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Positive effects of Lianhuaqingwen granules in COVID-19 patients: A retrospective study of 248 cases

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ABSTRACT

Ethnopharmacological relevance: Lianhuaqingwen (LHQW) is a Chinese medicine, developed from appropriate addition and reduction of combined traditional Chinese medicine (TCM) Yinqiao San and Maxing Shigan decoction. LHQW has been used in routine influenza treatment for decades and plays a role in a broad-spectrum therapy on various influenza viruses.

Aims of the study: The therapeutic effects of LHQW in coronavirus disease 2019 (COVID-19) have not been fully elucidated. A retrospective study was conducted in patients with COVID-19 to evaluate the influence of LHQW on laboratory results related to the disease, and to provide evidence for the clinical practice of TCM.

Materials and methods: We retrospectively collected 248 patients who met the moderate type COVID-19 diagnostic criteria, and received treatment in Tongji Hospital. Patients were divided into control (158 cases, standard treatment) and LHQW treatment (90 cases, standard treatment combined with LHQW) groups according to the different treatments administered. All laboratory data were obtained after 5–7 days’ treatment.

Results: In this study, the average patient age was 58.95 years and 131 patients were male. The two groups were comparable in demographic characteristics, symptoms, and treatment. Compared with in the control group, D-dimer and erythrocyte sedimentation rate were significantly lower in the LHQW treatment group (2.47 ± 4.67 vs. 1.68 ± 3.61; 44.47 ± 30.24 vs. 35.39 ± 27.43; both \( P < 0.05 \)). Lymphocyte counts, albumin and hemoglobin levels were higher in the LHQW treatment group than those in the control group (1.00 ± 0.46 vs. 1.13 ± 0.5; 34.39 ± 5.2 vs. 35.71 ± 4.76; 127.03 ± 16.58 vs. 131.11 ± 14.66; both \( P < 0.05 \)).

Conclusion: The study showed that LHQW significantly improved laboratory results of patients with COVID-19 and could be effectively applied alongside standard treatment of patients with moderate type COVID-19, providing preliminary clinical research evidence for the use of TCM in treatment of this disease.

1. Introduction

Coronavirus disease (COVID-19) has become a major epidemic that seriously endangers human health and public safety all over the world. A newly emerged coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recognized as being responsible for the occurrence of this disease (Pascarella et al., 2020). Similar to the other two highly pathogenic coronaviruses, SARS-CoV and MERS-CoV, SARS-CoV-2 can cause severe respiratory disorders and high mortality (Nkengasong, 2020). By 1st May 2021, more than 150 million confirmed...
cases of COVID-19 had been reported globally, including 2 million deaths, and a continuing increase is predicted. This disease inflicts enormous health, economic, and social crises, with no country escaping its effects.

At present, it is important to develop potential antiviral agents; however, these treatment strategies will take months, even years, to become available (Qiu et al., 2020). In 2003, patients with SARS who received traditional Chinese medicine (TCM) treatment had shorter hospital stays and fewer steroid-related side effects (Huang et al., 2020). The application of TCM can contribute to effective treatment as a complementary and alternative measure, reducing the rate of severe illness and death. From the start of the COVID-19 outbreak in Wuhan, Chinese physicians have adopted a combination of TCM and Western medicine (Ling, 2020), and the application of Lianhuaqingwen granules (LHQW) combined with standard treatment appears to be beneficial. LHQW is a Chinese medicine comprising 13 herbs, developed from appropriate addition and deletion of combined Yinqiao San and Maxing Shigan decoctions. Yinqiao San, derived from the traditional Wenbing Tiaobian, was mainly administered in the treatment of “warm disease” characterized by clinical symptoms including cough, fever and headache. Maxing Shigan decoction, stemming from the classical monograph Shanghan Lun, was typically used against diseases including measles, influenza, bronchitis, and pneumonia (Hsieh et al., 2012). LHQW has been used in routine influenza treatment for decades, and plays a role in broad-spectrum curative therapy for various influenza viruses, such as H7N9 and H1N1 (Chen et al., 2011; Ding et al., 2017). Lin et al. reported that LHQW significantly decreased the Visual Analog Scale and Sino-Nasal Outcome Test-22 scores in chronic rhinosinusitis patients in comparison with placebo group. Histologic changes in nasal mucosa were significantly improved only in LHQW group, including alveolar septum thickening, capillary congestion, interstitial edema, which might be associated with the levels of malonaldehyde, glutathione peroxidase, and super oxide dismutase, played significant roles in pathogenesis of lung injury. CD4+ and CD8+ T cells were decreased in the LHQW treatment group, but not in placebo group (Lin et al., 2020). In a prospective randomized controlled trial, the recovery rate was significantly higher in the LHQW therapy group compared with the control group (91.5% vs. 82.4%) in patients with COVID-19 (Hu et al., 2020). In a system review of COVID-19 (Liu et al., 2021), patients treated by LHQW combined with standard treatment have a higher overall effective rate and CT recovery rate compared with others treated by standard methods. Also, patients treated by LHQW combined with standard treatment have a lower incidence of diarrhea.

LHQW is usually used as a supplementary therapeutic agent, which is considered to relieve symptoms, improve drug efficacy, shorten the course of the disease, and reduce the proportion of severe cases. LHQW can be used alone in some diseases with chronic airway inflammation and mild type of COVID-19 or other acute respiratory inflammation. A study demonstrated that LHQW treatment alone control the inflammation in nasal mucosa and result in the improvement of chronic rhinosinusitis (Lin et al., 2020). In this study, a retrospective study was performed to provide evidence for treatment of moderate COVID-19 with LHQW.

2. Methods and materials

2.1. Participants

Moderate COVID-19 pneumonia was diagnosed in accordance with the New Coronavirus Pneumonia Diagnosis and Treatment Program (5th version) published by the National Health Commission of China. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology (Wuhan, China) (Approved No. TJ-C20200124).

2.2. Inclusion criteria

2.2.1. Inclusion criteria consisted of following:

(1) suspected cases with one of the following etiological evidences: a) RT-PCR assay for SARS-CoV-2 RNA; b) viral gene sequence is highly homologous to SARS-CoV-2;
(2) moderate severity of disease, indicated by fever and respiratory symptoms with radiological findings consistent with pneumonia;
(3) patients age over 18 years.

2.3. Exclusion criteria

Exclusion criteria consisted of the following:

(1) patients with severe or critical COVID-19, requiring mechanical ventilation;
(2) patients with acute respiratory disease not caused by SARS-CoV-2, but resulting from basic diseases such as primary immunodeficiency or acquired immunodeficiency disease, abnormal lung development, severe pulmonary interstitial disease, bronchiectasis, congenital respiratory tract malformation, congenital heart disease and gastrosophageal reflux disease;
(3) patients with asthma requiring daily treatment, respiratory bacterial infections, including acute tracheobronchitis, sinusitis, and other respiratory tracts diseases that may affect outcome;
(4) previous or present disorders that may affect outcome, including: malignant disease, severe liver disease, severe renal insufficiency or continuous renal replacement therapy, blood disease, and organ transplantation;
(5) pregnant or lactating women;
(6) allergy to the ingredients of LHQW;
(7) participation in other clinical trials within the last 6 months;
(8) patients who received other medications, in addition to standard treatment and LHQW.

2.4. Standard and LHQW treatments

The standard treatment comprised the following: (1) patients were restricted to bed rest and adequate nutrient intake, especially in terms of calories, was provided along with careful monitoring of water and electrolyte balance to maintain internal environment stability; (2) closely monitoring of vital signs and oxygen saturation, with provision of effective oxygen therapy; (3) according to patients’ conditions, monitoring of blood, and urine tests, c-reactive protein (CRP), coagulation function, biochemical indicators (liver enzyme, renal function, myocardial enzyme), arterial blood gas analysis, and chest CT-imaging; (4) antiviral therapy: arbidol, 200 mg, thrice daily.

LHQW granules were provided by Shijiazhuang Yiling Pharmaceutical Co., Ltd (Shijiazhuang, China). The major ingredients of LHQW consist of Forsythia suspensa, Isatis indigotinga, Ephedra sinica, Dryopteris crassirhizoma, Loniceria japonica, Pogostemon cablin, Houttuynia cordata, Glycyrrhiza uralensis, Rhodiola crenulata, Prunus sibirica, Rheum palmatum, and gypsum (see Supplementary File 1 for full details of LHQW granules). The LHQW treatment consisted of standard treatment plus LHQW granules (6 g/bag, 1 bag, thrice daily; Z20100040).

2.5. Study design and treatment procedure

We enroll a total of 248 patients with moderate type COVID-19, all receiving treatment in Tongji Hospital, between 5th March and March 15, 2020. After diagnosis, all patients were offered two treatment options (standard treatment and standard treatment plus LHQW treatment). Patients chose one of the treatment options and signed the informed consent form. The patients in the control group (n = 158) received standard treatment and the LHQW treatment group (n = 90)
received standard treatment plus LHQW granules for 5–7 days. Nurses supervised patients taking medications on time, followed up every day, and paid close attention to changes in their condition during the treatment.

2.6. Data collection and evaluation parameters

We retrospectively reviewed medical records and clinical data for enrolled patients with moderate severity COVID-19 pneumonia from Tongji Hospital. All laboratory data were obtained after 5–7 days’ treatment, including blood cell count, biochemical parameters, inflammation parameters, and coagulation function.

Blood cell counts were detected by flow cytometry, while white blood cell (WBC) count, neutrophil count (NC), lymphocyte count (LC), eosinophil count (EC), hemoglobin (HGB), and platelet (PLT) count were also collected for analysis. Blood biochemical parameters including alanine aminotransferase (ALT), glutelin (GLB), aspartate aminotransferase (AST), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH), creatinine (CR), urea nitrogen (UREA), estimated glomerular filtration rate (eGFR) and bicarbonate (HCO₃⁻) were assessed using colorimetric kits (Roche, Switzerland). Myohemoglobin (MB) and creatine kinase-muscle/brain (CK-MB) were examined by chemiluminescence microparticle immunoassay (Abbott, Chicago). N-terminal prohormone brain natriuretic peptide (NT-proBNP) was detected by electro-chemiluminescence immunoassay (Roche, Switzerland).

For inflammation parameters, erythrocyte sedimentation rate (ESR) was measured by the Wei method. High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and procalcitonin (PCT) were examined by electro-chemiluminescence (Roche). IL-1β, IL-2 receptor (IL-2R), IL-8, IL-10 and tumor necrosis factor α (TNF-α) were detected by chemiluminescence (Siemens, Munich Germany). Ferroprotein was tested by granule-enhanced immunoturbidimetry (Roche, Switzerland). Coagulation function, prothrombin time (PT), thrombin time (TT), activated partial prothrombin time (APPT) and fibrinogen (FIB) were detected by magnetic bead coagulation assay (Stago, USA); D-dimer was tested by immunoturbidimetry, and prothrombin activity (PTA) was tested by the chromophore substrate method. Internationally standardized ratio (INR) was calculated with PT ratio and International Standard Index. For urine protein, urine sediment dry chemistry was carried out by tape assay (GE Healthcare, Chicago, IL).

2.7. Statistical analysis

Differences in demographic characteristics (except age) between the two groups were analyzed by Chi square test; age was analyzed by T test. The Mann-Whitney U test was applied to assess differences in blood cell count, biochemical parameters, inflammation parameters and coagulation function between the two groups. All data analyses were performed with SPSS version 16.0 (SPSS Inc. Chicago, IL). P < 0.05 was considered statistically significant.

3. Results

3.1. Demographic characteristics of enrolled patients

As shown in Table 1, 248 patients (117 females and 131 males) with laboratory confirmed COVID-19 were enrolled. Of these, 45.16% (112/248) had at least one chronic disorder, such as cardiovascular and cerebrovascular diseases, or diabetes. All patients received standard treatment after COVID-19 diagnosis. The two treatment groups were comparable in terms of demographic characteristics, symptoms, and previous treatment (P > 0.05).

### 3.2. Blood cell count

As shown in Table 2, compared with in the control group, LC (Fig. 1A) and HGB (Fig. 1B) in blood routine analysis were significantly increased in the LHQW treatment group (P < 0.05), while no significant difference was found between the two groups in terms of NC, PLT, EC, and WBC (P > 0.05).

### 3.3. Biochemical parameters

As shown in Table 3, blood biochemistry demonstrated that ALB (Fig. 1C) was higher in the LHQW treatment group compared with in the control group (P < 0.05). However, no significant differences in ALT, AST, LDH, GLB, CR, UREA, MB, CK-MB, eGFR, HCO₃⁻, and NT-proBNP were found between the two groups.

### 3.4. Inflammation parameters

As shown in Table 4, differences in hs-CRP, IL-1β, TNF-α, IL-2R, IL-6, IL-8, IL-10, ferroprotein, and PCT between the two groups were not statistically significant (P > 0.05). However, ESR was significantly higher in the control group compared with in the LHQW treatment (P < 0.05) (Fig. 1D).

### 3.5. Coagulation function

As shown in Table 5, D-dimer in the control group was significantly higher than that in the LHQW treatment group (P < 0.05) (Fig. 1E). However, no significant differences in PT, PTA, INR, APPT, FIB, and TT were found between the two groups.
4. Discussion

In this study, we aimed to retrospectively identify differences in clinical indicators among patients receiving TCM in addition to standard Western treatments for COVID-19, to provide evidence for the efficacy of TCM in this disease. Overall, treatment with LHQW for 5–7 days resulted in significant improvements in LC, ESR, D-dimer, ALB and HGB in
improving the airway microenvironment, regulating the immune role in correcting ALB and HGB levels, which may be related to fibrinolysis due to the formation of extensive thrombus (Guan et al., 2020). Hypoproteinemia caused by fever and insufficient protein intake may lead to severe disease (Xu et al., 2020). In a recent study (Runfeng et al., 2020), the authors found that LHQW significantly inhibited SARS-COV-2 replication and reduced excessive expression of pro-inflammatory cytokines (IL-6, TNF-α and macrophage chemokine protein-1). LHQW also effectively reduced the expression of IL-1β, IL-2, and IL-13 and attenuated lung injury associated with inflammatory cell infiltration. These findings suggest that LHQW protects against SARS-CoV-2 and may be a potentially effective agent for controlling COVID-19.

The inflammatory cytokine storm has been identified as an over-defense response to various viruses, which can cause diffuse lung injury and lead to severe disease (Shaikh et al., 2019). The purpose of this retrospective study was to explore the effect of LHQW on routine blood, biochemical, and coagulation functions of patients with COVID-19 and provide evidence for further elucidating the mechanism of action of TCM. LHQW combined with antiviral treatment for moderate COVID-19 can improve therapeutic effects.

This study had some limitations. It should be noted that the sample size was small, and there was no comparison between the treatment efficiency and the rate of severe illness between the LHQW group and the control group. Finally, there is a lack of research regarding indicators and symptoms of LHQW side effects. In the future, prospective, double-blind, randomized controlled clinical studies are needed to further assess the clinical efficacy of LHQW.

5. Conclusion

LHQW has shown therapeutic effects in COVID-19 by improving LC, ALB, and HGB and reducing ESR and D-dimer. Considering the efficacy profiles, LHQW could be a potential agent for the treatment of COVID-19.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2021.114220.
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Funding acquisition: Chao Chen, Jing Li, Gang Chen.
Investigation: Pan Shen.
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Software: Gang Chen.
Supervision: Chao Chen.
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Writing – review & editing: Pan Shen, Yanran Wu, Shenhao Tu.

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