Evaluation of the Real-World Effectiveness of Traditional Chinese Medicine in Treating Coronavirus Disease-2019

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Liu *et al.*: To Evaluate the Effectiveness and Economy of Traditional Chinese Medicine

Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, has become a major public health event. In China, traditional Chinese medicine has played a crucial role in controlling epidemics. However, there is limited real-world evidence regarding the use of traditional Chinese medicine in routine clinical practice. The aim of this study is to analyze multi-center clinical record data during the epidemic; provide an in-depth description of traditional Chinese medicine application in coronavirus disease-2019 patients; and evaluate the effectiveness and economy of traditional Chinese medicine. This is a multicenter retrospective cohort study. Adult patients infected with severe acute respiratory syndrome coronavirus 2 will be included. We will use the observational medical outcomes partnership common data model to extract patient data from each hospital's electronic medical record and convert the data contained in different observational databases into a common structured format with a common representation (terminology, vocabulary, and coding scheme) that can be directly imported into common statistical software such as Statistical Analysis Systems, R and others. The outcomes of treatment regimens (traditional Chinese medicine under the national protocols *vs.* without traditional Chinese medicine under the national protocols) in the two groups will be compared, including clinical efficacy, public health impact and other exploratory indicators. Statistical analysis included propensity score matching, meta-analysis and sensitivity analysis. In the face of coronavirus disease-2019, the national diagnosis and treatment protocol for patients provides differential traditional Chinese medicine treatment for different types of syndromes. Randomized controlled trials or retrospective studies of a single drug or formulation cannot fully reflect the efficacy and therapeutic advantages of traditional Chinese medicine in the real world. This study can evaluate the effectiveness and economy of traditional Chinese medicine treatment under the application scenario of national diagnosis and treatment protocols, fill the gap of real-world evidence on traditional Chinese medicine treatment of coronavirus disease-2019, and inspire the application of traditional Chinese medicine in the prevention and treatment of infectious diseases in the future.

Key words: Traditional Chinese medicine, study design, coronavirus disease-2019, neurological diseases, thrombosis

Coronavirus Disease 2019 (COVID-19) is a global infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that emerged in 2019. To date, it has infected hundreds of millions of people and caused the death of millions of people worldwide, posing a series of challenges to the existing methods of diagnosis and treatment[1]. Coronaviruses are large, enveloped, single-stranded Ribonucleic Acid (RNA) viruses found in humans and other mammals, such as dogs, cats, chickens, cattle, pigs, and birds. These viruses cause respiratory, gastrointestinal, and neurological diseases. SARS-CoV-2 most commonly spreads *via* respiratory droplets during face-to-face exposure or surface contamination. It often causes respiratory symptoms, such as cough, fever, and shortness of breath, and may also lead to other symptoms, such as weakness, fatigue, nausea, vomiting, diarrhea, and loss of taste

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or smell[2]. In addition to the pathological changes of the respiratory system, it may also lead to thrombosis complications, myocardial dysfunction and arrhythmia, acute coronary syndrome, acute kidney injury, gastrointestinal symptoms, liver cell injury, hyperglycemia and ketosis, nervous system diseases, eye symptoms, and skin disease complications[3]. Even if the virus can no longer be detected in the body, patients may still have long-term sequelae, including fatigue, discomfort, dyspnea, and memory and attention problems[4]. Amidst the ongoing epidemic, experts from different countries have been actively developing vaccines and antiviral drugs. However, the speed of response and the economics of vaccines and drugs need to be improved. At the start of the epidemic, there were no targeted antiviral drugs or vaccines. During that time, supportive care, including supplemental oxygen, was the main treatment for most patients. The case fatality rate was high among patients hospitalized in the Intensive Care Unit (ICU)[1]. It was not until September 2020 that the World Health Organization (WHO) recommended the use of corticosteroids for the treatment of patients with severe and critical infections[5]. According to WHO guidelines, vaccination has played a large role in reducing hospitalization and mortality; however, many populations still do not have access to vaccines owing to financial barriers. In addition, because of the constant mutation of SARS-CoV-2, there is still uncertainty about the efficacy of the current vaccines and treatments available[6]. Thus, more treatment options are necessary to meet the needs of different groups of people. Traditional Chinese Medicine (TCM), as a kind of complementary and alternative medicine, is widely used in China's anti-epidemic process. Chinese government has issued a series of diagnosis and treatment protocols to guide TCM treatment. In China, at the early stage of the outbreak, doctors of traditional Chinese and Western medicine had given appropriate symptomatic treatment based on the clinical characteristics of the disease. The Chinese government has issued a series of special diagnosis and treatment plans to guide the treatment of traditional Chinese and Western medicine[7-14]. TCM has been widely used in China's fight against the epidemic. However, more evidence is required on the real-world role of TCM in treating COVID-19. The purpose of this study is to evaluate the efficacy, safety, and economy of TCM in real-world practice. This is a multicenter retrospective study on the diagnosis and treatment data of patients diagnosed with COVID-19 in China. Currently, we have completed the registration (ChiCTR2200062079) at the China Clinical Trial Center and aim to compare the prevention and treatment of two cohorts; patients given TCM treatment according to the national diagnosis and treatment protocol and patients not given TCM treatment according to the national diagnosis and treatment protocol. Real-world clinical data of patients with COVID-19 shall be collected from hospitals in China. These will then be integrated, cleaned and scientifically transformed to form a structured database and knowledge base for the treatment of COVID-19 using TCM. Modern econometric statistics and big data mining methods, such as causal inference, decision analysis, and ecological research, will be used to produce real-world evidence that includes clinical and public health effects of TCM in emergencies. Simultaneously, a standardized operation process should be formed according to the above steps. The study shall include the diagnostic and treatment data of adult patients with confirmed COVID-19, with complete documentation of the primary treatment plan and at least one outcome measure. Data deemed by the researchers to be of low quality or with safety concerns shall be excluded from the study. Considering the bias caused by the shortage of medical resources after the sudden relaxation of epidemic control, the data before the epidemic prevention and control lifted in November 2022 were mainly included. General hospitalized patients including the diagnosis and treatment data from hospitals in areas where the COVID-19 outbreak occurred, which have recorded data for no less than three consecutive months from the month of the outbreak; Fangcang shelter hospitalized patients including the diagnosis and treatment data of COVID-19 patients with mild symptoms registered in the outbreak area and asymptomatic infected patients including the diagnosis and treatment data of confirmed asymptomatic infected patients under the supervision of a COVID-19 outbreak specialist. Based on the International Classification of Diseases (ICD-11), the novel coronavirus pneumonia diagnosis and treatment program and the National Standards for Clinical Terminology in Chinese Medicine, a standardized structured database will be created by means of expert opinion and literature review. The process will follow the following steps; first, the raw data will be converted into the Observational Medical

Outcomes Partnership Common Data Model (OMOP-CDM). This process includes source data analysis, data table and field mapping, standard vocabulary mapping, and extract-transform-load implementation. Next, dual data entry and quality control will be performed. Two data entry personnel will perform independent entry on the same dataset. After completing the entry, the data will be compared and validated on the platform. Based on the validation results and the original data, necessary modifications will be made. In the third step, the data will be exported. Standard structured data will be exported directly from the platform to Statistical Analysis System (SAS) software for data cleaning and analysis. Text data that are difficult to standardize (unstructured data such as medical records) are also processed with natural language recognition and then incorporated into the database. The evaluated outcomes will include clinical efficacy, public health effects, safety and other exploratory measures. As shown in Table 1, important clinical efficacy outcomes of Guideline Development Group (GDP) consensus on WHO will be included in our analysis[6]. Considering that TCM may reduce symptoms and prevent the progression from mild to moderate disease, we will also evaluate the following outcomes; the proportion of asymptomatic or mild patients progressing to severe disease; time to progression from asymptomatic or mild disease to severe disease; the prevalence of common and important clinical symptoms, such as fever, cough, fatigue, shortness of breath, diarrhea, and generalized pain, or the prevalence of a cluster of symptoms and the total number of patients who progressed to severe, critical and all-cause death. The analysis of public health outcomes shall include the total medical expenses of the patient during the treatment of COVID-19. Other exploratory indicators may include markers that show significant changes during the study, such as symptom clusters, lung imaging indicators, or laboratory indicators that reflect the blood system, immune system, heart function, liver function, kidney function, etc. We shall use the mean (Standard Deviation (SD)) or median (range) for continuous variables and frequency (%) for categorical variables to describe the variables. Differences will be analyzed using the two-sample independent t-test, two-sample Wilcoxon test, Chi-square (χ^2) test, and Fisher's exact test, as appropriate. To assess the efficacy and safety of groups in the treatment of COVID-19, we shall use methods such as Propensity Score Matching (PSM), Cox regression, generalized Linear Mixed Effects Model (LCMM), and random effects Cox combined model. We will perform PSM by comprehensively calculating factors related to the treatment decisions of patients in different treatment groups to successfully control confounding factors and provide hazard ratio estimates and Kaplan-Meier survival plots for the outcomes of interest. Methods such as meta-analysis, decision tree, and sensitivity analysis will be used to explore the cost-effectiveness of different treatment strategies. All p-values are two-tailed, and statistical significance shall be set at a conventional cut-off of p<0.05. All data analysis will be performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina, United States of America) and the R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). Treatment regimen (TCM treatment according to the national protocol *vs.* no TCM treatment according to the national protocol) will be used as the variable, with time to nucleic acid conversion as the final outcome. The parameters were calculated as follows; two-sided significance level Alpha (α)=0.05 and certainty power=0.80. The ratio of patients who were treated with TCM according to the national protocol *vs.* patients who were not treated with TCM according to the national protocol was about 1:3. According to previous literature[15,16], the median nucleic acid conversion time for patients who were not treated with TCM according to the national protocol was 27.6 d, and the true median nucleic acid conversion time was 27.6 d in the control group and 27.6 d in the experimental group, if the control group and the experimental group were treated with the national protocol. If the median nucleic acid conversion time for the control group and the experimental group were 27.6 d and 23.4 d, respectively, and the time for inclusion of patients was 200 d, and the length of patient follow-up was 50 d, and the log-rank test was used, the number of patients needed to reject the hypothesis that there is no difference between the two treatments was 403:1209, and a total of 1612 valid cases were needed. All data obtained during clinical research will be handled properly to ensure the rights and privacy of the patients participating in the study. A dedicated data platform will be established and the data will be stored in the firewall of the Academy of Chinese Medical Sciences, which is physically isolated from the internet. The participating data staff will be managed in a

decentralized and domain-based manner. Data transmission shall be performed by special personnel using encrypted hard drives. Data analysis and reporting will be performed on data workstations that are not connected to the internet. Data analysts will be blinded to the patient's personal information. After the patient data are entered into the platform and cleaned, comprehensive checks will be conducted, including data integrity, outliers, and accuracy, which will be repeated every time new data are entered. Research quality and progress will be reviewed every 6 mo by third-party clinical experts and data management professionals. The research team will hire both domestic and foreign experts in disease control, symptom research, data management, machine learning, and statistical analysis to establish a technical advisory committee, hold regular project technical consultation meetings, and provide professional guidance from design to reporting. Through this, the design and methods can be continuously improved in response to the problems encountered. Patients and/or the public were not involved in the design, conduct, reporting or dissemination of this research. TCM has historically been effective and economical for treating infectious diseases. TCM has played an important role in China's fight against COVID-19 and has had an international impact as well. It is well documented that TCM has controlled and treated infectious diseases effectively in about 500 epidemics that have occurred in China over >3000 y[17]. The Chinese government has made a diagnosis and treatment protocol including TCM treatment using COVID-19, and the protocol has been continuously updated, especially at the beginning of the epidemic[7-14].

Several Randomized Controlled Trials (RCTs) and retrospective studies of Chinese patent medicines have confirmed their efficacy[18-23]. For instance, using the Qingfei Paidu decoction halved the risk of death without increasing the risk of acute liver injury or acute kidney injury[20]. The Lianhua Qingwen capsule has a therapeutic effect on COVID-19 by increasing the recovery rate, shortening the recovery time, and improving the recovery of abnormal chest radiation[19]. The results of meta-analysis also show that TCM is effective for both non-severe and severe patients[24,25]. A WHO Expert Meeting has also acknowledged that besides routine treatment, the studied TCMs are beneficial in COVID-19 treatment, particularly in mild-to-moderate cases, on the basis of clinically relevant outcome measures[15]. Furthermore, many countries have introduced proprietary Chinese medicines, and many people seek medical treatment in local TCM clinics[26,27]. However, current research on Chinese medicine cannot fully reflect the real-world treatment situation, and evidence is still insufficient. The most important characteristic of TCM is the provision of treatment based on syndrome differentiation. In the face of COVID-19, the national diagnosis and treatment protocol provides dialectical treatment protocol for different types of syndromes. To date, the available RCTs and retrospective studies of a single drug or formulation cannot fully reflect the real-world efficacy and therapeutic advantages of TCM. Therefore, this study is dedicated to evaluating the efficacy and economy of TCM based on the national diagnosis and treatment plan, and filling gaps in the real-world evidence for using TCM in the treatment of COVID-19.

TABLE 1: CLINICAL EFFICACY OUTCOMES VALUED BY GDP FROM WHO

Population	Outcome
Patients with non-severe illness	Admission to hospital
	Death
	Quality of life
	Time to symptom resolution
	Duration of hospitalization
	Duration of oxygen support
	Need for invasive mechanical ventilation
	New non-SARS-CoV-2 infection
	Time to viral clearance
	Duration of invasive mechanical ventilation

	Death
	Need for invasive mechanical ventilation
	Duration of invasive mechanical ventilation
	Quality of life
Patients with severe and critical illness	Duration of hospitalization
	Time to symptom resolution
	New non-SARS-CoV-2 infection
	Duration of oxygen support
	Time to viral clearance

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