ABSTRACT Objective: To observe the changes of symptoms, Chinese medicine (CM) syndrome, and lung inflammation absorption during convalescence in patients with coronavirus disease 2019 (COVID-19) who had not totally recovered after hospital discharge and whether CM could promote the improvement process.

Methods: This study was designed as a prospective cohort and nested case-control study. A total of 96 eligible patients with COVID-19 in convalescence were enrolled from Beijing Youan Hospital and Beijing Huimin Hospital and followed up from the hospital discharged day. Patients were divided into the CM (64 cases) and the control groups (32 cases) based on the treatment with or without CM and followed up at 14, 28, 56, and 84 days after discharge. In the CM group, patients received the 28-day CM treatment according to two types of CM syndrome. Improvements in clinical symptoms, CM syndrome, and absorption of lung inflammation were observed.

Results: All the 96 patients completed the 84-day follow-up from January 21 to March 28, 2020. By the 84th day of follow-up, respiratory symptoms were less than 5%. There was no significant difference in the improvement rates of symptoms, including fatigue, sputum, cough, dry throat, thirst, and upset, between the two groups (P>0.05). Totally 82 patients (85.42%) showed complete lung inflammation absorption at the 84-day follow-up. On day 14, the CM group had a significantly higher absorption rate than the control group (P<0.05) and the relative risk of absorption for CM vs. control group was 3.029 (95% confidence interval: 1.026–8.940). The proportions of CM syndrome types changed with time prolonging: the proportion of the pathogen residue syndrome gradually increased.

Conclusions: Patients with COVID-19 in convalescence had symptoms and lung inflammation after hospital discharge and recovered with time prolonging. CM could improve lung inflammation for early recovery. The types of CM syndrome can be transformed with time prolonging. (Registration No. ChiCTR2000029430)

KEYWORDS COVID-19, convalescent patient, Chinese medicine, syndrome evolution, pneumonia absorption
convalescent patients are unknown. Therefore, we designed a prospective cohort study enrolling the patients with COVID-19 in convalescence from the day after hospital discharge. The aim of this cohort study was to observe the disease outcomes for a long-term follow-up, including evolution of symptoms if lung inflammation showed absorption. Moreover, we designed a nested case-control study to observe whether Chinese medicine (CM) could affect the evolution of symptoms, syndromes, and the lung inflammation absorption of patients in convalescent period.

METHODS

Study Design

This study was designed as a prospective cohort and nested case-control study and approved by the Research Ethics Committee of Hubei Integrated Traditional Chinese and Western Medicine Hospital (No. [2020]002). It was registered at the Chinese Clinical Trial Registry (registration No. ChiCTR2000029430). Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Patients with COVID-19 in convalescence after hospital discharge were continuously enrolled as a prospective cohort and followed up for at least 84 days. A nested case-control study was designed according to the presence/absence of CM treatment.

Sample Size

The COVID-19 pandemic is a new infectious disease outbreak. The outcome of patients with COVID-19 in convalescence is unknown to researchers. The researchers hoped to continuously enroll and follow up all eligible patients. With the nationwide lock-down or shut-down strategy, the outbreak was controlled soon, and participants number reached peak to 118 in the middle of February, 2020. Ninety-six eligible patients with COVID-19 were enrolled in this study.

Participants

Participants in this study were patients with COVID-19 who had been diagnosed and discharged after treatment from Beijing Youan Hospital and Beijing Huimin Hospital. Inclusion criteria included (1) age > 16 years; and (2) definitive diagnosis of COVID-19 during hospitalization, with any disease type (common, severe, or critical). Exclusion criteria were (1) pregnancy; (2) organ failure; and (3) complete absorption of pneumonia on chest CT at discharge.

Patient Allocation for Nested Case-Control Study

Patients who had completed the 28-day CM treatment were allocated to the CM group. Those undergoing symptomatic treatment with Western medicine (WM) or not taking any medicines were allocated to the control group. CM used for the treatment was according to the "Beijing Guidelines for Prevention and Management of COVID-19 with Traditional Chinese Medicine". Patients in convalescence were classified into two CM syndrome types based on the following criteria: (1) pathogen residue syndrome: presenting with shortness of breath, chest tightness, cough, less sputum, or red or dark tongue with greasy moss; (2) both qi and yin deficiency syndrome: presenting with tiredness, spontaneous sweating, heart palpitations, anorexia, dry mouth or throat, or tongue with reddish color, yellow fur, or a little grease.

Treatment

All patients were advised to intake sufficient dietary nutrition and exercise properly after hospital discharge. In the control group, patients with symptoms, such as cough, sputum, insomnia, and constipation, were provided with symptomatic treatment with WM, and those without apparent symptoms, or with mild symptoms (such as weakness, fatigue, upset) but without suitable WM for treatment, were not provided with any medication.

In the CM group, patients received the 28-day CM treatment based on the two CM syndrome types. The oral formulae were as follows: (1) for the pathogen residue syndrome: Salvia miltiorrhiza 15 g, prepared Fructus hordei germinates 30 g, Fructus hordei germinates 30 g, Codonopsis pilosula 15 g, Adenophora stricta 15 g, Peach kernel 6 g, Melon burdock 20 g, Magnolia officinalis 10 g, Radix Reed 30 g, and Herba patriniae 30 g were decocted into decoction by the medicine room of Beijing Youan Hospital, 150 mL each time, twice daily; (2) for both qi and yin deficiency syndrome: Radix adenophorae 15 g, Ophiopogon japonicus 15 g, Rhizoma Dioscoreae 15 g, and Massa Fermentata 10 g were decocted, 150 mL each time, twice daily.

Follow-Up and Patient Monitoring

All patients in convalescence arrived at the
Outpatient Clinic in Beijing Youan Hospital for the follow-up. A multidiscipline team, consisting of CM experts, infectious disease experts, and radiologists from Beijing Youan Hospital, performed the follow-up and data collection in this study. Patients were followed up regularly at different time points, including 14, 28, 56, and 84 days after discharge.

Patients were asked to measure their axillary temperatures daily and monitored by a team of designated nurses who regularly had phone calls with patients for them to report their specific symptoms or adverse events. The terminologies and grading of severity were referred from the Common Terminology Criteria for Adverse Events version 5.0. (6)

**Data Collection**

The key data collection at each time point included: (1) CM syndrome: patients were asked if they had the following 11 symptoms at each follow-up: fatigue, cough, sputum, dry throat, thirst, upset, bitter taste, shortness of breath, chest tightness, anorexia, and insomnia. The tongue nature, tongue coating, and pulse were recorded combined with the symptoms associated with the CM syndrome by 2 experienced senior CM experts (chief physician) according to the aforementioned classification criteria for the type of CM syndrome; (2) laboratory examination: routine blood examination and liver function; (3) radiology: high-resolution CT (HRCT) was used to assess lung injury at each follow-up. Radiologic data were evaluated by an experienced radiologist (chief physician).

**Outcome Measurement**

Outcomes were measured in 3 layers. (1) Improvement rate of clinical symptoms: compared to the day after hospital discharge, the proportion of patients with improvement in specific symptoms among cohort patients was considered as the improvement rate. (2) Evolution of CM syndrome: CM syndrome can reflect the disease pathogenesis. Changes in the CM syndrome were described as disease evolution. (3) Complete lung inflammation absorption rate: based on chest CT, lung inflammation absorption was defined as the complete disappearance of previous lung imaging abnormalities, including ground-glass opacity, crazy-paving pattern, and consolidation, (7,8) judged by a radiologist on chest CT. At each follow-up, the proportion of patients with lung lesion remission out of the whole cohort of patients was recorded and compared between two groups.

**Statistical Analysis**

SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation (x ± s) for the data of normality. The median (min–max) was used for non-normal distribution parameters. Comparisons between groups were performed using the t-test (variance is even). The count data were expressed as percentage, and χ² test was used for comparison between groups. All data were tested on both sides, and a P-value less than 0.05 was considered to be statistically significant. The relative risk (RR) for the CM treatment vs. control was used to describe the effect of CM on the symptoms and the absorption of lung lesion, in which CM treatment was taken as the exposure factor and RR was calculated based on the improvement rate and the absorption rate.

**RESULTS**

**General Information**

A total of 96 patients were eligible for this study who had been discharged from hospital between January 21 and March 28, 2020, including 80 patients from Beijing Youan Hospital and 16 patients from Beijing Huimin Hospital. By May 21, 2020, all patients had completed 84-day follow-up. The study flowchart and general information of patients are shown in Figure 1 and Table 1, respectively.

**Symptom Improvement at Different Follow-Ups and Effect of CM on Symptom Improvement Rate**

The proportions of symptoms among patients
were ranked from high to low as follows: cough (38 cases, 39.58%), sputum (37 cases, 38.54%), dry throat (29 cases, 30.21%), thirst (27 cases, 28.12%), insomnia (28 cases, 29.17%), fatigue (25 cases, 26.04%), shortness of breath (25 cases, 26.04%), chest tightness (21 cases, 21.88%), bitter taste (19 cases, 19.79%), upset (16 cases, 16.67%), and anorexia (8 cases, 8.33%).

Cough and sputum improved significantly at 28 and 56 days after discharge. The improvement of dry throat, thirst, insomnia, and fatigue occurred mainly at 56 and 84 days after discharge. Chest tightness was mainly seen in a few patients with severe/critical type and had significantly improved at 84 days after discharge. By the 84th day of follow-up, respiratory symptoms were less than 5%, but there were some symptoms that affected the patient’s quality of life, including thirst (5.21%), insomnia (8.33%), fatigue (9.38%), bitter taste (8.33%), and upset (7.29%).

The improvement rate of symptoms was compared between the CM group and control group by the 28th day after discharge, when the CM treatment ended. There was no significant difference in the improvement rates of symptoms, including fatigue, sputum, cough, dry throat, thirst, and upset, between the two groups (P>0.05, Figure 2).

### Table 1. General Information of Patients

| Characteristic                      | Overall (96 cases) | CM group (64 cases) | Control group (32 cases) |
|------------------------------------|--------------------|---------------------|--------------------------|
| Gender [Case (%)]                  |                    |                     |                          |
| Male                               | 35 (36.46)         | 24 (37.50)          | 11 (34.38)               |
| Female                             | 61 (63.54)         | 40 (62.50)          | 21 (65.62)               |
| Age (Year, x ± s)                  | 49.02 ± 15.04      | 49.90 ± 15.54       | 47.47 ± 14.11            |
| Clinical type [Case (%)]           |                    |                     |                          |
| Common                             | 75 (78.12)         | 50 (78.12)          | 25 (78.12)               |
| Severe/critical severe             | 21 (21.88)         | 14 (21.88)          | 7 (21.88)                |
| CM syndrome type [Case (%)]        |                    |                     |                          |
| Pathogen residue                   | 48 (50.00)         | 36 (56.25)          | 12 (37.50)               |
| Both qi and yin deficiency         | 48 (50.00)         | 28 (43.75)          | 20 (62.50)               |
| Laboratory indicator (x ± s)       |                    |                     |                          |
| WBC (×10^9/L)                      | 5.96 ± 1.21        | 5.97 ± 1.25         | 5.94 ± 1.14              |
| LYM (×10^9/L)                      | 1.73 ± 0.51        | 1.75 ± 0.64         | 1.69 ± 0.55              |
| NLR                                | 1.52 ± 0.50        | 1.52 ± 0.50         | 1.53 ± 0.51              |
| ALT (U/L)                          | 29.56 ± 19.16      | 30.05 ± 20.80       | 28.55 ± 15.52            |
| AST (U/L)                          | 24.93 ± 11.95      | 25.14 ± 13.15       | 24.48 ± 9.15             |
| TBIL (μmol/L)                      | 11.94 ± 5.00       | 12.21 ± 5.29        | 11.38 ± 4.39             |
| CK [U/L, median (min–max)]         | 65 (26–425)        | 65 (26–425)         | 68 (30–378)              |
| MYO [ng/mL, median (min–max)]     | 33.5 (10–111)      | 31.0 (10–111)       | 30.5 (16–98)             |

Notes: CM: Chinese medicine; WBC: white blood cell; LYM: lymphocyte; NLR: neutrophil to lymphocyte ratio; ALT: alanine aminotransferase; AST: aspartate transaminase; TBIL: total bilirubin; CK: creatine kinase; MYO: myoglobin

Lung Inflammation Absorption on Chest CT and Effect of CM on Lung Inflammation Absorption

The chest CT results at 14, 28, 56, and 84 days after discharge showed that the cumulative number of patients with completely absorbed lung inflammation among the 96 patients were 28 (29.17%), 56 (58.33%), 79 (82.29%), and 82 (85.42%), respectively. Further, there were still 14 patients (14.58%) with persistent inflammation which also got improved.

The comparison results of complete lung inflammation absorption rates between the CM and control groups at follow-ups on days 14, 28, 56, and 84 are shown in Figure 3. On day 14, the CM group had a significantly higher absorption rate than the control group (P<0.05) and the RR of absorption for CM vs. control group was 3.029 (95% confidence interval: 1.026–8.940). On the other time points, there was no statistically significant difference between the two groups (P>0.05).
Effects of CM on Absorption of Lung Inflammation in Patients with Common or Severe/Critical Type in Convalescence

Seventy-five patients were diagnosed as the common type and the case numbers and cumulative proportions of pneumonia absorption on days 14, 28, 56, and 84 were 29 (38.67%), 54 (72.00%), 69 (92.00%), and 71 (94.67%), respectively. There were no significant differences in the cumulative proportions of patients with lung inflammation absorption between the two groups on any follow-up time points (P>0.05, Figure 4A).

Among 21 patients with severe/critical type, the case numbers and proportions of cumulative pneumonia absorption on days 14, 28, 56, and 84 were 0, 2 (9.52%), 10 (47.62%), and 10 (47.62%), respectively. At the 14-day follow-up, no patient showed absorption of pneumonia in either CM or control group. At the 28-, 56-, and 84-day follow-ups, there was no significant difference in the absorption of pneumonia between the two groups (P>0.05, Figure 4B). When comparing the common type with severe/critical type, it was shown that the common type had a significantly higher cumulative absorption rate by the 84-day follow-up (P<0.01).

Distribution of CM Syndromes of Patients with Complete Lung Inflammation Absorption

In total, 82 patients had gotten complete lung inflammation absorption by the 84-day follow-up. However, at different follow-ups, the proportions of CM syndrome types were different. With days lasted, the proportion of the pathogen residue syndrome gradually decreased and that of both qi and yin deficiency syndrome increased instead (P<0.01 for overall trend, Figure 5).

From another perspective, although the CM syndrome type distribution changed with time prolonging, for each follow-up, the two CM syndrome types had the similar percentage of patients with complete lung inflammation absorption (P>0.05, Figure 6).

DISCUSSION

COVID-19 is a newly emerging infectious
disease caused by SARS-CoV-2. It is highly infectious, and some cases can progress to severe illness. The integrative therapy was shown to be safe and superior to the standard therapy in suppressing disease progression of COVID-19.\(^9\) In convalescent patients, the virus is negative, and the lung inflammation is improved. However, how long the patient's symptoms can be totally relieved, when the lung inflammation can be fully absorbed, and whether CM can play a role during the recovery period needs further study.

The results of this prospective cohort study showed that nearly 40% of patients had symptoms, such as cough, sputum, dry throat, thirst, insomnia, fatigue, shortness of breath, chest tightness, etc., when discharged from the hospital. By the 84th day of follow-up, less than 5% patients still had respiratory symptoms, less than 10% patients still had other symptoms, including thirst, insomnia, fatigue, bitter taste, and upset. It was suggested that COVID-19 could affect the quality of life of patients for up to 3 months. The 28-day treatment with CM could have some advantages over control on improving symptoms such as fatigue, sputum, cough, dry throat, upset, however, the statistic results did not show significant difference. The small number of patients for statistical analysis might be the reason for no difference between the two groups. The different CMs were used for the pathogen residue syndrome and both qi and yin deficiency syndrome, aiming to clear away heat, dampness and toxics, or invigorate Pi (Spleen) and replenish the qi, respectively. CM could be used for relieving symptoms when patients recovered from the illness.

Lung abnormalities on chest CT showed the greatest severity approximately 10 days after the onset of symptoms and gradual resolution of consolidation.\(^10\) However, whether or not lung inflammation could be completely absorbed and when it could be completely absorbed were issues of clinical concern. HRCT is the best modality for detection of viral diseases during the recovery period.\(^11\) In this study, HRCT was used to observe the absorption of typical COVID-19 inflammation. The results showed that 82 patients (85.42%) had complete pneumonia absorption at 84 days after discharge. Further, 71 (94.67%) of 75 common patients showed complete absorption, and 10 (47.62%) of 21 severe/critically ill patients showed complete absorption. Compared to the SARS outbreak in 2003, the overall recovery was faster. A study reported that 49% of patients with SARS had persistent abnormalities on HRCT after approximately 2 months of discharge.\(^14\) Until 3 months after the onset, half of the patients with SARS completely returned to normal.\(^15\)

CM treatment had certain advantages in promoting pneumonia absorption, although the CM group was significantly higher only on day 14 after discharge compared with the control group (\(P<0.05\)). Factors affecting pneumonia absorption should be related to the severity of pneumonia during patient hospitalization. The pneumonia absorption rate of patients with common type was significantly higher than those with severe/critical type (\(P<0.01\)). CM is not the only factor affecting pneumonia absorption.

In regard to the CM syndrome types, the proportion of patients with the pathogen residue syndrome in the recovery period gradually decreased, and the proportion of patients with both qi and yin deficiency syndrome gradually increased. In patients with complete pneumonia absorption, those with the both qi and yin deficiency syndrome type also gradually increased. The syndrome evolution was consistent with the understanding of the pathogenesis of the "healthy qi deficiency with pathogen-lingering" in this disease.\(^16\)

In conclusion, patients with COVID-19 had varying degrees of symptoms and lung inflammation at the time of discharge from the hospital. Intervention with CM may play a role in promoting the improvements of symptoms and lung inflammation. The proportion of patients who had complete pneumonia absorption after 84 days of discharge could reach 85.42%. During the recovery process, the type of CM syndrome could change from the pathogen residue to both qi and yin deficiency. The case data of follow-up in this study was relatively complete. However, the number of cases was small, and there were certain limitations of the non-randomized controlled study design, which need to be improved in the further study.

Conflict of Interest
The authors declared no conflict of interest.

Author Contributions
Li XH designed the study, Li L, Li XM, Gou CY, Wang XJ,
Li HY, and Li HY followed up the patients. Song WY reviewed the imaging results. Li L and Li XH analyzed the data. Li L wrote the manuscript and Li XH reviewed the manuscript. All authors read and approved the final version of the manuscript.

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