

Comparison of the clinical features and therapeutics of COVID-19 in cardio-cerebrovascular disease (CCVD) and non-CCVD patients

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Abstract Cardio-cerebrovascular disease (CCVD) is a major comorbidity of coronavirus disease 2019 (COVID-19). However, the clinical characteristics and outcomes remain unclear. In this study, 102 cases of COVID-19 from January 22, 2020 to March 26, 2020 in Xixi Hospital of Hangzhou were included. Twenty cases had pre-existing CCVD. Results showed that compared with non-CCVD patients, those with CCVD are more likely to develop severe disease (15% versus 1%), and the proportion of pneumonia severity index grade IV was significantly higher (25% versus 3.6%). Computed tomography images demonstrated that the proportion of multiple lobe lesion involvement was significantly higher in the CCVD group than in the non-CCVD group (90% versus 63.4%). Compared with non-CCVD group, the levels of C-reactive protein, fibrinogen, D-dimer, and serum amyloid-A were higher, whereas the total protein and arterial partial PaO₂ were lower in the CCVD group. Although no statistical difference was observed in the outcomes between groups, CCVD patients received more intensive comprehensive treatment to improve COVID-19 symptoms compared with non-CCVD patients. Integrated Chinese and Western medicine treatments have certain advantages in controlling the severe conversion rate and mortality of COVID-19. In addition, given that COVID-19 patients are usually related to coagulation disorders and thrombosis risk, the application of Chinese medicine in promoting blood circulation and removing stasis should be strengthened.

Keywords COVID-19; cardio-cerebrovascular disease; traditional Chinese medicine; clinical features; clinical therapeutics

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly emerging, highly contagious coronavirus [1]; it mainly invades the respiratory tract and lungs, leading to a new type of coronavirus pneumonia [2]. On December 31, 2019, the first case of severe pneumonia in

humans was reported [3]. In February 2020, the World Health Organization (WHO) designated this case as coronavirus disease 2019 (COVID-19) [4]. On March 11, 2020, the WHO declared COVID-19 as a public health emergency of international concern [5]. According to the data received by the WHO from national authorities at 10:00 CEST on June 29, 2020, the COVID-19 outbreak has infected 10 021 401 individuals and caused 499 913 deaths (approximately 4.99% mortality) globally [6]. The transmission routes of COVID-19 include direct contact, droplet, and possible aerosol transmission [7]. Populations are generally susceptible to COVID-19. Moreover, individuals with hypertension, cardiovascular disease, and cerebrovascular disease are more susceptible to severe or

Received May 28, 2020; accepted September 16, 2020

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critical disease and often admitted to the intensive care unit (ICU) [8]. Zhou *et al.* [9] investigated 191 cases of COVID-19 in Wuhan and observed that the elderly with comorbidities of hypertension (30%), coronary heart disease (8%), and diabetes (19%) are prone to develop acute respiratory distress syndrome. Chen *et al.* [10] collected data from 249 laboratory confirmed cases and reported cardio-cerebrovascular disease (CCVD) as the most common comorbidity (21.7%). However, the clinical characteristics and outcomes of patients with COVID-19 and CCVD remain unclear.

This study aimed to compare the clinical features of COVID-19 in CCVD and non-CCVD patients and summarize the effects of integrated Chinese and Western medicine on the treatment of COVID-19.

Methods

Study design and participants

In this single-center retrospective study, we recruited patients at Xixi Hospital of Hangzhou (the designated COVID-19 treatment hospital in Hangzhou, China) from January 22, 2020 to March 26, 2020. Based on the presence or absence of CCVD in COVID-19 patients before admission, the patients were divided into the CCVD and non-CCVD groups. CCVD was defined as hypertension, coronary heart disease, angina pectoris, myocardial infarction, cerebral infarction, cerebral hemorrhage, ischemic stroke, and hyperlipidemia. The study was approved by the Ethics Committee of Xixi Hospital of Hangzhou (Approval No.: 2020-14).

Diagnosis criteria

In accordance with the Chinese national guidelines for COVID-19 diagnosis and treatment (7th edition) [11] and WHO interim guidance [12], all patients diagnosed with COVID-19 in the considered hospital were enrolled in this study. Clinically diagnosed case was defined as a suspected case with one of the following etiological or serological evidence: (1) positive result of SARS-CoV-2 nucleic acid testing (real-time reverse transcription polymerase chain reaction (RT-PCR) assay); (2) viral gene sequencing that is highly homologous to that of the novel coronavirus; (3) positive result of SARS-CoV-2-specific IgM and IgG antibody, SARS-CoV-2-specific IgG antibody changing from negative to positive, or SARS-CoV-2-specific IgG antibody in the recovery period of COVID-19 four times higher than that in the acute phase. The diagnostic criteria for clinical classification of COVID-19 were referred to the Chinese national guidelines for COVID-19 diagnosis and treatment (7th edition) [11] (Table 1).

Data collection

Epidemiological and demographic data, symptoms, signs, underlying comorbidities, laboratory findings, chest CT scans, treatment, and outcome data were obtained from patients' medical records. All data were checked by two physicians (Yuhan Xu and Yilei Guo), and a third researcher (Yu He) adjudicated any difference in interpretation between the two primary reviewers.

Laboratory procedures

SARS-CoV-2 in respiratory specimens (throat/nasal swab) was detected via real-time RT-PCR or next-generation sequencing methods. Throat/nasal swab specimens were obtained for SARS-CoV-2 PCR re-examination every other day after remission of clinical symptoms (fever, cough, and dyspnea).

Routine blood examinations (e.g., blood cell counts, blood cell ratio, arterial blood gas analysis, coagulation profile, C-reactive protein, and serum amyloid A), serum biochemical tests (e.g., renal and liver function, creatine kinase, lactate dehydrogenase, procalcitonin, and electrolytes), and chest radiographs or CT scans were conducted for all inpatients.

Evaluation of clinical results

The clinical characteristics, chest CT images, treatment, and outcomes were compared between the CCVD and non-CCVD groups. The criteria for healing and discharge were referred to the Chinese national guidelines for COVID-19 diagnosis and treatment (7th edition) [11]: (1) absence of fever for at least 3 days; (2) clinical remission of respiratory symptoms and with both lungs showing substantial improvement in chest radiographs or CT scan; (3) two throat/nasal swab samples (obtained at least 24 h apart) negative for SARS-CoV-2 RNA.

The pneumonia severity index (PSI) is used by medical practitioners to calculate the probability of morbidity and mortality among patients with pneumonia. The evaluation criteria of PSI score and grade were referred to the work of Liu *et al.* [13]. The higher the PSI total score and grade were, the poorer the condition.

Statistical analysis

All statistical analyses were performed with SPSS software version 24.0 (IBM Corporation, Chicago, IL, USA). Continuous variables were presented as median (inter-quartile range (IQR)). Categorical variables were presented as N (%). Comparison between the two groups was analyzed using two-sample Student's *t*-test (normal distribution) or Mann-Whitney U test (abnormal

Table 1 Diagnostic criteria for clinical classification of COVID-19

Classification	Diagnostic criteria
Mild	Mild clinical symptoms and no evident abnormality in chest computed tomography (CT)
General	With fever, respiratory symptoms, and imaging characteristics of pneumonia
Severe	Compliance with any of the following: 1. Dyspnea and respiratory rate ≥ 30 per min; 2. $\text{SPO}_2 \leq 93\%$ on room air; 3. $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (1 mmHg = 0.133 kPa) Pulmonary imaging showed that the lesions progressed more than 50% within 24–48 h
Critical	Compliance with any of the following: 1. Respiratory failure occurrence and mechanical ventilation requirement; 2. Shock; 3. Combination with other organ failure; intensive care unit monitoring and treatment requirement

distribution) for continuous variables and Chi-square test or Wilcoxon test for categorical variables, where appropriate. A difference with a two-side α less than 0.05 was considered statistically significant.

Results

Basic clinical and epidemic features of COVID-19 patients on admission

During the study period, 102 COVID-19 patients, including 46 (45.0%) males, were involved. The patients aged 4–88 years old and had a median age of 40 years (IQR: 33–56). The most common symptoms upon admission were fever (72, 70.5%) and cough (63, 61.5%), followed by fatigue (24, 24.5%) and expectoration (22, 21.5%). Six (5.8%) patients had no symptoms. A total of 76 (74.5%) patients had a clear epidemiological exposure, 13 (12.7%) patients denied epidemiological exposure history, and 13 (12.7%) patients had no clear epidemiological exposure history. In addition, nearly half of the patients had comorbidities. Digestive system diseases (39, 38.2%) and electrolyte disorders (39, 38.2%) were the most common comorbidities, followed by CCVDs (20, 19.6%) and urinary system diseases (12, 11.7%). In all 102 COVID-19 cases, the majority comprised mild and common cases. Four (3.9%) cases were severe, and eight (7.8%) were PSI grade IV on admission (Table 2).

Comparison of the basic clinical characteristics and epidemic features between CCVD and non-CCVD patients

Among the 102 COVID-19 patients, 20 (19.6%) had CCVDs. The median ages of the CCVD and non-CCVD

groups were 56 (IQR: 42–62) and 38 years (IQR: 31–51), respectively, showing a statistically significant difference ($P < 0.001$). Moreover, significant differences were observed in the distribution of clinical classification between the two groups ($P = 0.012$). In the study, 15% of patients with CCVDs developed severe symptoms. By contrast, 1% developed severe symptoms in the non-CCVD group after admission. In addition, the proportion of PSI grade IV in the CCVD group was significantly higher than that in the non-CCVD group ($P < 0.01$). The results showed that 25% of patients with CCVD were PSI grade IV, whereas 3.6% of patients without CCVD were PSI grade IV (Table 2).

Comparison of chest CT and laboratory results between the two groups

The findings in CT images can usually reflect the severity of COVID-19. Most patients with COVID-19 had typical imaging features, such as ground-glass opacities (GGO), mixed GGO and consolidation, and nodules (Figs. 1 and 2). However, seven patients in the non-CCVD group had no evident abnormality in the CT images. The proportion of multiple lobe lesion involvement in the CCVD group was higher than that in the non-CCVD group ($P < 0.05$; Table 3).

The distributions of C-reactive protein, fibrinogen, D-dimer, total protein, and serum amyloid A showed a significant difference between the CCVD and non-CCVD groups ($P < 0.05$). We observed that patients with CCVD were more likely to have C-reactive protein > 10 mg/L, fibrinogen > 3.5 g/L, D-dimer > 1 mg/L, and total protein < 65.0 g/L. Serum amyloid A in the CCVD group was significantly higher than that in the non-CCVD group ($P < 0.05$). However, the arterial partial PaO_2 in the CCVD group was significantly lower than that in the non-CCVD group ($P < 0.05$; Table 3).

Comparison of treatments and outcomes between the two groups

After admission, all patients (102, 100%) received integrated Chinese and Western medicine treatment. A total of 97 (95.1%) patients received lopinavir and arbidol tablets, 85 (83.3%) patients received interferon, 14 (13.7%) patients received immunoglobulin, 9 (8.8%) patients received antibiotics, 7 (6.8%) patients received corticosteroids, and all patients (102, 100%) received traditional Chinese medicine (TCM) treatment. After treatment, no mild nor general symptoms of COVID-19 observed during admission became severe, and all patients (102, 100%) were treated and discharged (Table 4). The median length of stay in the hospital was 16 days (IQR: 11.0–21.3), the median duration of viral shedding was 14 days (IQR: 10.0–20.0) from illness onset, the median time

Table 2 Clinical and epidemiologic features of COVID-19 on admission

Variable	Total (n = 102)	CCVD (n = 20)	Non-CCVD (n = 82)	P value
Age and gender				
Age, year (median (IQR))	40 (33–56)	56 (42–62)	38 (31–51)	<0.001
Male (N (%))	46 (45.0%)	8 (40%)	38 (46.3%)	0.795
Vital signs				
Respiratory rate, per min	18 (18–19)	18 (18–20)	18 (18–19)	
Heart rate, per min	87 (78–100)	86 (80–101)	88 (76–101)	
Systolic blood pressure (mmHg)	128 (115–137)	136 (126–144)	125 (112–136)	
Body temperature (°C)	36.9 (36.7–37.5)	36.9 (36.7–37.2)	36.9 (36.7–37.7)	
Signs and symptoms at admission (N (%))				
Fever	72 (70.5%)	14 (70%)	58 (70.7%)	1.000
Cough	63 (61.7%)	15 (75%)	48 (58.5%)	0.271
Expectoration	22 (21.5%)	6 (30%)	16 (19.5%)	0.472
Rhinorrhea	5 (4.9%)	1 (5%)	4 (4.8%)	1.000
Sore throat	12 (11.7%)	2 (3%)	10 (12.1%)	1.000
Diarrhea	9 (8.8%)	3 (15%)	6 (7.3%)	0.518
Inappetence	7 (6.8%)	3 (15%)	4 (4.8%)	0.266
Fatigue	25 (24.5%)	3 (15%)	22 (26.8%)	0.481
Dizziness and headache	15 (14.7%)	3 (15%)	12 (14.6%)	1.000
Asymptomatic	6 (5.8%)	1 (5%)	5 (6.09%)	1.000
Exposure history (N (%))				
Yes	76 (74.5%)	15 (75%)	61 (74.3%)	0.333
No	13 (12.7%)	4 (20%)	9 (10.9)	
Not clear	13 (12.7%)	1 (5%)	12 (14.6%)	
Comorbidity (N (%))				
CCVD	20 (19.6%)	/	/	
Digestive system disease	39 (38.2%)	10 (50%)	29 (35.3%)	0.342
Urinary system disease	12 (11.7%)	5 (25%)	7 (8.5%)	0.097
Respiratory system disease	7 (6.8%)	0 (0%)	7 (8.5%)	0.389
Endocrine system disease	9 (8.8%)	4 (20%)	5 (6.0%)	0.127
Chronic hepatitis B virus infection	10 (9.8%)	2 (10%)	8 (9.7%)	1.000
Electrolyte disorder	39 (38.2%)	10 (50%)	29 (35.3%)	0.342
Clinical classification (N (%))				
Mild	19 (18.6%)	2 (10%)	17 (20.7%)	0.012
General	79 (77.5%)	15 (75%)	64 (78.0%)	
Severe	4 (3.9%)	3 (15%)	1 (1.2%)	
PSI grades				
I	36 (35.2%)	0 (0%)	36 (43.9%)	<0.001
II	43 (42.1%)	8 (40%)	35 (42.6%)	
III	15 (14.7%)	7 (35%)	8 (9.7%)	
IV	8 (7.8%)	5 (25%)	3 (3.6%)	<0.01

CCVD, cardio-cerebrovascular disease; IQR, interquartile range; PSI, pneumonia severity index.

course of symptom disappearance was 17 days (IQR: 12–22), and the median time course of cough disappearance was 20 days (IQR: 14–25.3) (Table 4).

Patients with pre-existing CCVD received more inten-

sive integrated treatments to manage their symptoms of COVID-19 than non-CCVD patients. The CCVD group registered a higher need for lopinavir and arbidol tablets (100% versus 93.9%), interferon (85% versus 82.9%),

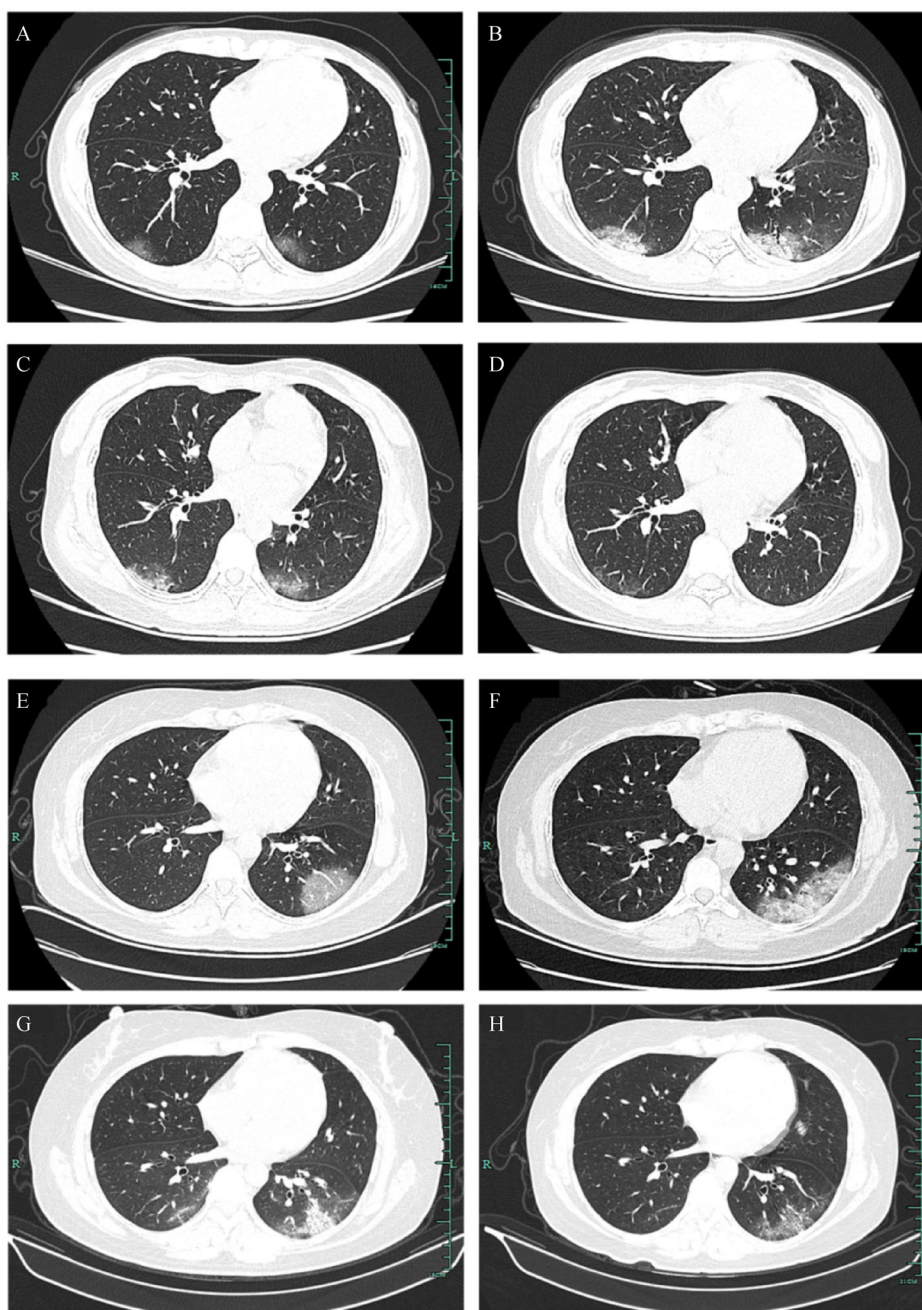


Fig. 1 CT scans of two patients. (A–D) Case 1: (A) Chest CT scans upon admission of a 43-year-old female with CCVD on day 2 after fever, manifested by bilateral multiple GGO. (B) CT scan showing worsening on day 7. The area of subpleural lesions in the lower lobes of both lungs was remarkably enlarged; mixed GGO and consolidation were the main features. (C) Improvements of original lesions on day 12. Lesions in the lower lobes of both lungs reduced in scope and density, presenting as light GGO with patchy consolidations. (D) CT re-examination 14 days after patient's discharge showing that lesions in the lower lobes of both lungs were basically absorbed, presenting as a small light GGO. (E–H) Case 2: (E) Chest CT scans on admission of a 40-year-old female, manifesting multiple GGO in the inferior lobe of the left lung, on day 3 after onset of symptoms. (F) The scope of lesion in the inferior lobe of the left lung was significantly enlarged, with mixed GGO and consolidation on day 7. (G) Improvement of original lesions on day 11; the scope of lesion in the inferior lobe of the left lung was reduced, presenting as light GGO with patchy consolidations. (H) CT re-examination showing further absorption of original lesions 7 days after patient's discharge.

antibiotics (15% versus 7.3%), and immunoglobulin (20% versus 12.1%) compared with the non-CCVD group. No

significant difference was observed in terms of treatment and outcomes in both groups (Table 4).

Table 3 Chest CT and laboratory results of COVID-19 patients on admission

Variable	Total (n = 102)	CCVD (n = 20)	Non-CCVD (n = 82)	P value
CT results				0.042
No remarkable abnormality and single lobe lesion	32 (31.4%)	2 (10%)	30 (36.6%)	
Multiple lobe lesions	70 (68.6%)	18 (90%)	52 (63.4%)	
Laboratory indicators at admission				
White blood cells ($\times 10^9/L$)	5.24 (4.31–7.29)	5.6 (4.12–7.37)	5.17(4.48–6.74)	0.696
Lymphocytes ($\times 10^9/L$)	1.24 (0.88–1.82)	1.29 (0.86–1.87)	1.12 (0.85–1.46)	0.067
C-reactive protein (mg/L)				0.023
0–10	70 (68.6%)	9 (45%)	61 (74.4%)	
>10	32 (31.4%)	11 (55%)	21 (25.6%)	
Fibrinogen (g/L)				0.014
≥ 1.8 to ≤ 3.5	58 (56.9%)	6 (30%)	52 (63.4%)	
>3.5	44 (43.1%)	14 (70%)	30 (36.6%)	
D-dimer (mg/L)				0.017
≤ 0.5	75 (73.5%)	10 (50%)	65 (79.3%)	
>0.5 to ≤ 1	8 (7.8%)	2 (10%)	6 (7.3%)	
>1	19(18.6%)	8 (40%)	11(13.4%)	
Total protein (g/L)				0.034
<65.0	17 (16.7%)	7 (35%)	10 (12.2%)	
≥ 65.0 to ≤ 85	85 (83.3%)	13 (65%)	72 (87.8%)	
AST/ALT				0.942
<1	29 (28.4%)	5 (25%)	24 (29.3%)	
≥ 1	74 (72.5%)	15 (75%)	58 (70.7%)	
Globulin (g/L)	28.6 (25.6–32)	30.4 (25.3–32.6)	29.3 (26.4–32.8)	0.019
Albumin (g/L)	40.8 (34–43.8)	35 (32.3–43.2)	42.6 (39.4–45.5)	0.477
Arterial partial PaO ₂ (mmHg)	93.9 (62.4–113)	79.6 (49.4–93.9)	112 (92.2–182)	0.028
Oxygen saturation (%)	97.8 (94.2–98.6)	96.1 (83.9–98.0)	99.5 (98.5–98.9)	0.386
Serum amyloid A (mg/L)	55 (11–147)	113 (28–150)	37 (10–122)	0.044

Discussion

In this study, we observed that COVID-19 patients with pre-existing CCVD presented poorer clinical characteristics, CT image, and laboratory indicators than those without CCVD. The CCVD group showed higher incidences of severe COVID-19, PSI grade IV, and multiple lobe lesions in CT scan compared with the non-CCVD group. Laboratory analysis showed that C-reactive protein, fibrinogen, D-dimer, and serum amyloid A levels were notably higher in the CCVD group compared with the non-CCVD group. The total protein and arterial partial PaO₂ levels were lower in the CCVD group compared with the non-CCVD group.

The 102 COVID-19 patients admitted in this study were treated with integrated TCM and Western medicine treatment protocol. After treatment, no mild nor general symptoms of COVID-19 on admission became severe, and no death was recorded. Compared with domestic and foreign data of the same period (as of March 26, 2020,

COVID-19 had caused approximately 4.05% mortality in China but approximately 4.51% mortality globally [14,15]), our findings reflect the advantages of integrated Chinese and Western medicine treatment. At present, no specific antiviral drugs nor vaccine against COVID-19 infection is available [16]. Western medicine treatment strategies include effective oxygen therapy, antiviral treatment (α -interferon atomization inhalation, lopinavir, ritonavir, arbidol, and chloroquine phosphate), antibacterial treatment, etc. Importantly, clinical practice proves that early intervention with TCM can effectively prevent the development of severe symptoms of COVID-19. In TCM, COVID-19 is classified under plague [12]. In this study, our TCM therapeutic principles of COVID-19 were as follows:

(1) Early stage of COVID-19. In this stage, fear of cold, dry cough, dry throat, fatigue, choking sensation in the chest, stomach flatulence, hiccup, loose stool, pale tongue with slimy tongue fur, and floating pulse are usually observed in patients with COVID-19. The basic

Table 4 Treatment and outcomes

Variable	Total (n = 102)	CCVD (n = 20)	Non-CCVD (n = 82)	P value
Treatment				
Lopinavir and arbidol tablets	97 (95.1%)	20 (100%)	77 (93.9%)	0.579
Interferon	85 (83.3%)	17 (85%)	68 (82.9%)	1.000
TCM	102 (100%)	20 (100%)	82 (100%)	–
Antibiotic	9 (8.8%)	3 (15%)	6 (7.3%)	0.518
Immunoglobulin	14 (13.7%)	4 (20%)	10 (12.1%)	0.584
Corticosteroid	7 (6.8%)	1 (5%)	6 (7.3%)	1.000
Outcomes				
Healed and discharged	102 (100%)	20 (100%)	82 (100%)	–
Hospital length of stay, day	16 (11–21.3)	15 (11.3–22.8)	16 (11–21)	0.918
Duration of viral shedding after COVID-19 onset, day	14 (10–20)	13.5 (9–21.5)	14 (10–19)	0.743
Time course of symptom disappearance, day	17 (12–22)	18.5 (12.5–26.3)	16 (12–21)	0.412
Time course of cough disappearance, day	20 (14–25.3)	20.5 (14–30.5)	19 (14–24)	0.156

prescription is Qingjie Xuantou Feiwei formula: 10 g honeysuckle (Jinyinhua), 10 g *Polygonum cuspidatum* (Huzhang), 10 g *Pueraria* (Gegen), 6 g *Ephedra* (Mahuang), 9 g apricot kernel (Xingren), and 10 g licorice (Gancao). Based on symptoms, herbs are added or subtracted correspondingly. The usage and dosage are one dose daily; water decoction is 200 mL, twice a day.

(2) Middle stage of COVID-19. Patient in this stage usually have the following symptoms: fever, cough with yellow phlegm, abdominal distension and constipation, chest tightness with shortness of breath, dyspnea, red tongue with yellow greasy tongue fur, and rolling and rapid pulse. Basic prescription: 30 g gypsum (*Shigao*), 9 g raw *Ephedra* (Shengmahuang), 12 g *Lepidium* seed (Tinglizi), 10 g *Scutellaria* root (Huangqin), 10 g raw rhubarb (Shengdahuang), 15 g *Polygonum cuspidatum* (Huzhang), 9 g apricot kernel (Xingren), 9 g *Areca catechu* (Binlang), and 10 g honeysuckle (Jinyinhua). Herbs are added or subtracted based on symptoms. Usage and dosage are the same as those in the early stage of COVID-19.

(3) Convalescence of COVID-19. In this stage, patients are mostly divided into those with Qi or Qi-yin deficiency syndrome. Qi deficiency syndrome is often accompanied by shortness of breath, fatigue, poor appetite, nausea and vomiting, loose stool, and pale and enlarged tongue with white and greasy tongue fur. Basic prescription of Qi deficiency syndrome: 10 g *Codonopsis pilosula* (Dangshen), 15 g *Astragalus membranaceus* (Zhihuangqi), 9 g Pinelliae Rhizoma Praeparatum (Fabanxia), 10 g Dried Tangerine Peel (Chenpi), 9 g Poria Cocos (Fuling), 10 g Agastache Rugosus (Huoxiang), 6 g Fructus Amomi (Sharen), and 15 g Rhizoma Dioscoreae (Shanyao). Qi-yin deficiency syndrome is often accompanied by fatigue, dyspnea, thirst, red tongue with little coating, and weak

pulse. Basic prescription of Qi-yin deficiency syndrome: 10 g Radix Glehniae (Beishashen), 10 g Radix Pseudostellariae, 10 g *Polygonatum odoratum* (Yuzhu), 10 g *Ophiopogon japonicus* (Maidong), 12 g Radix Trichosanthis (Tianhuafen), 6 g *Scutellaria* root (Huangqin), 9 g apricot kernel (Xingren), 10 g honeysuckle (Jinyinhua), 10 g Radix Paeoniae Rubra (Chishao), 10 g Rhizoma Dioscoreae (Shanyao), and 6 g licorice (Gancao). Herbs are added or subtracted based on symptoms. Usage and dosage are the same as those in the early stage of COVID-19.

(4) Severe and critical cases of COVID-19. Given that the severe and critical cases of COVID-19 always lead to kidney, liver, and other organ failure and shock and require ICU monitoring [17], patients cannot take Chinese medicine orally. Therefore, Chinese medicine injections, including Xingnaojing, Xuebijing, Danhong (DHI), and Shenmai injections, should be applied.

Given that elderly patients with COVID-19 are usually accompanied by CCVD and other systemic diseases, they are likely to develop severe and critical diseases with high mortality [18]. Studies published on patients admitted to the ICU with COVID-19 show that COVID-19 is linked to coagulopathy and thrombotic risk [8,19–23]. Klok *et al.* [24] confirmed the extremely high cumulative incidence (31% of 184 patients) of thrombotic complications (symptomatic acute pulmonary embolism, ischemic stroke, myocardial infarction, systemic arterial embolism, and deep vein thrombosis) in critical COVID-19 patients of three Dutch hospitals, and patients with thrombotic complications had a more than fivefold higher risk of all-cause death. Helms *et al.* [25] conducted a multicenter study of 150 COVID-19 patients and found a 43% prevalence of thrombosis, which occurred despite

prophylactic or therapeutic anticoagulation. These pieces of evidence suggest that we should focus on the application of TCM for promoting blood circulation and removing stasis, such as DHI (China Food and Drug Administration approval No. Z20026866). DHI is extracted from *Salvia miltiorrhizae* Radix and *Carthami tinctorii* Flos, and it can be used to treat CCVD [26–30].

The present study has several limitations. First, given the retrospective nature of the study, recall biases might have existed in patient signs and symptoms at admission. Second, all data were obtained from Xixi Hospital of Hangzhou, Zhejiang Province, China, which mainly received mild and general cases of COVID-19 patients. Therefore, this study lacks the analysis of severe and critical patients. Third, we did not quantify the viral load of SARS-CoV-2, and the PCR results of upper respiratory samples have the potential to be false negative [19]. Hence, studies on the dynamic changes in viral load are still warranted. Finally, this study is a single-center, small-sample retrospective study and may inadequately reflect the overall complexity of the general population. Therefore, large-scale prospective cohort studies will be required to further gain insights into the clinical features of patients with COVID-19 and pre-existing CCVD.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81930111) and Zhejiang Province High-level Talents Project (No. 2019R51002).

Compliance with ethics guidelines

Yu Wang, Lan Li, Yuanjiang Pan, Yu He, Zuhua Chen, Yunhao Xun, Yuhan Xu, Yilei Guo, Jiehong Yang, Jianchun Guo, and Haitong Wan declare no conflict of interest. Given the retrospective nature of this study, informed consent was waived. The study was approved by the Ethics Committee of Xixi Hospital of Hangzhou (Approval No.: 2020-14).

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