How can traditional Chinese medicine contribute to the therapeutic approach in coronavirus disease 2019 (COVID-19)? A review of the registered clinical trials

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Research Article

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Abstract

Background: Since the outbreak of coronavirus disease 2019 (COVID-19) in January 2020, Traditional Chinese Medicine (TCM) has been fully and deeply involved in the treatment of COVID-19 in China. An increasing number of clinical trials has been registered to evaluate the effects of TCM in the prevention and therapeutic management of COVID-19.

Objective: This study aims to review the existing TCM registered trials, identify promising and available TCM therapies, in order to provide reference for the global management of COVID-19.

Methods: All clinical trials on TCM for COVID-19 registered in eight registry platforms worldwide were searched up to May 14, 2020. The data of registration trend, design, objective, interventions, current status, and relevant information were reviewed and summarized. Supportive information on the progress, results and potential value of the included registered trials were searched and reviewed from databases and official websites.

Results: 161 TCM trials registered in three registries from January 26 to May 14 were included. 94 (58.4%) were randomized controlled trials, followed by controlled clinical trials (25, 15.5%), single-arm clinical studies (18, 11.2%) and others (24, 14.9%). 114 trials (70.8%) assessed therapeutic effects; while the remaining were for prevention, rehabilitation, and TCM syndrome epidemiology. The three most evaluated TCM interventions were Chinese herbal medicine (CHM) in the preparation forms of formulae decoction/granule (41.7%), Chinese patent medicine (24.8%) and Chinese herbal-derived injections (8.1%). The common outcomes in therapeutic trials were symptoms and signs (65.8%), time to viral clearance on PCR (50.9%), and improvement in CT images (43.9%). 78 trials (48.4%) had started recruiting and six trials (3.7%) had completed recruiting. Among the TCM interventions identified from the registered trials, the following are worthy of attention and may have the potential feasibility of being evaluated and then used worldwide due to their rigorous design, previous evidence and availability: for prevention in high-risk populations or suspected cases, moxibustion, Huoxiang Zhengqi pill and Jinye Baidu granule could be considered; for treatment, Qingfei Paidu decoction or granules in mild, moderate and severe cases, Huashi Baidu decoction, Lianhua Qingwen caplsule, Toujie Quwen granule and Xiyanping injection in mild and moderate cases, and Xuebijing injection in severe cases could be considered. For rehabilitation of cured patients, the effect of Tai Chi and Liuzijue on the patients' lung function and quality of life deserves attention.

Conclusion: A series of promising potentially effective TCM interventions including CHM formulae, Chinese patent medicines, herbal-derived injections and non-drug therapies have been identified in clinical practice and are being evaluated by registered clinical trials. Available and applicable interventions within relevant trials are worthy of worldwide attention and application, in order to contribute to the global management of COVID-19 epidemic.

Introduction

The coronavirus disease 2019 (COVID–19) pandemic has become a major public health problem facing the world. The World Health Organization (WHO) raised the risk assessment of COVID–19 from “high” to “very high” at the global level on February 28, 2020. As of May 19, 2020, 4,731,458 cases of confirmed infections have been reported from 212 countries, areas or territories around the world [1]. Since the outbreak in Hubei, China in January 2020, the Chinese government established a prevention and control policy involving both traditional Chinese medicine (TCM) and western medicine (WM) [2]. Therefore, TCM has been fully involved in the management of the epidemic in China. Up to now, the National Health Commission of China has issued seven versions of guidelines for COVID–19, and TCM remedies have been included since the third version in January 23, 2020 [3]. For prevention of the epidemic, 23 out of 31 provinces (including autonomous regions, and municipalities) in mainland China had officially issued preventive programs by recommending Chinese herbal formulae [4]. According to official data, among the confirmed COVID–19 cases, 74,187 were given TCM, accounting for 91.5% of the total, and preliminarily clinical observations showed that the total effective rate of TCM in improving symptoms exceeded 90% [5].

At present, China has achieved a staged success in the management of COVID–19. As of May 19, 2020, among the 82,965 confirmed cases in mainland China, 78,244 have been cured and discharged from hospital, accounting for 94.3%, and 4,634 have died, accounting for 5.6% [6]. Since March 12, the number of new indigenous cases in China has been below 13 every day [7]. The under-reporting of cases and deaths of COVID–19 in China is believed almost non-existent due to the strict implementation of non-pharmaceutical interventions (including isolating ill persons, contact tracing, quarantine of exposed persons, travel restrictions, school and workplace closures, cancellation of mass gatherings, and hand washing, among others) [8], and the rapid establishment of large health-care facilities (Fangcang shelter hospitals) to leave no virus patient unattended [9], and the combination of TCM and WM is believed to have played a substantial role in prevention and treatment and has attracted increasing attention worldwide [5]. In order to evaluate the effectiveness and safety of specific TCM therapies such as Chinese patent medicines, formulae and complex treatment, many clinical trials have been registered and carried out in China in the past four months [10]. Therefore, this study was conducted to comprehensively collect and evaluate the characteristics, current status and prospects of existing TCM registered clinical trials for COVID–19, aiming to providing a reference for the global epidemic prevention and control.

Methods

Data source and search strategy

All the TCM clinical trials on COVID–19 registered before May 14 2020 on eight trial registry platforms were retrieved without limitation of study objectives or design. These platforms were as follows: Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org.cn), ClinicalTrials.gov (http://clinicalTrials.gov), Acupuncture-Moxibustion Clinical Trial Registry (AMCTR) (http://www.acmctr.org/index.aspx), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au), Japan Primary Registries Network (https://jrct.niph.go.jp), the United Kingdoms’ ISRCTN registry (http://www.isrctn.com), Clinical Trials

Registry-India (http://ctri.nic.in) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The search terms included COVID–19, coronavirus disease 2019, 2019-nCoV, novel coronavirus, and SARS-CoV–2. The registered TCM trials were identified by screening the title or content of the search results. If a Covid–19 collection is available from their websites (for example ChiCTR and ClinicalTrials.gov), TCM trials would be screened from the collection.

Supportive information related to these registered TCM trials were searched on PubMed, Embase, Google Scholar, China National Knowledge Infrastructure (CNKI), Wanfang Data, and government websites or official media websites in China. The search terms were the same as the search on the trial registry platforms.

Data extraction and analysis

The basic characteristics of registered TCM trials were extracted, including registration identifier, date of registration, title, country and province, design, study objectives, anticipated start date, interventions and control, population, sample size, outcomes and recruiting status. The overall status of registered TCM clinical trials on COVID–19 was reviewed by descriptive statistics. The study progress or results were extracted from supportive information if possible.

Trials with good design and potential global application value of their interventions were screened with data extracted and summarized to provide further recommendations. The criteria for trials worthy of attention were defined as follows: (1) Those with a rigorous design, reasonable sample size, and important outcomes; (2) Those testing a intervention with a good rationale for safety and effectiveness, with existing evidence of human studies on COVID–19, pneumonia, severe acute respiratory syndrome (SARS), influenza, and other viral diseases, or included in China's guideline of COVID–19 [3]; (3) Interventions are easily available and applicable worldwide.

Results

Search for Registered TCM trials

169 registered TCM clinical trials on COVID–19 were initially identified from three registries. The majority (155, 91.7%) were registered in ChiCTR, the representative registry of China in the World Health Organization International Clinical Trial Registration Platform, accounting for 23.7% (155/653) of all trials on COVID–19 up to May 14. 10 trials (5.9%) were registered in ClinicalTrials.gov, and 2 (1.2%) in AMCTR. No records were found from other registries. Eight trials were excluded after screening the full text of protocols, of which Six (ChiCTR2000030118; ChiCTR2000030168; ChiCTR2000030478; ChiCTR2000030483; ChiCTR2000030762; ChiCTR2000030765) were cancelled by the investigator; four (ChiCTR2000030420 & ChiCTR2000030467; ChiCTR2000030382 & AMCTR-OCN–20000332) were duplicate registrations, and the more recently registered one was included. Therefore, 161 registered trials were finally included in this study. The lists of the 161 trials were shown in Supplementary Material.

Characteristics of registered TCM clinical trials

All of the registered TCM clinical trials were planned to be conducted in China, involving a total sample size of 58,501 (range: 20 to 20,000; average: 404; median: 132). The first protocol of a TCM clinical study (NCT04285190) on COVID–19 was registered on January 26, 2020, and the most recent was on May 9. The number of registrations on February 1 was the largest, up to 9. The number of newly confirmed cases has dropped significantly since February 17, with a total of 11,683 cases reported, accounting for 14.1% (11683/82918) of all cases; while during this period, 91 trials were registered, accounting for 56.5% (91/161) of all trials. Six trials (ChiCTR2000029433, ChiCTR2000029434, ChiCTR2000029479, ChiCTR2000030619, ChiCTR2000032717, and ChiCTR2000032767) have completed participant recruitment.

The trends of newly registered TCM trials and confirmed cases of COVID–19 from January 26 to May 14 are presented in Figure 1. The details on the characteristics of registered TCM clinical trials including study design, objectives, participants, and sample size, interventions, outcome measure, and current status are shown in Table 1.

Table 1 The characteristics of the registered trials

Items	Details	Number of trials	Percent (%)
Study type	Randomized controlled trials	94	58.4%
	Controlled clinical trials	25	15.5%
	Single-arm trials	18	11.2%
	Real world clinical studies	10	6.2%
	Retrospective studies	10	6.2%
	Cross-sectional studies	4	2.5%
Objective	Prevention	12	7.5%
	Treatment	114	70.8%
	Rehabilitation	23	14.3%
	TCM syndrome epidemiology	4	2.5%
	Multi-objective	8	5.0%
Sample size	≤100	63	39.1%
	101-300	65	40.4%
	301-500	16	9.9%
	501-1000	11	6.8%
	>1000	6	3.7%
Participants (in 114 treatment trials)	Suspected cases*[1]	10	8.8%
	Mild or moderate patients	55	48.2%
	Severe patients	32	28.1%
	Critical patients	3	2.6%
	Confirmed patients (no details on severity)	39	34.2%
TCM Interventions	Chinese patent medicine	40	24.8%
	Decoction or granule of fixed formulae	50	31.1%
	Decoction or granule based on TCM syndrome differentiation	17	10.6%
	Chinese herbal-derived injections	13	8.1%
	TCM exercises (Qigong/Daoyin/Liuzijue/ Tai Chi/Baduancao)	12	7.5%
	Moxibustion	5	3.1%
	Acupuncture/acupoint stimulation	4	2.5%
	TCM psychological intervention	1	0.6%
	TCM interventions with no details	36	22.4%
Comparisons (in 157 interventional studies)	TCM plus WM vs WM	75	47.8%
	Single arm	28	17.8%
	Multiple comparisons	14	8.9%
	TCM vs WM*[2]	10	6.4%
	TCM vs no intervention (in preventive study)	11	7.0%
	TCM plus WM vs Placebo plus WM	9	5.7%
	TCM vs Placebo (in rehabilitation study)	7	4.5%
	Others	3	1.9%
Recruitment status	Have not started recruiting	75	46.6%
	Have started recruiting	78	48.4%
	Completed	6	3.7%
	Suspended	2	1.2%

Note: 1. Suspected case is defined as a patient with a history of epidemiology and clinical manifestations, yet to be confirmed by etiological or serological tests according to China's guideline of COVID-19.[3]

2. TCM: traditional Chinese medicine; WM: western medicine, defined as conventional treatment according to China's guideline of COVID-19, including symptomatic treatment, antiviral drugs, antibiotics, respiratory and circulatory support, etc.[3]

Registered Clinical trials and interventions worthy of attention

Trials of preventive interventions

12 registered trials are preventive studies, including six randomized controlled trials (RCTs), three controlled clinical trials (CCTs), two single-arm studies, and one retrospective study. Participants included the general population in two trials and high-risk populations in close contact with confirmed cases in ten trials. The sample sizes ranged from 80 to 20,000, with a total of 28766, average of 2398, and median of 550. Preventive interventions included six Chinese patent medicines, moxibustion, and herbal decoction. Among ten controlled studies, nine had no intervention in the control group and one used placebo. 58.3% (7/12) of trials reported the infection rate diagnosed by nucleic acid PCR test as the primary outcome.

Amongst the 12 trials, three therapies in five trials might be worthy of attention due to their previous clinical evidence and inclusion by relevant guidelines or expert consensus:

(1) Moxibustion was recommended by the China Association of Acupuncture-Moxibustion [11] and tested in two registered trials including one RCT (Registration number: AMCTR-IPR–20000326) and one case series study (ChiCTR2000030386). However, both are assessing relief in scores of emotion and symptom scale, rather than infection rate by nucleic acid PCR test as their primary outcome measurement.

(2) Huoxiang Zhengqi pill (□□□□□, HXZQ) was recommended in the guideline for COVID–19 (from the fourth version) issued by the National Health Commission of China for suspected cases under medical observation with fatigue and gastrointestinal discomfort symptoms [3]. Two RCTs (ChiCTR2000029602 and ChiCTR2000029479) tested HXZQ were planned to compare with health education and no intervention in high-risk populations or healthy people in the community. Both used the incidence of COVID–19 based on nucleic acid PCR test as the primary outcome, and the sample sizes were 600 and 20000 respectively. The study of ChiCTR2000029479 has been published in *China Journal of Chinese Materia Medica* on April 30, 2020, showing that the incidence rate of cold in TCM group combined use of HXZQ and another Chinese patent medicine (10627 cases) was significantly lower than that in non-intervention group (10972 cases) (0.02% versus 0.23%, P<0.001), no confirmed COVID–19 case occurred in either group [12].

(3) Jinye Baidu granule (□□□□□□, JYBD) was officially recommended for preventing COVID–19 in some provinces of China [4]. JYBD was developed by Tongji hospital, Huazhong University of Science and Technology, and had been used for preventing SARS in Tongji Hospital in 2003 [13]. Some experimental

and clinical studies found that JYBD had an antiviral effect [14–16]. One retrospective single-arm study (ChiCTR2000029728) evaluated the preventive effect of JYBD for COVID–19.

The details of the above interventions and trials are shown in Table 2.

Table 2 Characteristics of TCM preventive interventions and trials worthy of attention

Intervention	Category	Trials	Rationality	Ingredients
Moxibustion	TCM external treatment	AMCTR-IPR-20000326	Included in guideline	*Artemisiae Argyi Folium* (Aiye)
Huoxiang zhengqi pill	Chinese patent medicine	ChiCTR2000029602 ChiCTR2000029479	Included in guideline	*Pericarpium Arecae* (Dafupi), *Radix Angelicae Dahuricae* (Baizhi), *Caulis Perillae* (Zisu), *Poria* (Fuling), *Rhizoma Pinelliae Preparata* (Banxiaqu), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Pericarpium Citri Reticulatae* (Chenpi), *Cortex Magnoliae Officinalis* (Houpo), *Radix Platycodi* (Jiegeng), *Pogostemonis Herba* (Huoxiang), *Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle* (Zhigancao), *Rhizoma Zingiberis Recens* (Shengjiang), *Fructus Jujubae* (Dazao)
Jinye baidu granule	Chinese patent medicine	ChiCTR2000029728	Used for preventing SARS	*Lonicerae Japonicae Flos* (Jinyinhua), *Isatidis Folium* (Daqingye), *Taraxaci Herba* (Pugongying), *Houttuyniae Herba* (Yuxingcao)

Table 3 Characteristics of TCM treatment interventions and trials worthy of attention

Intervention	Category	Trials	Rationality	Ingredients
Qingfei Paidu Decoction	New formula for COVID-19	ChiCTR2000030810, ChiCTR2000029778; ChiCTR2000030864; ChiCTR2000030883; ChiCTR2000030806; ChiCTR2000032767	Included in guideline	*Ephedrae Herba* (Mahuang) *Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle* (Zhigancao), *Armeniacae Semen* (Xingren), *Gypsum Fibrosum* (Shengshigao), *Cinnamomi Ramulus* (Guizhi), *Alismatis Rhizoma* (Zexie), *Polyporus* (Zhuling), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Poria* (FulLing), *Bupleuri Radix* (Chaihu), *Scutellariae Radix* (Huangqin), *Pinellinae Rhizoma Praeparatum* (Jiangbanxia), *Zingiberis Rhizoma recens* (Shengjiang), *Asteris Radix* (Ziwan), Farfarae *Flos* (Kuandonghua), *Belamcandae Rhizoma* (Shegan), *Asari Radix et Rhizoma* (Xixin), *Dioscoreae Rhizoma* (Shanyao), *Aurantii Fructus immaturus* (Zhishi), *Citri reticulatae Pericarpium* (Chenpi), *Pogostemonis Herba* (Huoxiang).
Huashi Baidu decoction	New formula for COVID-19	ChiCTR2000030988	Included in guideline	*Ephedrae Herba* (Shengmahuang), *Armeniacae Semen* (Xingren), *Gypsum fibrosum* (Shengshigao), *Glycyrrhizae Radix Et Rhizoma* (Gancao), *Pogostemonis Herba* (Huoxiang), *Magnoliae officinalis Cortex* (Houpo), *Atractylodis Rhizoma* (Cangzhu), *Tsaoko Fructus* (Caoguo), *Pinellinae Rhizoma Praeparatum* (Fabanxia), *Poria* (Fuling), *RheiRadix et Rhizoma* (Shengdahuang), *Astragali Radix* (Shenghuangqi), *Lepidii/Descurainiae Semen* (Tinglizi), *Paeoniae Radix rubra* (Chishao).
Lianhua Qingwen Capsule	Chinese patent medicine	ChiCTR2000029433; ChiCTR2000029434	Included in guideline; used for treating H1N1 influenza	*Forsythiae Fructus* (Lianqiao), *Lonicerae Japonicae Flos* (Jinyinhua), *Ephedrae Herba* (Mahuang), *Armeniacae Semen Amarum* (Kuxingren), *Gypsum Fibrosum* (Shigao), *Isatidis Radix* (Banlangen), *Dryopteridis Crassirhizomatis*

				Rhizome (Mianmaguanzhong), *Houttuyniae Herba* (Yuxingcao), *Pogostemonis Herba* (Guanghuoxiang), *Rhei Radix Et Rhizome* (Dahuang), *Rhodiolae Crenulatae Radix Et Rhizome* (Hongjingtian), *L-Menthol* (Bohenao), *Glycyrrhizae Radix Et Rhizoma* (Gancao)
Xuebijing	Chinese herbal-derived injection	ChiCTR2000029381; ChiCTR2000030388	Included in guideline; used for treating severe community-acquired pneumonia	*Radix Paeoniae Rubra* (Chishao), *Radix Angelica Sinensis* (Danggui), *Chuanxiong Rhizoma* (Chuanxiong), *Carthami Flos* (Honghua), *Radix Salviae Miltiorrhizae* (Danshen)
Xiyanping	Chinese herbal-derived injection	ChiCTR2000029756, ChiCTR2000030117, ChiCTR2000030218/NCT04275388	Included in guideline	*Sulfonate Andrographolide* (Chuanxinlian)
Toujie Quwen granule	New formula for COVID-19	ChiCTR2000031089; ChiCTR2000031888	Evidence from case series study for treating COVID-19	*Forsythiae Fructus* (Lianqiao), *Cremastrae Pseudobulbus* (Shancigu), *Lonicerae Japonicae Flos* (Jinyinhua), *Scutellariae Radix* (Huangqin), *Bupleuri Radix* (Chaihu), *Artemisiae Annuae Herba* (Qinghao), Cicad*ae Periostracum* (Chantui), *Peucedani Radix* (Qianhu), *Fritillariae Cirrhosae Bulbus* (Chuanbeimu), *Mume Fructus* (Wumei), *Scrophulariae Radix* (Xuanshen), *Eupolyphaga Steleophaga* (Tubiechong), *Atractylodis Rhizoma* (Cangzhu) *Astragali Radix* (Huangqi), *Pseudostellariae Radix* (Taizishen), *Poria* (Fuling)

Trials of treatment interventions

114 registered trials are treatment trials, including 67 RCTs, 18 CCTs, 12 single-arm studies, 10 real world clinical studies, and 7 retrospective studies. Participants in the majority of trials (91.2%, 104/114) were

confirmed COVID–19 cases, while 5.3% (6/114) recruited both confirmed and suspected cases, and 3.5% (4/114) recruited only suspected cases. Suspected cases were defined as patients with a history epidemiology and clinical manifestations of COVID–19, yet to be confirmed by etiological or serological tests according to China's guideline of COVID–19.[3] The sample sizes ranged from 20 to 3,000, with the total of 28,109, average of 247 and median of 120, and the majority (94/114, 82.5%) of trials had a sample size below 300. Therapeutic interventions included herbal decoction/granules (in 52 trials), Chinese patent medicines (22), herbal-derived injections (12), acupuncture/ acupoint stimulation (4), TCM exercise (Daoyin, Qigong, Liuzijue, Baduanjin) (5), and TCM psychological intervention (1). The remaining trials did not report details of the interventions. Eight trials used TCM interventions alone in the treatment group, while the remaining used a combination of TCM and WM, and the same WM interventions were used in the control group. Outcome measures used the treatment trials are shown in Figure 2.

Amongst the 114 trials, six Chinese patent medicines, formulae and injections in 20 trials might be worthy of attention due to the comprehensive consideration of their availability, previous evidence, current clinical application and study progress, and inclusion by the national guidelines. The background and protocol information are as follows:

(1) Qingfei Paidu decoction (□□□□□, QFPD): It was recommended by China's guideline for treating COVID–19 at mild, moderate, severe, and critical stages since February 7, 2020 [17]. Six registered trials evaluated the effect of QFPD: One (ChiCTR2000030810) was a registered RCT comparing QFPD versus WM with sample size of 100; one (ChiCTR2000029778) was a controlled clinical trial comparing QFPD plus WM versus WM with sample size of 600; Three (ChiCTR2000030864,ChiCTR2000030883, and ChiCTR2000032767) were single-arm studies; one (ChiCTR2000030806) was a retrospective study evaluating the effectiveness of QFPD plus ulinastatin, a human urinary trypsin inhibitor. According to preliminary statistics on national data [18], 1265 confirmed cases in 10 provinces were treated with QFPD decoction up to March 23, 2020, none of mild or moderate patients converted to severe or critical stage, 98% of cases had been cured and discharged.

(2) Huashi Baidu decoction/granule (□□□□□, HSBD): It was formulated by the national medical team of TCM in Hubei and recommended by the national guideline (7th version) for treating severe COVID–19 [3]. One RCT (ChiCTR2000030988) with sample size of 204 evaluated the effectiveness of HSBD granule comparing with WM. Besides, three clinical studies on HSBD had been carried out in Jinyintan Hospital (75 severe cases), Dongxihu Fangcang Hospital (124 moderate cases), and Jiangjunlu Street Health Center (894 mild and moderate cases), respectively. The results showed significant improvement in CT images of lungs and symptoms, reduction in the time of hospitalization and rate of viral clearance on PCR, and no adverse events or liver and kidney damage were found [19]. The clinical registration information on the three trials has not been found on the trial registry platforms, a RCT (ChiCTR2000030288) undertaken by Huang Luqi to evaluate the effect of a TCM formula (without name and details) for treating severe COVID–19 in Jinyintan Hospital might related to the above three trials, so it is also worthy of attention.

(3) Lianhua Qingwen Capsule (□□□□□□, LHQW) is a Chinese patent medicine developed in 2003 for treating SARS, and also showed a similar therapeutic effectiveness reduction of the duration of illness and duration of viral shedding compared with Oseltamivir in the treatment of influenza A (H1N1) virus infection [20], and was safer and cheaper than Oseltamivir [21]. A newly study showed that it exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV–2) [22]. LHQW was recommended by the national guideline (from the 4th version) for treating COVID–19 [3]. Two multicenter RCTs (ChiCTR2000029433 and ChiCTR2000029434) evaluated the effectiveness of LHQW plus WM versus exclusive WM on 240 suspected cases and 240 confirmed cases, respectively. The results of one study (ChiCTR2000029434) were firstly revealed by Zhong Nanshan, leader of the study, China's top respiratory expert when he shared COVID–19 experience with medics overseas on a live program held by China Global Television Network in April 16, 2020. Comparing with control group, LHQW group showed higher overall recovery rate (91.5% vs. 82.4, P = 0.022), faster symptom recovery (median: 7 vs. 10d, P<0.001), and higher rate of improvement in chest CT manifestations (83.8% vs. 64.1%, P = 0.017) in mild and moderate COVID–19 patients [23]. Recruitments to the two trials has been completed.

(4) Xuebijing injection (□□□□□□): Its efficacy in treating patients with severe community-acquired pneumonia was demonstrated by a multicenter randomized placebo control trial published in *Critical Care Medicine* in 2019 [24]. It was recommended by the national guideline (from the 4th version) for treating severe COVID–19 [3]. Two trials evaluated the effectiveness of Xuebijing in the treatment of severe patients with COVID–19. A multicenter controlled clinical trial (ChiCTR2000029381) compared Xuebijing with WM in 400 patients; the RCT (ChiCTR2000030388) compared Xuebijing plus WM with WM in 60 patients. In the first study (ChiCTR2000029381), Xuebijing inhibited the cytokine storm and controlled the progress of severe or critical COVID–19 during the ongoing clinical trial [19].

(5) Xiyanping injection (□□□□□□) was recommended by the national guideline (from the 5th version) for treating COVID–19 [3]. Four RCTs (ChiCTR2000029756, ChiCTR2000030117, ChiCTR2000030218/NCT04275388, and ChiCTR2000032412) evaluated the effectiveness of xiyanping plus WM (Lopinavir / ritonavir, alpha-interferon) versus WM on mild or moderate cases, and their sample sizes were 238, 80, 348, and 426 respectively. It should be noted that ChiCTR2000030218 and NCT04275388 are probably the same study due to the same applicant, study period, design, sample size, and interventions.

(6) Toujie Quwen granule (□□□□□□, TJQW), formulated by Guangzhou Eight People's Hospital, has been used for treating COVID–19 in several hospitals of Guangdong province [25]. Two multicenter controlled studies (CCT: ChiCTR2000031089; RCT: ChiCTR2000031888) evaluated the effectiveness of Toujie Quwen granule plus basic treatment versus basic treatment with or without antiviral therapy for moderate or mild patients. A previous case series study involving 121 non-severe patients found that the proportion of patients with improved symptoms and/or chest CT manifestations improvements ranged from 71%~84% after taking TJQW for six days [25].

(7) TCM individualized treatment in the real world A RCT (ChiCTR2000029763) evaluated TCM treatment on moderate patients with COVID–19 in a mobile cabin hospital (known as Fangcang shelter hospital [9]). Another RCT (ChiCTR2000029601) evaluated TCM treatment based on individual syndrome differentiation on 400 cases of suspected patients. According to a recent report, intervention of CHM decoctions on suspected patients in community promoted by Prof. Tong Xiaolin, the chief investigator of study ChiCTR2000029601, significantly reduced the infection rate of suspected patients and prevented the mild/moderate patients from progression; none of the 564 mild/moderate patients in Jiangxia TCM Fangcang Hospital converted to severe [26]. Therefore, these two trials could represent the effect of individualized CHM in the real world treatment of suspected, mild and moderate patients to a certain degree, and worthy of attention.

The details of the above interventions and trials are shown in Table 3.

Trials of rehabilitation inventions

23 registered trials are rehabilitation trials, including 18 RCTs, two CCTs, and three single-arm studies. Participants were cured and discharged patients with negative results of nucleic acid PCR tests. The total sample size is 5080, with ranging from 28 to 1500, average of 221, and median of 120. TCM rehabilitation interventions included Chinese patent medicines, herbal decoction, moxibustion, and TCM exercise (Tai Chi, Liuzijue, Qigong, Baduancao). Outcome indexes included aerobic exercise capacity measured by the six-minute walk test, quality of life, positive conversion rate tested by PCR, and chest CT manifestations. Amongst the interventions evaluated in the 23 trials, moxibustion, Tai Chi, and Liuzijue were recommended by China's rehabilitation guideline for cured COVID–19 patients [27]. Two TCM interventions were worthy of attention due to their availability and study design.

(1) Tai Chi (□□□): it is a kind of traditional Chinese shadow boxing. Patients with moderate COVID–19 were trained in Tai Chi by TCM doctors in some mobile cabin hospitals in Wuhan, Hubei province of China. A RCT (ChiCTR2000029460) involving 100 cured cases with viral clearance on PCR after treatment evaluated the effect of Tai Chi plus conventional rehabilitation therapy versus conventional rehabilitation therapy on the lung function and quality of life.

(2) Liuzijue (□□□) is a traditional breathing training exercise of Qigong in TCM. A previous study found that Liuzijue promoted functional capacity of lung and quality of life in older adults with chronic obstructive pulmonary disease (COPD) at 6 months and was a good alternative home exercise program for older adults in the rehabilitation of COPD [28]. A RCT (ChiCTR2000030933) evaluated the effectiveness of Liuzijue compared with respiratory muscle training for respiratory function in 108 COVID–19 patients who had been cured and discharged. Maximal inspiratory pressure, 6-minute walking test, activities of daily living and scale of lung function were measured.

Discussion

China was the first country in the world to encounter the SARS-CoV–2, a hitherto unknown human virus. From the outbreak in January to basic control in March, China accumulated rich experience in coping with COVID–19, and TCM constituted an important part of this. The application of TCM in the prevention and control of epidemics is a conventional practice in China, both in historical and contemporary management of SARS and H1N1 influenza [4, 29, 30]. In response to the new communicable disease COVID–19, TCM practitioners used the existing Chinese patent medicines or Chinese herbal-derived injections previously designed for other virus infections and pathologies like SARS and H1N1 influenza, which have been tested for effectiveness and safety [31], and also developed and applied new herbal formulae in clinical practice (Table 3). Therefore, a series of clinical studies were registered and conducted to evaluate the efficacy and safety of these interventions [10, 32].

This study systematically reviewed all of the available TCM registered trials on COVID–19. 161 TCM clinical trials were registered from the outbreak to May 14, which were all conducted in China. The majority of trials were RCTs and CCTs evaluating the effect of TCM interventions in the treatment of COVID–19. The number of TCM trials registered in ChiCTR accounted for 23.8% of all trials, and the research scope covered prevention, treatment, rehabilitation, and TCM syndrome epidemiology, indicating that TCM has been fully involved in the management of COVID–19 in China. Through the whole process of clinical practice and plenty of clinical trials, the combination of TCM and WM showed significant effectiveness in fighting the epidemic, and were known as a major feature and highlight of China's management of COVID–19 [33]. After the screening through clinical practice and research, several effective CHM formulae, Chinese patent drugs and injections were included in the various versions of the national guidelines and were subsequently recommended for nationwide use [3].

Based on the analysis of the contents of the existing registered trials and the current epidemic situation in China, we suggest that several TCM interventions within some trials are promising and have the potential to be applied abroad. However, most of them might not be able to continue, or may have little significance to the application of TCM in the global management of COVID–19, which might be explained by the following three aspects: firstly, due to the rapid control of the epidemic, the number of new cases in China reduced greatly and a large number of existing patients had been cured, making it difficult for clinical trials to recruit a sufficient sample size. The increase of registered trials lagged behind the growth of new confirmed cases. In fact, both RCTs of Remdesivir in China, one (NCT04257656) [34] in severe patients and the other (NCT04252664) in mild and moderate patients were terminated or suspended because no eligible patients could be enrolled (available at: https://clinicaltrials.gov). Secondly, the generally low methodological quality and planned small sample size made many trials unlikely to generate strong evidence about the effectiveness of both TCM and WM in China [10, 32, 35, 36]. Lastly, the generalizability of interventions was an issue in trials that evaluated the effectiveness of TCM complex interventions or individual treatment based on syndrome differentiation. Even if they were rigorously designed and successfully completed, these interventions are difficult to replicate without the guidance of TCM doctors, but can provide readers with knowledge of the effectiveness and safety of TCM for COVID–19 in the real-world practice.

For the application of TCM experience in the management of the COVID–19 pandemic worldwide, there are some suggestions. Firstly, collaboration between TCM and WM in China's epidemic prevention and control, as well as the effect of TCM in treating COVID–19: the majority (91.5%) of patients received integrated Chinese and western medicine treatment in China. At present, a series of clinical observations, studies and systematic reviews have initially found that the combination of TCM and WM was superior to WM alone in improving symptoms, shortening the course of disease and length of hospital stay, and reducing moderate-severe conversion rate [5, 18, 23, 37–42]. Secondly, based on the principle of compassionate use of a drug, as well as the national conditions of and relevant medical and pharmacy laws and regulations, countries with severe epidemics could consider the feasibility of introducing potential promising TCM therapies including herbal formulae, patent medicines, injections, or non-drug therapies for prevention, treatment and rehabilitation. Thirdly, it is worth paying attention to the study progress of the promising TCM therapies in relevant registered trials and applying the available TCM interventions that have widely used evidence in China.

Regarding the specific TCM interventions for the global prevention, treatment and rehabilitation of COVID–19, the following therapies could be recommended. For prevention on high-risk population or suspected cases, moxibustion, Huoxiang Zhengqi oral liquid, and Jinye Baidu granule could be considered (Table 2). For treatment, Qingfei Paidu decoction or granules in mild, moderate and severe cases, Huashi Baidu decoction, Lianhua Qingwen Capsule, Toujie Quwen Granule and Xiyanping injection in mild and moderate cases, and Xuebijing injection in severe cases could be considered (Table 3). For rehabilitation of cured patients, two TCM exercises including Tai Chi and Liuzijue might be beneficial to the patients' lung function and quality of life. We suggested that interim analyses be conducted if no eligible patients could be enrolled in these on-going trials in China. If the trials have some preliminary promising evidence suggesting safety and effectiveness on COVID–19, their interventions can continue to be recruit participants for clinical study and be used in clinical practice outside China, in compliance with local laws.

This study has two main limitations. Firstly, due to the inadequate reporting of key details in some registered trials and lack of timely updates on research status in the registries, there may be some bias in the judgment of research methodological quality and potential value. Secondly, for some prescriptions or drugs (for example, Jinhua Qinggan granule [38], Xuanfei Baidu decoction, Shufeng Jiedu capsule [41]) recommended by China's guideline for COVID–19, we failed to find their clinical registration information, but the researchers introduced the research progress of these drugs at a press conference on Mar 23 2020 [19]. The reasons might be that trials on these interventions were not registered, or the protocol of registration did not describe the name and details of the intervention, so that we could not judge. Therefore, the review on the registered TCM clinical trials dose not fully represent the overall situation of the management of COVID–19 by TCM.

Conclusion

The application of TCM is a unique experience in the prevention, treatment, and rehabilitation of COVID–19 in China. A series of promising TCM interventions including herbal formulae, patent medicines, injections and non-drug therapies have been identified in clinical practice, and are being evaluated by registered clinical trials. Amongst these, several available and applicable interventions and relevant trials are worthy of worldwide attention and application, in order to contribute to the global prevention and therapeutic management of the COVID–19 pandemic.

Abbreviations

CCT: Clinical controlled trial; ChiCTR: Chinese Clinical Trial Registry; COVID–19: Coronavirus disease 2019; CHM: Chinese herbal medicine; RCT: Randomized controlled trial; TCM: Traditional Chinese medicine; WHO: World Health Organization; WM: Western medicine;

Declarations

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Authors' contributions

Hui Luo, Ming Yang, and Jianping Liu conceived of the design and carried out the study. Hui Luo drafted the manuscript. Qiaoling Tang participated in literature search, data extraction and analysis. Xiaoyang Hu and Merlin L. Willcox revised the manuscript and provided important perspectives. Jianping Liu supervised the study and revised the manuscript. All authors read and approved the manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

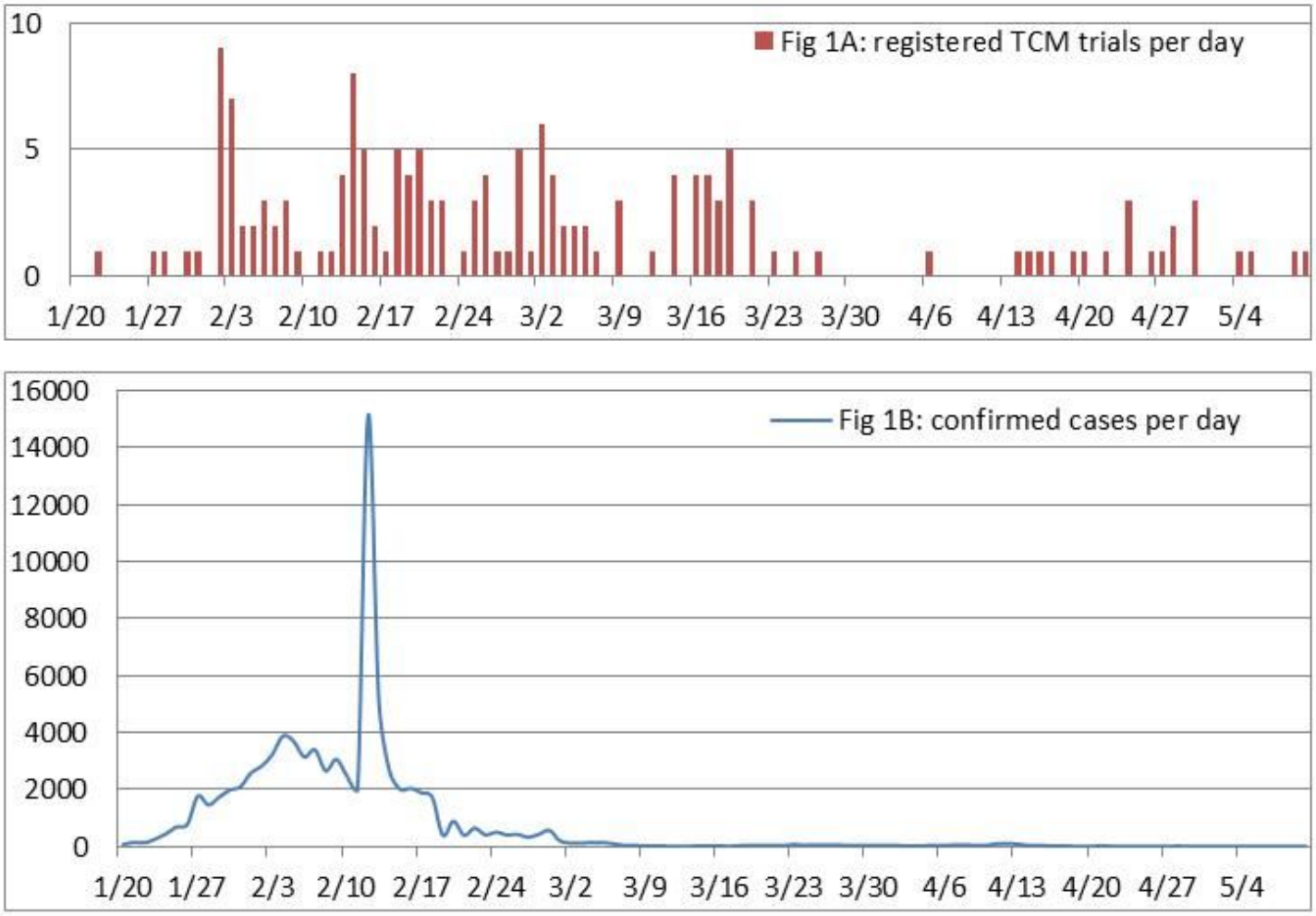

Figure 1 Trends of newly registered TCM trials and confirmed cases in China

Figure 1

Trends of newly registried TCM trials and confirmed cases in China

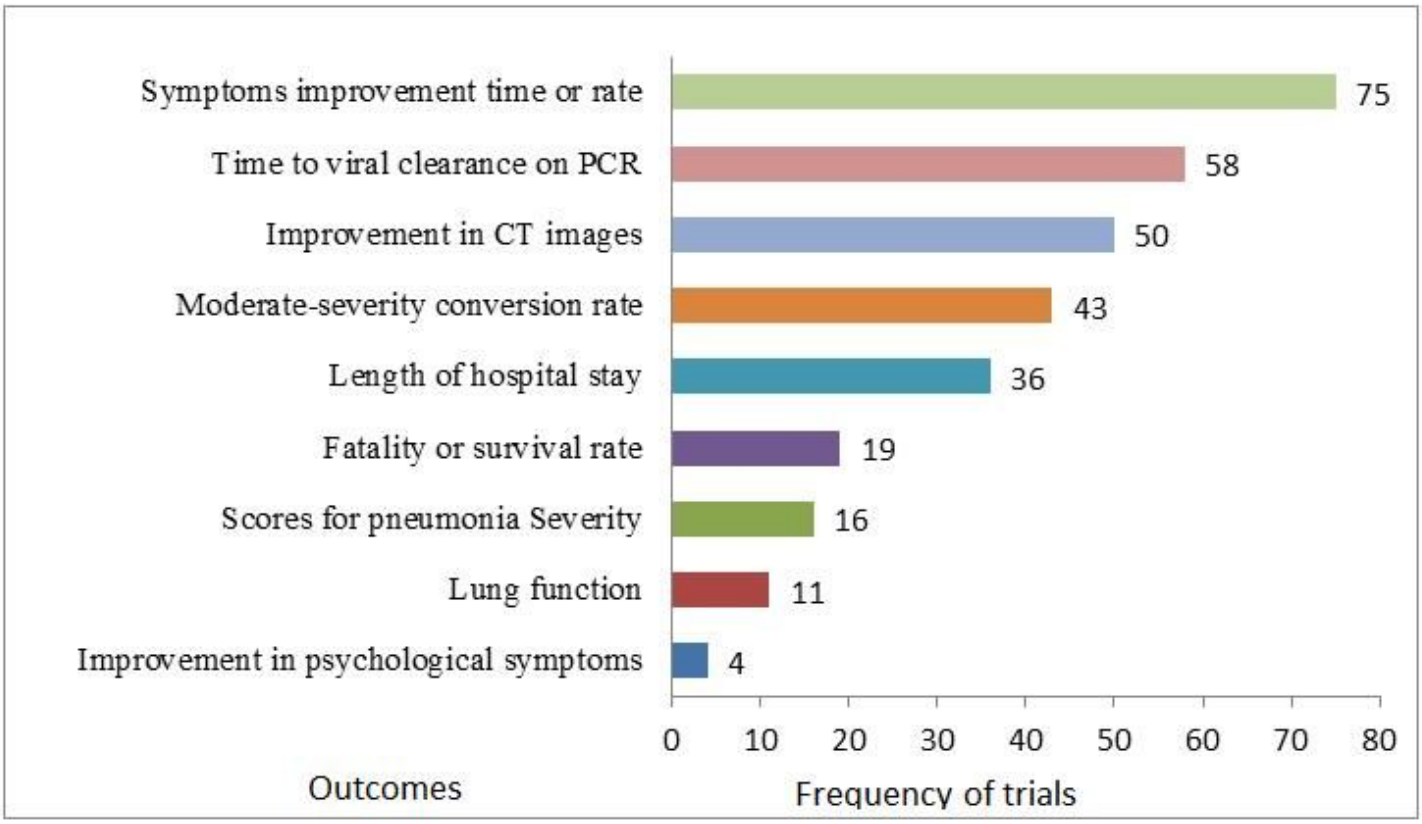

Figure 2 Outcomes used in the TCM treatment trials on COVID-19

Figure 2

Outcomes used in the TCM treatment trials on COVID-19

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