Citri Grandis) and Baibai (Stemona Japonica) are the assistant drugs. Danshen (Salvia Miltiorrhiza) can dissipate blood stasis, so as to promote the absorption and dissipation of Xie qi including dampness, toxin, heat et al Huangqin (Scutellaria Baicalensis Georgi) and Jinyinhua (Lonicer a) can dispel external and internal pathogen(nei xie and wai xie) to the surface of the body, clear away heat and detoxify. Exocarpium Citri Grandis can reduce phlegm and relieve a cough. Baibai (Stemona Japonica) can also relieve a cough and make respiratory tract unobstructed. Both Huajuhong (Exocarpium Citri Grandis) and Baibai (Stemona Japonica) enhance the roles of Sangbaipi (Cortex Mori) and Gualoupi (Pericarpium Trichosanthis). Baibai (Stemona Japonica) was mainly used to strengthen the roles of Huangqi (Radix Astragali), Taizishen (Radix Pseudostellariae), Huoxiang (Agastache Rugosa) and Jinyinhua (Lonicer a), improving symptoms in this patient. A good prognosis has been obtained through the above treatments in this case, no side effects associated with our TCM formula have been found. Moreover, this formula is much cheaper than some antiviral Western drugs with uncertain curative effects. Numerous data have showed that the early intervention of TCM has positive effects on shortening hospital stay and ameliorating symptoms, reducing the development of mild and moderate case to severe case and the mortality rate, improving the cure rate and the rehabilitation of the recovery population of COVID-19 patients.

TCM should be prescribed early, and the sooner the better, so as to prevent the disease from progressing to a serious condition. For the severe and critical cases, incorporating TCM into conventional treatment methods is also recommended so as to generate synergistic effect by the combinational therapy of Chinese and Western medicine. In general, the use of TCM is encouraged as early as possible and in the whole process of disease.

4. Conclusion

We reported the successful treatment of critically ill type of COVID-19 using a complementary therapy. The successful results of this case provide an importantly adjunctive option and warrant further studies of TCM for treatment of COVID-19.

Author statement

Maolu Tian: Drafted the manuscript and followed up the patient.
Kui Zhang: Contributed to write the manuscript and search the literature, treated and evaluated the patients.
Yang Zeng: Contributed to write the manuscript and search the literature.
Linwen Wang: Contributed to write the manuscript and search the literature.
Shu Luo: Contributed to manuscript revision.
Wei Xia: Contributed to manuscript revision.
Xiangyan Zhang: Treated and evaluated the patients.
Yan Zha: Treated and evaluated the patients. All authors read and approved the final manuscript for publication.

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Declaration of Competing Interest

The authors declared that there was no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doi:https://doi.org/10.1016/j.ctim.2020.102473.

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