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RESEARCH ARTICLE

Chinese herbal medicine reduces mortality in patients with severe and critical coronavirus disease 2019: a retrospective cohort study

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Abstract **This study aimed to evaluate the efficacy of Chinese herbal medicine (CHM) in patients with severe/critical coronavirus disease 2019 (COVID-19). In this retrospective study, data were collected from 662 patients with severe/critical COVID-19 who were admitted to a designated hospital to treat patients with severe COVID-19 in Wuhan before March 20, 2020. All patients were divided into an exposed group (CHM users) and a control group (non-users). After propensity score matching in a 1:1 ratio, 156 CHM users were matched by propensity score to 156 non-users. No significant differences in seven baseline clinical variables were found between the two groups of patients. All-cause mortality was reported in 13 CHM users who died and 36 non-users who died. After multivariate adjustment, the mortality risk of CHM users was reduced by 82.2% (odds ratio 0.178, 95% CI 0.076–0.418; $P < 0.001$) compared with the non-users. Secondly, age (odds ratio 1.053, 95% CI 1.023–1.084; $P < 0.001$) and the proportion of severe/critical patients (odds ratio 0.063, 95% CI 0.028–0.143; $P < 0.001$) were the risk factors of mortality. These results show that the use of CHM may reduce the mortality of patients with severe/critical COVID-19.**

Keywords COVID-19; CHM; mortality; a retrospective cohort study

Introduction

In December 2019, a breakout of coronavirus disease 2019 (COVID-19) was reported. The World Health Organization (WHO) has declared COVID-19 as a global pandemic [1]. At present, the number of death cases from COVID-19 is increasing rapidly, and its mortality rate is significantly higher than that of influenza [2]. By March 29, 2020, the total number of confirmed cases worldwide was 634 835, and the number of deaths was as high as 29 891 [3]. No vaccine or antiviral medicine has confirmed clinical effect to prevent or treat COVID-19 currently, which has brought great difficulties to the prevention and control of the epidemic [4]. A recent clinical study has reported that the antiviral drugs lopinavir and ritonavir have no clinical benefit in the treatment of patients with severe COVID-19 [5].

China has constantly emphasized on the use of Chinese and Western medicine in the fight against COVID-19. Chinese herbal medicine (CHM), which is the main component of complementary and alternative medicine, plays an important role in the whole process. In the fifth edition of the *Diagnosis and Treatment Guideline for COVID-19 (Trial Version)* released by the National Health Commission of the People's Republic of China, CHM treatment has been included. Clinical effects of CHM or integrated Chinese and Western medicine treatments on patients with mild COVID-19 have been recently reported [6]. However, no studies have reported the efficacy

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evaluation and clinical outcomes of CHM intervention in patients with severe COVID-19. The present study aimed to analyze the influence of demographics, clinical treatment, laboratory test, and other factors on the mortality of patients with severe/critical COVID-19 and to evaluate the effect of CHM in reducing the mortality of these patients.

Materials and methods

Study design and participants

We performed a single-center, retrospective cohort study in a hospital in Wuhan, China, which is one of the largest designated hospitals to treat patients with severe COVID-19 by using integrated Chinese and Western medicine. We retrospectively analyzed patients with severe/critical COVID-19 who were admitted to hospital and had clinical outcomes before March 20, 2020. The patients were diagnosed and typed in accordance with the fifth edition of the *Diagnosis and Treatment Guideline for COVID-19 (Trial Version)* [7]. Severe cases in accordance with the following criteria were included: (1) respiratory distress ($\geqslant$ 30 breaths/min); (2) oxygen saturation $\leqslant$ 93% at rest; (3) arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) $\leqslant$ 300 mmHg (1 mmHg = 0.133 kPa). Cases with chest imaging showing obvious lesion progression within 24–48 h $>$ 50% were managed as severe cases. Critical cases in accordance with the following criteria were included: (1) respiratory failure and requiring mechanical ventilation; (2) shock; (3) with other organ failure that requires intensive care unit care. The clinical outcome was discharge or death, and the criteria for hospital discharge were absence of fever for at least 72 h, substantial improvement in both lungs in chest computed tomography (CT), clinical remission of respiratory symptoms, and two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart.

This study was approved by the institutional ethics board of Wuhan Integrated TCM and Western Medicine Hospital (No. [2020]8) and was registered with chictr.org.cn (ChiCTR2000030719). Due to the retrospective nature of the study, the requirement of informed consent was waived.

Data collection

Data for the study were obtained from the HIS electronic medical records in the hospital, including demographics, clinical symptoms, laboratory examinations, treatment measures, and outcomes. Two researchers from the hospital manually collected and examined the data, and a dispute between the first two researchers was settled by a third researcher.

Procedures

Patients were treated with oxygen, antivirals (such as interferon or ribavirin), antibiotics (such as moxifloxacin, cefoperazone sodium, and sulbactam sodium), and Chinese medicine based on the *Diagnosis and Treatment Guideline for COVID-19 (Trial Version)*. Critical patients were treated with noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation to support life. All CHM treatments were administered in accordance with the traditional Chinese medicine (TCM) treatment of the abovementioned guideline. The CHM mainly consisted of Fuling (*Poria cocos* (Schw.) Wolf.), Huangqi (*Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao.), Huoxiang (*Pogostemon cablin* (Blanco) Benth.), Kuxingren (*Prunus armeniaca* L. var. ansu Maxim.), Baizhu (*Atractylodes macrocephala* Koidz.), Banxia (*Pinellia ternata* (Thunb.) Breit.), Gancao (*Glycyrrhiza uralensis* Fisch.), Houpo (*Magnolia officinalis* Rehd. et Wils.), Mahuang (*Ephedra sinica* Stapf), Guizhi (*Cinnamomum cassia* Presl), Huangqin (*Scutellaria baicalensis* Georgi.), Sharen (*Amomum villosum* Lour.), Jiegeng (*Platycodon grandiflorum* (Jacq.) A.DC.), Peilan (*Eupatorium fortunei* Turcz.), and Dangsheng (*Codonopsis pilosula* (Franch.) Nannf.) purchased from Hubei Tianji TCM Decoction Pieces Co., Ltd. This TCM decoction "Mahuang Liu Jun Tang" was administered orally 200 mL each time, twice a day in hospital days.

The laboratory examinations were standardized in the laboratory department of the hospital. Throat-swab specimens were obtained for SARS-CoV-2 PCR examination at the time of admission and during hospitalization, and the SARS-CoV-2 nucleic acid detection kit (fluorescent PCR) was purchased from Shanghai Zhijiang Biotechnology Co., Ltd. Routine blood examinations included complete blood count, coagulation profile, and serum biochemical tests (including renal and liver function, creatine kinase, myocardial enzymogram, high-sensitivity troponin, electrolytes, humoral immune function, and C-reactive protein). CT scan was also performed for all inpatients. Frequency of examinations was determined by the treating physician.

Outcomes

The primary outcome was all-cause mortality. The considered factors were age, sex, disease duration, medical history, treatment measures (including oxygen, antivirals, antibiotics, Chinese patent medicine, and CHM). Cause of death was considered from the aspects of respiratory failure, septic shock, gastrointestinal bleeding, heart failure, stroke, multiple organ dysfunction syndrome (MODS), and surgery.

Propensity score

Propensity score matching (PSM) was used. Three variables (age, sex, and disease stage) in the propensity score were chosen on the basis of clinical significance. Each patient who received CHM was matched to a patient who did not on propensity score by using the greedy nearest neighbor matching without replacement within a caliper. The caliper width was 0.05 of the logit-transformed propensity score. The absolute standardized difference was used to evaluate the balance of baseline characteristics between the two groups after matching, and all were checked to be less than 0.25.

Statistical analyses

Continuous and categorical variables were presented as median (IQR) and *n* (%), respectively. The Mann–Whitney U test, χ^2 test, or Fisher's exact test was performed to compare differences between CHM users and non-users where appropriate. Univariable and multivariable logistic regression models were performed to explore the risk factors associated with the mortality of patients with severe/critical COVID-19. PSM was used to balance the two groups considering the known confounders. Using the application of CHM as the dependent variable, we incorporated multiple clinically relevant covariates into our analysis as independent variables (all baseline characteristics). Statistical significance was considered at $P < 0.05$. Statistical analyses were conducted using SAS version 9.4.

Results

Demographic and patient characteristics

By March 20, 2020, 1476 cases of COVID-19 patients were hospitalized in Wuhan Integrated TCM and Western Medicine Hospital. After excluding 170 transferred patients and 644 mild patients, we included 662 patients for the final analysis, including 484 CHM users and 178 non-users (Fig. 1). The 662 patients were composed of 562 (84.9%) severe patients and 100 (15.1%) critical patients. A total of 71 (10.7%) patients died, and 591 (89.3%) patients were discharged from the hospital. Of the 71 deaths, 49 were due to acute respiratory failure (69.0%), 1 (1.4%) was due to respiratory failure with heart failure, and 1 (1.4%) was due to respiratory failure with myocardial infarction. Respiratory failure with tumors occurred in 2 (2.8%) cases, respiratory failure with septic shock in 4 (5.6%) cases, septic shock in 5 (7%) cases, MODS in 3 (4.2%) cases, death after the operation in 2 (2.8%)

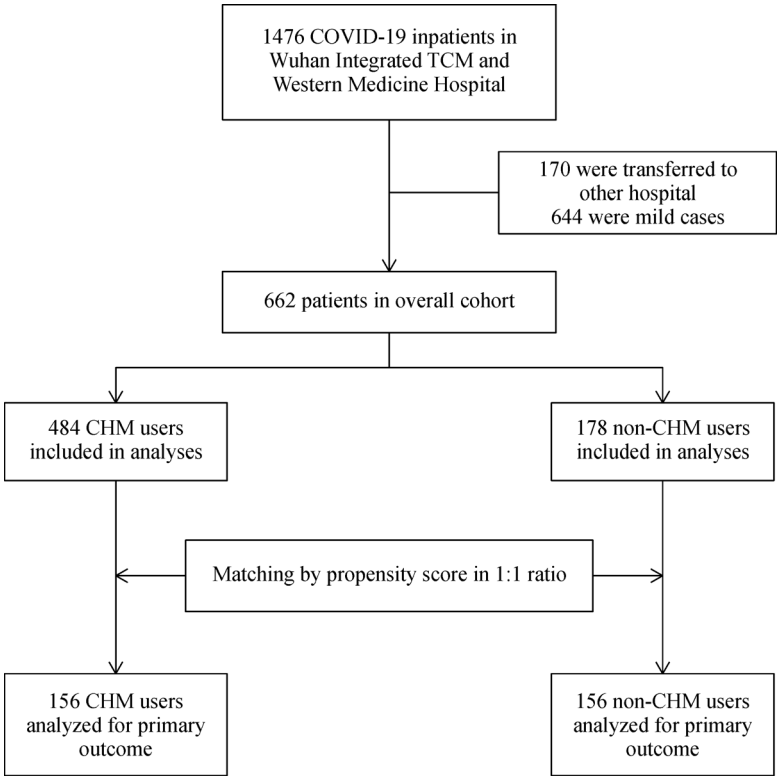

Fig. 1 Study profile.

cases, gastrointestinal bleeding in 1 (1.4%) case, acute myocardial infarction in 2 (2.8%) cases, and stroke in 1 (1.4%) case.

Baseline characteristics before PSM

In the group of CHM users, 444 patients (91.7%) were severe and 40 patients (8.3%) were critical. In the group of non-users, 118 (66.3%) were severe and 60 (33.7%) were critical. A total of 15 (3.1%) CHM users died and 56 (31.5%) non-users died. We analyzed clinical variables between the two groups. Differences in age, sex, medical history, antibiotics, hormone treatment, and oxygen therapy were found between the two groups. Differences in signs and symptoms, such as fever and constipation, were also detected. With respect to laboratory tests, differences were found in the levels of leukocytes, lymphocytes, monocytes, C-reactive protein, creatine kinase, and troponin-I between the two groups. In terms of treatment, the two groups showed significant differences in antibiotics, Chinese patent medicine, and oxygen therapy (Table 1).

Table 1 Baseline characteristics of study patients

	Total (n = 662)	CHM users (n = 484)	CHM non-users (n = 178)	P value
Age (year)	60 (47, 70)	57 (45, 68)	66 (54, 76)	<0.001
Sex				0.011
Men	296 (44.7%)	202 (41.7%)	94 (52.8%)	
Women	366 (55.3%)	282 (58.3%)	84 (47.2%)	
Smoking history				0.348
Never	575 (86.9%)	417 (86.2%)	158 (88.8%)	
Ever	15 (2.3%)	12 (2.5%)	3 (1.7%)	
Current	20 (3.0%)	18 (3.7%)	2 (1.1%)	
Other	52 (7.9%)	37 (7.6%)	15 (8.4%)	
Comorbidity	354 (53.5%)	246 (50.8%)	108 (60.7%)	0.024
Chronic obstructive lung disease	19 (2.9%)	10 (2.1%)	9 (5.1%)	0.041
Hypertension	208 (31.4%)	147 (30.4%)	61 (34.3%)	0.338
Cardiovascular disease	53 (8.0%)	40 (8.3%)	13 (7.3%)	0.686
Diabetes	94 (14.2%)	69 (14.3%)	25 (14.0%)	0.945
Malignancy	12 (1.8%)	7 (1.4%)	5 (2.8%)	0.321
Cerebrovascular disease	38 (5.7%)	26 (5.4%)	12 (6.7%)	0.502
Chronic kidney disease	3 (0.6%)	0 (0.0%)	3 (0.5%)	0.568
Chronic liver disease	8 (1.2%)	5 (1.0%)	3 (1.7%)	0.449
Signs and symptoms	658 (99.4%)	481 (99.4%)	177 (99.4%)	1.000
Fever	450 (68.0%)	345 (71.3%)	105 (59.0%)	0.003
Dry cough	408 (61.6%)	298 (61.6%)	110 (61.8%)	0.957
Expectoration	184 (27.8%)	129 (26.7%)	55 (30.9%)	0.280
Fatigue	298 (45.0%)	209 (43.2%)	89 (50.0%)	0.118
Shortness of breath	221 (33.4%)	153 (31.6%)	68 (38.2%)	0.111
Nasal obstruction	21 (3.2%)	18 (3.7%)	3 (1.7%)	0.186
Pharyngalgia	39 (5.9%)	33 (6.8%)	6 (3.4%)	0.095
Hemoptysis	4 (0.6%)	1 (0.2%)	3 (1.7%)	0.062
Chills	46 (6.9%)	33 (6.8%)	13 (7.3%)	0.828
Headache	45 (6.8%)	30 (6.2%)	15 (8.4%)	0.312
Myalgia	74 (11.2%)	55 (11.4%)	19 (10.7%)	0.803
Vomiting	35 (5.3%)	22 (4.5%)	13 (7.3%)	0.160
Diarrhea	71 (10.7%)	55 (11.4%)	16 (9.0%)	0.381
Constipation	12 (1.8%)	5 (1.0%)	7 (3.9%)	0.020
Laboratory tests				
White blood cell count, $\times 10^9$ /L	5.39 (4.30, 6.87)	5.46 (4.42, 7.00)	5.02 (3.83, 6.60)	0.020
Red blood cell count, $\times 10^9$ /L	4.200 (3.860, 4.590)	4.205 (3.870, 4.610)	4.150 (3.810, 4.560)	0.314
Neutrophil count, $\times 10^9$ /L	3.200 (2.380, 4.460)	3.260 (2.430, 4.530)	3.010 (2.210, 4.000)	0.089
Lymphocyte count, $\times 10^9$ /L	1.38 (0.96, 1.81)	1.44 (1.01, 1.88)	1.19 (0.84, 1.58)	<0.001
Monocyte count, $\times 10^9$ /L	0.51 (0.37, 0.66)	0.52 (0.39, 0.68)	0.46 (0.34, 0.61)	0.002
Platelet count, $\times 10^9$ /L	208.00 (161.00, 274.00)	211.00 (166.00, 277.00)	202.00 (149.00, 260.00)	0.093

(*Continued*)

	Total (n = 662)	CHM users (n = 484)	CHM non-users (n = 178)	P value
Hemoglobin, g/L	128.00 (118.00, 140.00)	128.00 (118.00, 141.20)	128.00 (118.00, 138.00)	0.515
C-reactive protein, mg/L	7.00 (3.11, 30.04)	4.60 (3.11, 26.50)	14.00 (3.11, 41.50)	<0.001
Albumin, g/L	35.70 (32.35, 39.00)	35.70 (32.50, 39.00)	35.50 (32.20, 38.60)	0.102
Alanine aminotransferase, U/L	22 (14, 36)	23 (14, 37)	20 (14, 32)	0.207
Aspartate aminotransferase, U/L	25 (19, 37)	25 (19, 37)	25 (19, 37)	0.879
Blood urea nitrogen, mmol/L	4.10 (3.30, 5.30)	4.10 (3.30, 5.30)	4.00 (3.20, 5.40)	0.703
Creatinine, μmol/L	63.0 (54.0, 77.4)	63.0 (54.0, 77.0)	62.0 (54.0, 79.4)	0.937
Creatine kinase, U/L	61.00 (41.00, 94.00)	58.00 (39.00, 85.00)	70.00 (46.00, 143.00)	0.002
Lactate dehydrogenase, U/L	211.0 (163.0, 285.0)	207.0 (161.0, 285.0)	223.5 (170.0, 309.0)	0.195
High-sensitivity cardiac troponin I, pg/mL	0.007 (0.002, 0.034)	0.006 (0.002, 0.020)	0.012 (0.004, 2.900)	0.004
IgG, g/L	10.40 (8.15, 12.90)	10.40 (8.17, 13.90)	10.60 (7.94, 11.90)	0.555
IgA, g/L	2.19 (1.56, 2.94)	2.27 (1.83, 3.12)	2.05 (1.36, 2.51)	0.071
IgM, g/L	0.95 (0.73, 1.33)	0.94 (0.63, 1.38)	0.96 (0.83, 1.33)	0.516
C3, g/L	1.07 (0.92, 1.24)	1.05 (0.91, 1.25)	1.14 (0.93, 1.24)	0.355
C4, g/L	0.270 (0.206, 0.340)	0.245 (0.192, 0.326)	0.303 (0.253, 0.349)	0.066
Imaging features				
Consolidation	522 (78.9%)	386 (79.8%)	136 (76.4%)	0.322
Pleural effusion	28 (4.2%)	16 (3.3%)	12 (6.7%)	0.050
Treatment				
Antibiotics	516 (77.9%)	362 (74.8%)	154 (86.5%)	0.001
Antiviral treatment	553 (83.5%)	407 (84.1%)	146 (82.0%)	0.525
Chinese patent medicine	437 (66.0%)	331 (68.4%)	106 (59.6%)	0.033
Hormone	149 (22.5%)	95 (19.6%)	54 (30.3%)	0.003
Oxygen therapy				<0.001
Mask oxygen inhalation	454 (68.6%)	361 (74.6%)	93 (52.2%)	
Nasal tube of oxygen inhalation	161 (24.3%)	107 (22.1%)	54 (30.3%)	
Noninvasive mechanical ventilation	45 (6.8%)	16 (3.3%)	29 (16.3%)	
Invasive mechanical ventilation	2 (0.3%)	0 (0.0%)	2 (1.1%)	

Baseline characteristics and all-cause mortality after PSM

To balance the differences in baseline characteristics and reduce confounding factors, we performed PSM by incorporating age, sex, and disease severity as independent variables. After PSM in a 1:1 ratio, the CHM users and non-users were both 156. The two groups showed differences in terms of medical history, antibiotics, and hormone treatment at baseline (Table 2). The mortality rates of the CHM and non-CHM groups were 8.3% and 23.1%, respectively.

Univariate logistic regression analysis of the death outcomes of the two groups revealed significant differences in the effects of CHM, age, and disease severity on the mortality rate, and multivariate logistic regression analysis showed significant differences in the effects of CHM, age, and medical history on the mortality rate (Table 3). The risk of death in the CHM group reduced by 88.1% compared with that in the non-CHM group. Age was also one of the important factors influencing the mortality rate. For every 1 year of age increase, the risk of death increased by 5.0%.

Discussion

Since the outbreak of COVID-19, the rising mortality has caused widespread concern. Existing research results suggest that male, age, and organ failure severity are the risk factors of death in patients with COVID-19 [8,9]. Our study has confirmed that age is an important factor affecting mortality in patients with COVID-19, which is consistent with the results of previous studies [10]. In the fifth edition of the *Diagnosis and Treatment Guideline for COVID-19 (Trial Version)* released by China, patients with severe and critical COVID-19 were classified based on whether respiratory failure or other organ failure occurred. In this study, disease severity was relevant to organ failure severity, which also validated the results of previous studies that organ failure severity is an important risk factor affecting mortality.

Table 2 Baseline characteristics of study patients after PSM

	Total (n = 312)	CHM users (n = 156)	CHM non-users (n = 156)	P value
Age (year)	63 (51, 72)	63 (54, 72)	63 (49, 73)	0.973
Sex				0.495
Men	142 (45.5%)	68 (43.6%)	74 (47.4%)	
Women	170 (54.5%)	88 (56.4%)	82 (52.6%)	
The stage of disease				1.000
Severe cases	236 (75.6%)	118 (75.6%)	118 (75.6%)	
Critical cases	76 (24.4%)	38 (24.4%)	38 (24.4%)	
Comorbidity	174 (55.8%)	77 (49.4%)	97 (62.2%)	0.023
Imaging features	287 (92.0%)	147 (94.2%)	140 (89.7%)	0.144
Treatment				
Antibiotics	251 (80.4%)	116 (74.4%)	135 (86.5%)	0.007
Antiviral treatment	266 (85.3%)	136 (87.2%)	130 (83.3%)	0.338
Chinese patent medicine	200 (64.1%)	107 (68.6%)	93 (59.6%)	0.098
Hormone	84 (26.9%)	33 (21.2%)	51 (32.7%)	0.022
Oxygen therapy				0.657
Mask oxygen inhalation	184 (59.0%)	95 (60.9%)	89 (57.1%)	
Nasal tube of oxygen inhalation	95 (30.4%)	46 (29.5%)	49 (31.4%)	
Noninvasive mechanical ventilation	31 (9.9%)	15 (9.6%)	16 (10.3%)	
Invasive mechanical ventilation	2 (0.6%)	0 (0.0%)	2 (1.3%)	

Table 3 Risk factors associated with in-hospital death after PSM

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
CHM (vs. non-CHM)	0.303 (0.154, 0.598)	<0.001	0.178 (0.076, 0.418)	<0.001
Female (vs. male)	0.698 (0.379, 1.287)	0.249		
Age (year)*	1.068 (1.040, 1.096)	<0.001	1.053 (1.023, 1.084)	<0.001
Severe cases (vs. critical cases)	0.065 (0.032, 0.133)	<0.001	0.063 (0.028, 0.143)	<0.001
Comorbidity present (vs. not present)	1.305 (0.699, 2.435)	0.403		
Imaging features present (vs. not present)	0.724 (0.258, 2.031)	0.539		
Treatment (vs. non-treatment)				
Antibiotics	1.095 (0.500, 2.399)	0.820		
Antiviral treatment	0.619 (0.284, 1.347)	0.227		
Chinese patent medicine	0.780 (0.418, 1.455)	0.435		

*Per 1 unit increase.

Given the lack of effective therapies for COVID-19, supportive care, including symptom control and complication prevention, remains the most commonly used treatment option [11]. In addition, glucocorticoid treatment is beneficial for specific patients [12]. Many antiviral drugs, including arbidol [13,14] and remdesivir [15,16], are recommended for the treatment of COVID-19, and some pharmacological studies also support the use of these drugs to inhibit SARS-CoV-2. However, the use of antiviral drugs in many clinical trials, including this study, is not a key factor affecting mortality. This phenomenon may be attributed to the fact that in patients with mild COVID-19 [16], antiviral drugs can reduce the clinical symptoms and promote the elimination of virus. However, in patients with severe and critical COVID-19, antiviral therapy is only a basic treatment. Whether or not it is combined with organ failure is a more important risk factor; thus, the treatment used to improve the condition of patients may be more significant [11].

Although CHM has been applied to treat many patients with COVID-19, limited studies have confirmed its clinical effects on this disease [17]. In China, traditional Chinese medicine (TCM) has been widely used in the prevention and treatment of COVID-19, and some studies showed that CHM can reduce the antipyretic time in mild patients [18], shorten the average hospital stay, and improve the CT improvement rate [19]. However, the sample sizes of these studies were small, and limited clinical evidence was

achieved to support the application of CHM in patients with COVID-19. In addition, studies examining the use of CHM in patients with severe or critical COVID-19 are lacking. This retrospective cohort study is the first to reveal that the use of CHM in patients with severe/critical COVID-19 can reduce mortality. Thus, TCM may be also an option in the treatment of patients with severe or critical COVID-19 in addition to antiviral and supportive therapies.

In TCM theory, the main principles include opening the inhibited lung energy and relieving cough, resolving dampness and detoxicating, and tonifying qi and strengthening middle warmer, focusing on improving patients' healthy qi and dispelling the evil factors to regulate the internal environment, enhance immunity, improve antiviral activity, inhibit inflammatory response, improve patient symptoms, prevent organ failure, and reduce mortality. The main herbs involved in this study are Mahuang, Kuxingren, Fuling, Baizhu, Huoxiang, Peilan, Huangqi, Dangshen, and so on. Pharmacological studies revealed that Mahuang [20], Kuxingren [21], Peilan [22], and Huangqi [23] can relieve bronchial mucosal edema; relax bronchial smooth muscle and eliminate phlegm; improve cough, dyspnea, and other symptoms; and protect the bronchial mucosa. Huoxiang [24] and Mahuang [25] have certain antiviral and anti-inflammatory effects. Huangqi [26,27], Dangshen [28,29], Baizhun [30], and Fuling [31,32] can enhance immunity and improve failure of organs, such as the heart and the brain, caused by ischemia and hypoxia. We also discovered an effective CHM against COVID-19 by using the TCMATCOV platform in another study [33]. Results showed that the "multi-component and multi-target" characteristics of CHM act on COVID-19 disease-specific factors, including SOCS3, IL7, CXCI10, IL2, TNF, IL10, CCL2, and CCL3 directly or indirectly, and exert anti-inflammatory, antiviral and immune-modulating effects at multiple targets and levels.

Although this study has important clinical and research significance to guide the application of CHM in patients with severe/critical COVID-19, it still have some important limitations that need to be considered. First, this retrospective cohort study failed to include all baseline characteristics and patients' medical records before hospitalization, which possibly affected the authenticity of the study results. The baseline levels of all indicators between the groups were not completely balanced. The two groups showed significant differences in terms of sex, age, disease duration, medical history, antibiotics treatment, application of Chinese patent medicines, and oxygen therapy. PSM was performed in this study to maintain the baseline balance between the two groups. However, only the main variables were matched because of the sample size. Therefore, even after PSM, variables in comorbidities can still affect the study results. In addition, the sample size of the study after PSM decreased from 662 to 312, and the loss of a large amount of patient information may lead to selective bias. Therefore, a larger sample cohort study or a randomized controlled study is necessary in the future to improve the reliability of results.

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Compliance with ethics guidelines

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