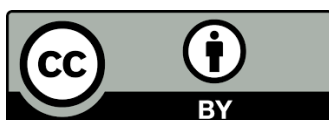


Original Research

The Effect of Chinese Medicine for Rehabilitation of Discharged COVID-19 Patients: A Protocol for Multi-Center Observational Study

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Abstract

The COVID-19 pandemic has lasted for more than 16 months, and there have been over 169 million confirmed cases worldwide. Besides, after treatment with Western medicine or undergoing home quarantine, COVID-19 patients are still severely or mildly functionally impaired. Though COVID-19 patients were discharged from the hospital, most of them still exhibit certain clinical symptoms such as fatigue, poor appetite, shortness of breath, and poor sleep. The syndromes, linked with the Chinese Medicine (CM) body constitutions, could be due to pre-COVID-19 infections, suffering from the infection, or a post-infection consequence. CM has been used by humans for thousands of years in Asia, especially in Hong Kong, and it is gaining increasing attention and popularity. This study aimed to evaluate the efficacy of CM on alleviating the clinical symptoms of the discharged COVID-19 Patients. This was a multicenter observational and comparative study. One hundred and fifty participants discharged from Hong Kong hospitals were recruited. The patients received three to six months of treatment using CM and were assessed by questionnaires and lung function tests each month during the treatment period and on the 9th month follow-up visit. In light of this global pandemic, we hope this study will bring new opportunities for CM, and facilitate patient recovery and rehabilitation. We believe that this may be the key to promoting rehabilitation.

Keywords

COVID-19; rehabilitation; observational study; Chinese medicine; respiratory system; lung function; Quality of Life; body constitutions

1. Introduction

In March 2020, the World Health Organization (WHO) declared the outbreak of a coronavirus disease 2019 (COVID-19) to be a pandemic. Worldwide, governments are fighting the virus and, at the same time, taking action to contain its spread. Fortunately, the vaccines were ready and publicly available in early January 2021. In fact, COVID-19 has lasted for more than 16 months, with over 169 million confirmed cases all over the world [1]. Though after Western medicine treatment or undergoing home quarantine, the functionality of COVID-19 patients is still severely or mildly impaired. These include not only physical weakness but also problems of the pulmonary, physical, and psychosocial domains [2]. In 2003, Hong Kong experienced the outbreak of a severe acute

respiratory syndrome (SARS) epidemic. A review of the publications during and after the SARS crisis enabled us to get an objective view of the true value of the adjuvant therapy using Chinese medicines (CMs) [3].

According to the WHO, most patients had mild or uncomplicated forms of COVID-19, while approximately 14% were estimated to be associated with a severe acute respiratory infection and required hospitalization and oxygen support, and 5% required admission to the intensive care unit (ICU) [4]. Even while patients with COVID-19 are discharged from hospitals, they still present significant clinical symptoms such as fatigue, poor appetite, shortness of breath, and poor sleep. They experience not only physical weakness but may also suffer from pulmonary, physical, and psychosocial problems. This disease has not been understood completely. Hence, its sequelae and long-term effects on pulmonary rehabilitation in COVID-19 need further evaluation.

For thousands of years, CM has been used by humans in Asia, and it is gaining increasing attention globally. Being the epicenter of the outbreak, China developed the National COVID-19 Diagnosis and Treatment Guidelines, and has constantly been updating information about the disease. To facilitate the implementation of integrative Chinese-Western Medicine in COVID-19 management, CM has been recommended in the 7th edition of the national guidelines released in March 2020 [5]. For this reason, CM rehabilitation treatment guidelines for those patients were also released simultaneously [6-10]. With the aim to strengthen the rehabilitation for health management of discharged COVID-19 patients, and help them recover and return to society safely, CM has been used as a treatment in China during the outbreak. Some of the early papers reported that >85% of COVID-19 infected patients in China were receiving CM treatment, with an overall effective rate of $\geq 90\%$ [11]. Among them, the symptoms of majority of patients ($\geq 60\%$) improved markedly, while the illness of others (30%) was stabilized [12].

Although the number of published papers on COVID-19 has increased, many questions still remain, and available treatment options are limited [5]. CM Practitioners (CMPs) in Hong Kong have extensive experience in using CM to prevent and treat disease. It is, therefore, important to draw on their experience and summarize the evidence for the effectiveness of CM on post-COVID-19 rehabilitation. Since early January 2020, there has been a response to the COVID-19 pandemic in Hong Kong. As of 20 May 2021, a total of 11,828 COVID-19 cases have been confirmed, and 11542 patients were discharged, according to the Centre for Health Protection of the Department of Health in Hong Kong [13].

2. Materials and Methods

2.1 Overview of Study Design

This was a multicenter observational study. One hundred and fifty discharged COVID-19 patients who are Hong Kong Chinese aged 18 years or older were recruited. The patients received three to six months of individualized CM treatment based on CM guidelines on COVID-19 rehabilitation, and individual clinical symptoms. All participants were assessed by questionnaires and lung function tests each month during the treatment period and on follow-up visit.

This study was divided into two parts:

Retrospective syndrome survey: Medical history of participants during COVID-19 hospitalization was collected during the baseline visit, after obtaining informed consent from the participants. This

was done with the aim to delineate disease severity with the CM syndrome, which includes COVID-19 diagnosis date, hospitalization period, and other chronic illnesses in the case report by semi-structured questionnaire and the self-developed Body Constitutions Questionnaire.

CM therapeutic assessment: Participants were treated with CM based on syndrome differentiation. The improvement of clinical symptoms and the status of body constitutions were periodically evaluated. The examinations included clinical CM diagnostic pattern and clinical characteristics assessments, lung function tests, and quality of life assessment at each visit for nine months.

2.2 Recruitment

Participants who were discharged from Hong Kong hospitals and seek CM treatment at the Chinese Medicine Clinic cum Training and Research Centres (CMCTRs), which are the government-subsidized tri-partite CM out-patient clinics, were recruited. One hundred and fifty participants were found to be eligible for the program. We had seven clinical sites in total, and we assumed that 20-30 participants could be recruited from each site. The study protocol was approved by the corresponding Ethics Committee(s). Participants who had recovered from COVID-19 were enrolled upon their capacity to give written informed consent voluntarily.

2.3 Eligibility Criteria

Inclusion Criteria: We recruited participants (aged 18 years or older) under the COVID-19 Rehabilitation Program who had been previously diagnosed to be infected with COVID-19 and discharged from local hospitals after treatment with Western medicine, and with negative results from COVID-19 virus detection test.

Exclusion Criteria: Participants were excluded if they had one or more of the following: 1) inability to communicate (e.g., cognitive impairment), and 2) history of CM allergies.

2.4 Interventions

The participants received three to six months of CM treatment based on their recommended prescription, individual CM syndrome, and clinical symptoms [14-17]. Each participant was assessed monthly during the treatment and follow-up. The treatment and assessments were conducted by a registered CM practitioner with at least three years of clinical experience.

Treatment was offered based on the CM clinical practice guidelines for COVID-19 patients (The National Health Commission of the People's Republic of China, 2020), which has been suggested by numerous clinical studies and guidelines [14].

2.5 Outcomes Measures

The primary outcome includes the scores of CM Diagnostic Pattern & Clinical Characteristics Assessments and Body Constitution Questionnaires using a Scoring Checklist, which covered two main syndromes (lung and spleen qi deficiency and qi and yin deficiency), and each included three major symptoms and five accompanying symptoms. A four-point scale (0, 2, 4, 6 and 0, 1, 2, 3) was used depending on symptom severity. The scores summed up to a range of 0 to 33, with higher scores indicating more severe levels of disease (Please refer to **Appendix 1**). Questionnaire on body

constitution was classified into nine specific types of questionnaires based on Traditional Chinese Medicine (TCM) theories, which has been recognized by the China Association of Chinese Medicine as the standard of body constitution (China Association of Chinese Medicine, 2009) [18-20].

The secondary outcomes include forced expiratory volume in 1 s (FEV-1), lung function-related assessments (Lung Function Questionnaire, and the 6-min walk test), lung function test assessed by the handheld basic spirometry, quality of life (WHO-QOL BREF HK) and the frequency of clinic or hospital visits for Western medicine during the treatment and follow up period.

The key spirometry measurements include the Forced Vital Capacity (FVC) and Forced expiratory volume (FEV). FVC is the largest volume of air that the participants can forcefully exhale after breathing in as deeply as they can. A lower than normal FVC reading indicates restricted breathing. FEV-1 is the volume of air the participants can force out of their lungs in one second. Lower FEV-1 readings indicate more significant pulmonary obstruction.

Lung Function Questionnaire is a simple, brief, self-administered instrument to identify patients' suitability for further lung function evaluation. It is a five-items questionnaire about the breathing and/or cough ailments of the participants. It was validated in China and widely used in primary care [21].

The WHO Quality of Life Brief Assessment [WHOQOL-BREF (HK)] (Leung, K F; Tay, M., Cheng, S. S. W., Lin, 1997) was validated in Hong Kong and has been widely used in academia and by clinicians since 1997. This is a 5-point Likert scale with a total of 28 questions to identify the perceived QOL of the participants. There are four domains, namely physical health, psychological, social relationships, and environment domains with a maximum score of 100.

2.6 Participant Timeline

The participants received three to six months of individualized CM treatment, based on CM guidelines on COVID-19 rehabilitation and individual clinical symptoms. Each participant was assessed by questionnaires and lung function tests monthly during the treatment period and on follow-up visit. (Please refer to **Table 1**)

Table 1 The Schedule for Outcome Measurement.

Assessment	Baseline	Program Intervention							Follow-up
Visit	1	2	3	4	5*	6*	7*	8	
Study Months	0	1	2	3	4*	5*	6*	9	
Informed Consent	✓								
History	✓								
CM Diagnostic Pattern & Clinical Characteristics Assessments	✓	✓	✓	✓	✓	✓	✓	✓	
Lung Function Assessments FEV/FVC 6-MWT	✓	✓	✓	✓	✓	✓	✓	✓	
Quality of Life Assessments (WHO-QOL BREF HK)	✓	✓	✓	✓	✓	✓	✓	✓	
Body Constitution Questionnaires (CCMQ)	✓	✓	✓	✓	✓	✓	✓	✓	

Assessments on the Frequency of WM Visits	√	√	√	√	√	√	√	√
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* The extended treatment is optional.

Remarks: There will be 8 study visits in total

Visit 1: is a Baseline visit

Visit 2 to Visit 7: Patients will receive Chinese medicine treatment and will be assessed by questionnaires and lung function tests on the same day

Visit 8: follow-up visit after three months at V7

2.7 Data Collection, Management, and Analysis

All analyses were conducted according to the intention-to-treat (ITT) principle. Missing values were inputted by the last-observation-carried-forward method. The statistical analysis was performed using the Statistical Product and Service Solutions (SPSS) for Windows version 25.0. A P-value of <0.05 was considered statistically significant. Numerical variables needed to be first tested for normality and were then reported as mean if the data were satisfied with normal distribution; otherwise, the median was used. Comparisons of numerical variables before and after Program intervention were analyzed by repeated measures of ANOVA for categorical variables, and chi-squared test or Fisher's exact test were used for analysis.

2.8 Ethics Statement

This study protocol was approved by Hong Kong Baptist University Research Ethics Committee (Approval no. REC/19-20/0468) and Hospital Authority (Approval no. HA 105/48 PT35), and was registered at the ClinicalTrials.gov on 3 September 2020 (NCT04544605).

3. Discussion

The role of CM is to enhance anti-epidemic efforts, particularly in relation to prevention and rehabilitation treatment, and to raise the capability of CMPs in the areas. To date, there is no reported long-term treatment and no long-term observational study for the discharged COVID-19 patients. Our team has gained preliminary satisfactory treatment outcomes with the application of CM for patients who still exhibit certain clinical symptoms such as fatigue, poor appetite, shortness of breath, and poor sleep.

Today the Chinese alternative medicine branch, collectively known as CM, is becoming increasingly relevant as the world fights the deadly spread of the coronavirus disease. CMs have their own characteristics such as holistic concept, the balance of *Yin* and *Yang*, syndrome differentiation and treatment, and strengthening the body resistance to eliminate pathogenic factors.

This study will provide evidence for further research on the changes in body constitutions, and evaluate the therapeutic effects of CM based on individualized treatment. Improvement in clinical symptoms and body constitution could also be assessed specifically in the Hong Kong population. The effects of CM on the respiratory system by lung function assessments included FEV in 1 s, a 6-min walk test, and the Lung Function Questionnaire. In light of the global pandemic, the development of CM may bring new opportunities and hope to provide references for control and

rehabilitation of COVID-19 patients around the world, and we believe that this may be the key to promoting rehabilitation resolution.

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Additional Materials

The following additional materials are uploaded at the page of this paper.

1. **Appendix 1:** The scores of CM Diagnostic Pattern & Clinical Characteristics Assessments.

Author Contributions

All authors contributed equally to this study and submission. The author(s) read and approved the final manuscript.

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Competing Interests

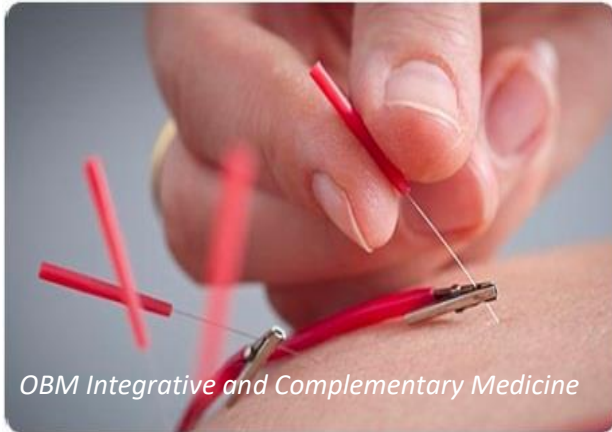
The authors have declared that no competing interests exist.

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