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Jieji Xuanfei Chuyi granules in the treatment of COVID-19

A randomized, open-label, parallel-controlled clinical trial

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Abstract

Background: New drugs are needed for coronavirus disease 2019 (COVID-19).

Methods: We conducted a randomized, open-label, positive-drug parallel-controlled trial to evaluate Jieji Xuanfei Chuyi granules (JJXFCY), a Chinese patent medicine, administered within 7 days of the onset of symptoms of mild-to-moderate, laboratory-confirmed COVID-19 in adults. Participants (n = 120) received JJXFCY or Lianhua Qingwen granules (LHQW), as control, 3 times daily. The primary outcome was the time for negative reverse transcription-PCR severe acute respiratory syndrome coronavirus 2 test and symptom relief after 7 days of treatment. The primary safety end point was adverse events.

Results: Baseline characteristics were mostly similar in the JJXFCY and LHQW groups. After 7 days of treatment, clinical symptoms were relieved in both groups to a certain extent. Fever, nausea, vomiting, and sticky stool disappeared on day 7. After 15 days, cough, sputum, and nasal congestion were mainly observed. After 28 days, cough, shortness of breath, phlegm, and runny nose still existed in some subjects. No deaths were observed. Adverse events occurred in 21.7% (13/60) and 15% (9/60) of JJXFCY and LHQW groups, respectively.

Conclusion: JJXFCY has therapeutic effects in treating mild COVID-19 cases. It reduced the persistence of COVID-19 symptoms, improved outcomes, and reduced the risk of hospitalization or death in adults with COVID-19.

Abbreviations: COVID-19 = coronavirus disease 2019, JJXFCY = Jieji Xuanfei Chuyi granules, LHQW = Lianhua Qingwen granules, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, TCM = traditional Chinese medicine.

Keywords: COVID-19, Jieji Xuanfei Chuyi granules, prognosis, randomized controlled trial, traditional Chinese medicine, treatment

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally. It is characterized by high infectivity and wide susceptibility of the population. Whole genome sequencing of infected specimens from Jilin Province, China, in 2022, revealed that all viruses belonged to the Omicron variant BA.2 evolutionary branch.[1] This variant is 30% more infectious than the original variant and is more adept at evading the immune system, with a stronger transmission force and faster transmission speed, though reduced virulence. Most patients with COVID-19 in Jilin Province showed mild or moderate disease. Thus, despite the large-scale vaccination efforts, the proportion of asymptomatic infected patients has increased.

Traditional Chinese medicine (TCM) has long been used to combat outbreaks of disease, such as severe acute respiratory syndrome, H7N9 bird flu, Ebola, and influenza. These diseases can cause large-scale epidemics, physical damage, or even death as "plague" or "Hapline gas."[2] Recently, TCM has been widely used in the clinical management of COVID-19.[3,4] TCM has been shown to alleviate symptoms, promote negative conversion of SARS-CoV-2, and improve the prognosis of COVID-19, with remarkable curative effects.[5–9]

Jieji Xuanfei Chuyi granules (JJXFCY) are an oral Chinese patent medicine with a variety of benefits, such as relieving

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

The trial was conducted in accordance with the Declaration of Helsinki and relevant Chinese clinical research norms and regulations and approved by the institutional ethics committees (protocol No. JJCY-2022-NCOV-1.0). The study has been registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/; registration number: ChiCTR2200058245, April 3, 2022). Written informed consent was obtained from all participants.

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muscle pain, clearing heat, promoting lung function, eliminating phlegm, and strengthening immunity. According to TCM theory, the pathogenesis of COVID-19 is due to a cold-damp constitution, leading to "evil spirits trapping the skin's surface and the body becoming mixed with cold and heat." To address this, Professor Wang Tan developed JJXFCY based on 2 classical prescriptions: Chaige Jieji decoction and Maxing Shigan decoction.[10] Chaige Jieji decoction is used to treat exterior syndrome due to wind-cold and heat caused by stagnation and has been proven effective for treating and preventing influenza, upper respiratory tract infection, nosocomial infection, relapses of respiratory infection, and chronic bronchitis.[10] Maxing Shigan decoction helps clear the lungs and reach lung qi; it has been demonstrated to have antiviral and anti-inflammatory effects through network pharmacology and experimental verification.[11,12] It is also effective in improving airway hyperresponsiveness, antiallergy, and anti-inflammatory responses.[13] Jiawei Maxing Shigan Tang has been shown to improve the recovery of patients with COVID-19, without increasing the risk of adverse reactions, and promote positive outcomes.[14]

Lianhua Qingwen granules (LHQW) are another Chinese patent medicine that has been widely used in China.[15–18] Many clinical studies have demonstrated that LHQW has a significant effect on alleviating COVID-19 symptoms such as fever, cough, expectoration, and body pain.[16,19–21] In China, it is also listed as one of the traditional Chinese patent medicines and simple preparations recommended by the government for the treatment of COVID-19. Pharmacodynamic studies have shown that LHQW can reduce the viral content in the cell membrane and cytoplasm, regulate the expression of inflammatory cytokines,[22] significantly inhibit virus replication, delay the activity of novel coronavirus,[23,24] and affect the virus morphology.[25] It also exerts anti-influenza activity by interfering with the virus and host response.[26]

Here, we conducted a randomized, open-label, positive-drug parallel-controlled trial to evaluate the efficacy and safety of JJXFCY granules in comparison with LHQW for the treatment of COVID-19 infection. JJXFCY and LHQW are both traditional Chinese patent drugs, and their formulations are also in the form of granules, which can reduce the variables in clinical trials. We selected adults with mild-to-moderate, laboratory-confirmed COVID-19 symptoms from Jilin Province as the participants and examined the effect of JJXFCY granules on the clinical symptoms of patients. Our findings may help provide clinical evidence for the development of new drugs for the treatment of COVID-19 infection.

2. Materials and methods

2.1. Study design and randomization

After reviewing the literature regarding the treatment of the novel coronavirus using TCM, we hypothesize that the efficacy rate (p1) of the experimental group is 84.7%, while the efficacy rate (p2) of the control group is 60.1%. With a type I error rate (α) of 0.05, a type II error rate (β) of 0.2, and an experimental-to-control sample size ratio (k) of 1:1, we used the following formula to determine sample size:

$$n_2 = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \left[p_1 (1 - p_1)/k + p_2 (1 - p_2)\right]}{{p_1 - p_2}^2}, \quad n_1 = k * n_2$$
$$\text{and } z_{1-\alpha/2} = 1.96, \; z_{1-\beta} = 0.84.$$

Plugging in the given values and calculations, we determined that the sample size for the experimental group should be 48, and for the control group, it should be 48. Assuming a 20% potential dropout rate, we conclude that a minimum sample size of 60 is required for both the trial and control groups.

This randomized, open-label, positive-drug parallel-controlled trial was designed by the Department of Respiratory Medicine, Affiliated Hospital of Changchun University of Chinese Medicine (Jilin, China). The trial was conducted in accordance with the Declaration of Helsinki and relevant Chinese clinical research norms and regulations and approved by the institutional ethics committees (protocol No. JJCY-2022-NCOV-1.0). The study has been registered in the Chinese Clinical Trial Registry. Written informed consent was obtained from all participants. Safety oversight was performed by the sponsor and an independent data monitoring committee. Data collection was conducted by the investigators and site personnel, analysis was performed by statisticians employed by the sponsor, and interpretation of the results was done by the authors. The authors vouch for the accuracy, completeness, and fidelity of the trial to the protocol.

The study evaluating the safety and efficacy of JJXFCY granules in adults with COVID-19 was initiated in March 2022 when the first participant was screened. On the basis of the positive results from our analysis, all participants (target enrollment) were followed through day 28 (June 2022).

2.2. Eligible subjects

This study included adults with laboratory-confirmed SARS-CoV-2 infection no more than 72 hours after exhibiting at least 1 symptom of COVID-19 such as fever, cough, or fatigue. Exclusion criteria included patients with severe COVID-19, underlying diseases and complications, allergic constitution, psychopathology or lack of self-awareness, pregnancy, and unwillingness to use contraception during the intervention period and those deemed unsuitable for participation in the clinical trial. For further details, please refer to the Diagnosis and Treatment Protocol for COVID-19 (trial version 9) and World Health Organization guidance.[27,28]

2.3. Drug intervention process

JJXFCY is a TCM compound made into brown granules with a mild fragrance and bitter taste. It was produced by the Pharmaceutical Center of the Affiliated Hospital of Changchun University of Chinese Medicine (batch number: Z20221202) with a specification of 15 g per grid. The ingredients include *Bupleurum chinense* DC., *Schizonepeta tenuifolia* Eriq., *Saposhnikovia divaricata* (Turcz.) Schischk., *Ephedra sinica* Stapf, *Prunus armeniaca* L. var. ansu Maxim., *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch., *Scrophularia ningpoensis* Hemsl., *Pueraria lobata* (Willd.) Ohwi, *Notopterygium incisum* Ting exH. T. Chang, *Angelica dahurica* (Fisch, exHoffm.) Benth., *Gypsum fibrosum*, *Gardenia jasminoides* Ellis, *Anemarrhena asphodeloides* Bge., and *Forsythia suspensa* (Thunb.) Vahl. The drug quality standards for medicines comply with the provisions of Part I of the 2015 Edition of the Chinese Pharmacopoeia.

LHQW is a TCM compound composed of *F suspensa* (Thunb.) Vahl, *E sinica* Stapf, *Lonicera japonica* Thunb., *Isatis indigotica* Fortune, *Mentha haplocalyx* Briq., *Dryopteris crassirhizoma* Nakai, *Rhodiola rosea* L., *G Fibrosum*, *Pogostemon cablin* (Blanco) Benth., *Rheum palmatum* L., *Houttuynia cordata* Thunb., *G uralensis* Fisch., and *Armeniaca sibirica* (L.) Lam.[16,18] It was produced by Beijing Yiling Pharmaceutical Co Ltd (batch number: Z20100040) with a specification of 6 g per bag.

Both drugs are individually packaged brown particles with the same appearance. Set 2 types of drugs as 1 treatment cycle for 7 days and 4 cycles as the complete course of treatment. During the medication process, if the patient's symptoms improve, the medication can be stopped.

Participants were randomly assigned in a 1:1 ratio to receive either JJXFCY granules or LHQW granules, administered orally 3 times daily. Participants and investigators were

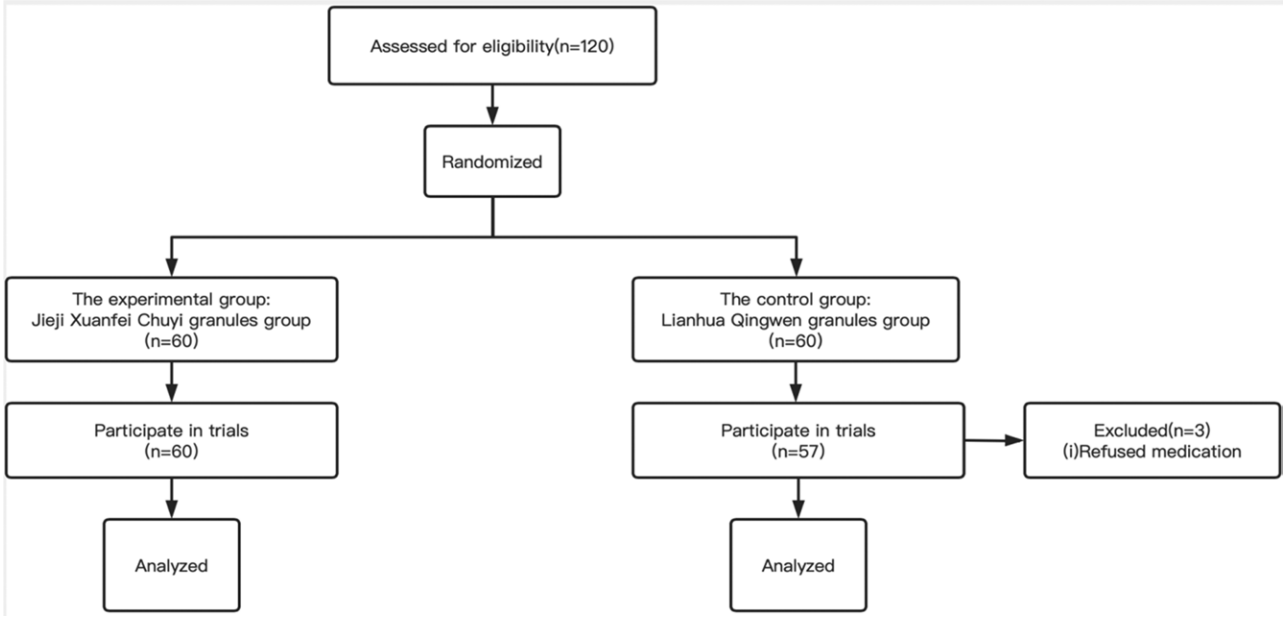

Figure 1. Flow diagram of study patients according to the consolidated standards of reporting trials for randomized controlled trials.

unaware of the treatment assignments until all actively enrolled participants had undergone the follow-up visit. Participants were monitored daily to record their medication status. A reverse transcription-PCR (RT-PCR) SARS-CoV-2 test was conducted after 7 consecutive days of medication. Medication was stopped when the RT-PCR SARS-CoV-2 test result was negative. Follow-up was conducted on the 14th and 28th days after drug withdrawal.

In accordance with guidelines, all patients were required to undergo unified isolation management and standard-of-care treatment. The patient's medication status was tracked daily throughout the treatment period. The use of any other treatments intended for COVID-19, including oral drugs such as antipyretic agents, anti-inflammatory agents, glucocorticoids, or a combination, was prohibited through day 28.

COVID-19 signs and symptoms were reported daily. Throat swabs were collected on days 7 (end-of-treatment visit), 14, and 28 for quantitation of SARS-CoV-2 RNA using a PCR assay at a central laboratory. Assessments of hospitalization status, length of hospital stay, vital signs, laboratory tests, and physical examinations were also performed on those days. Adverse events were assessed during the treatment period and for 14 days after the end of the treatment period. Data on serious adverse events considered by the investigator to be related to the assigned regimen were collected until the end of the study.

2.4. End points

The primary outcome was the time until the RT-PCR SARS-CoV-2 test was negative and the resolution of symptoms after 7 days of treatment. Secondary outcomes were the incidence of symptomatic respiratory infection (cough, pharyngitis, coryza, runny nose, myalgia, arthralgia, fever, or anosmia) with a positive test for SARS-CoV-2 by RT-PCR over a 28-day period. The efficacy end points were the incidence of a critical security incident (defined as ≥24 h of acute care in a hospital or any similar facility). The primary safety end point was the incidence of adverse events. Safety outcomes, including percentages of participants with adverse events, were evaluated in the safety population, which consisted of all participants who had undergone randomization and had received at least 1 dose of JJXFCY or LHQW granules.

2.5. Statistical analysis

The SAS V9.4 was used for statistical analysis. The 2-sided test was used, with $\alpha = 0.05$. Comparison of quantitative data between groups, such as the number of cases, mean, standard deviation, minimum, maximum, median, upper quartile, and lower quartile, was analyzed using *t* tests or Wilcoxon rank-sum tests. Covariance analysis was used to evaluate the influence of covariates. Comparison of qualitative data between groups, such as frequency tables, percentages, and constituent ratios, was performed using the Fisher exact test or the Wilcoxon rank-sum test. The Cochran-Mantel-Haenszel test and the logistic regression analysis were performed to evaluate the influence of confounding factors.

3. Results

3.1. Participants

A total of 120 participants were initially included and randomly assigned to the experimental group and the LHQW granules group in a 1:1 ratio. However, 3 participants in the LHQW group refused to take medication and withdrew from the study. Therefore, 117 participants from 4 sites in Jilin Province were enrolled (Figure 1; Table 1).

As shown in Table 1, the baseline demographic and clinical characteristics were generally similar in the 2 groups.

As shown in Table 2, in the JJXFCY granules group, participants reported cough (86.7%), expectoration (78.3%), fatigue (55%), nasal congestion (45%), sore throat (41.7%), muscle soreness (40%), runny nose (38.3%), chest tightness (35%), shortness of breath (31.7%), poor sleep (28.3%), loss of appetite (26.7%), dysgeusia (25%), fever (20%), olfaction disorder (20%), diarrhea (16.7%), emotional tension (16.7%), chills (15%), dry stool (10%), sticky stool (8.3%), nausea (5%), and vomit (3.3%). In the LHQW granules group, participants reported cough (86.7%), expectoration (80%), nasal congestion (59.6%), sore throat (47.4%), fatigue (46.7%), runny nose (38.6%), muscle soreness (35.1%), poor sleep (29.8%), shortness of breath (26.3%), dysgeusia (24.6%), emotional tension (22.8%), diarrhea (14.0%), chest tightness (14.0%), loss of appetite (14.0%), chills (14.0%), dry stool (10.5%), olfactory disorder (10.5%), fever (7.0%), nausea (7.0%), sticky stool

Table 1

Demographic of the participants at baseline.

Characteristic		Jieji Xuanfei Chuyi granules group (60)	Lianhua Qingwen granules group (60)	*P*
Sex	Female	23/60	22/60	.850
	Male	37/60	38/60	
Underlying disease		15/60	10/60	.261
Allergic history		1/60	7/60	.061
COVID-19 severity	Mild	54/60	52/60	.570
	Moderate	6/60	8/60	
Age	Mean ± SD	40.967 ± 13.844	41.150 ± 14.005	.943
	95% CI	37.390–44.543	37.532–44.768	
	Min–Max	20.000–72.000	18.000–69.000	
	Q1–Q3	31.750–50.500	30.000–51.500	
	Median	40	40	
Height	Mean ± SD	167.517 ± 8.740	168.500 ± 8.020	.522
	95% CI	165.259–169.774	166.428–170.572	
	Min–Max	150.000–190.000	150.000–183.000	
	Q1–Q3	160.000–174.000	163.500–175.000	
	Median	168	170	
Weight	Mean ± SD	68.275 ± 15.369	71.467 ± 14.447	.244
	95% CI	64.305–72.245	67.735–75.199	
	Min–Max	44.000–120.000	40.000–100.000	
	Q1–Q3	56.875–76.250	60.750–80.000	
	Median	67.75	70.5	
BMI	Mean ± SD	24.194 ± 4.467	25.095 ± 4.438	.270
	95% CI	23.040–25.348	23.949–26.242	
	Min–Max	17.578–34.928	16.955–36.731	
	Q1–Q3	21.011–26.760	22.287–27.770	
	Median	23.195	24.509	
Smoking history	0	39	46	.152
	Occasionally	6	3	
	<5	1	3	
	5–20 sticks	10	7	
	>20	4	1	

COVID-19 = coronavirus disease 2019, SD = standard deviation.

Table 2

Clinical characteristics of the participants at baseline.

	Jieji Xuanfei Chuyi granules group (60)		Lianhua Qingwen granules group (60)		
	None	Have	None	Have	*P*
Fever	48/60	12/60	56/60	4/60	.058
Cough	8/60	52/60	8/60	52/60	1.000
Fatigue	27/60	33/60	32/60	28/60	.361
Shortness of breath	41/60	19/60	45/60	15/60	.418
Diarrhea	50/60	10/60	52/60	8/60	.609
Muscle soreness	36/60	24/60	40/60	20/60	.449
Expectoration	13/60	47/60	12/60	48/60	.822
Sore throat	35/60	25/60	33/60	27/60	.713
Nasal congestion	33/60	27/60	26/60	34/60	.201
Runny nose	37/60	23/60	38/60	22/60	.850
Chest tightness	39/60	21/60	52/60	8/60	.006
Emotional tension	50/60	10/60	47/60	13/60	.487
Olfactory disorder	48/60	12/60	54/60	6/60	.125
Dysgeusia	45/60	15/60	46/60	14/60	.831
Chills	51/60	9/60	52/60	8/60	.793
Loss of appetite	44/60	16/60	52/60	8/60	.068
Nausea	57/60	3/60	56/60	4/60	1.000
Vomit	58/60	2/60	59/60	1/60	1.000
Sticky stool	55/60	5/60	59/60	1/60	.207
Dry stool	54/60	6/60	54/60	6/60	1.000
Poor sleep	43/60	17/60	43/60	17/60	1.000

(1.8%), and vomit (1.8%). The most common symptoms were cough, expectoration, nasal congestion, fatigue, and sore throat.

We compared and analyzed the changes in white blood cell count, lymphocyte count, and neutrophil count between the 2 groups before and after treatment (Table 3). The white blood cell counts, lymphocyte counts, and neutrophil counts of both groups before and after treatment were within the normal range.

3.2. Efficacy

As shown in Tables 4 and 5, after 7 days of treatment, the 7-day nucleic acid negative rate of the JJXFCY granules group was 68.3% (41 cases) and that of the LHQW granules group was 61.4% (35 cases). Excluding the participants without a definite positive time, the 7-day nucleic acid negative rate of the JJXFCY granules group was 65% (39 cases) and that of the LHQW granules group was 56.1% (32 cases). This indicates that both treatments influenced the nucleic acid negative rate of patients with COVID-19, and the effect of the JJXFCY granules may be slightly better than that of the LHQW granules.

As shown in Table 6, there was only a small difference between the 2 groups in terms of the number of hospital days and prehospital waiting time. This result suggests that JJXFCY granules had a comparable curative effect on patients with COVID-19 compared with LHQW granules.

As shown in Tables 7 and 8, after 7 days of treatment, both groups experienced relief of clinical symptoms to varying degrees, and the symptoms such as fever, nausea, vomiting, and sticky stool were all gone. In addition, the JJXFCY granules group reported the disappearance of diarrhea and muscle soreness on day 7, indicating that the JJXFCY granules may be preferable to the LHQW granules in regard to these symptoms.

After 15 days of treatment, ≈12 clinical symptoms were still present, including cough, fatigue, and shortness of breath, as shown in Table 9. The symptoms of muscle soreness and dry stool disappeared in the JJXFCY granules group, while the symptoms of emotional tension and olfactory disorder disappeared in

Table 3

White blood cell count, neutrophil count, and lymphocyte count of the participants at baseline.

		Jieji Xuanfei Chuyi granules group (60)		Lianhua Qingwen granules group (60)	
	N	Before therapy	After therapy	Before therapy	After therapy
White blood cell count	Mean ± SD	5.093 ± 1.609	6.357 ± 1.490	5.021 ± 1.540	6.106 ± 1.649
	95% CI	4.677–5.509	5.972–6.742	4.623–5.419	5.680–6.532
	Min–Max	2.520–9.520	4.020–11.410	2.030–9.350	2.170–10.080
	Q1–Q3	3.948–5.790	5.215–7.213	3.968–6.113	4.935–7.525
	Median	4.835	6.305	4.815	5.645
Lymphocyte count	Mean ± SD	1.805 ± 0.624	2.225 ± 0.605	1.882 ± 0.590	2.213 ± 0.674
	95% CI	1.644–1.966	2.068–2.381	1.729–2.034	2.039–2.387
	Min–Max	0.770–3.580	0.690–3.770	0.840–3.290	0.810–3.930
	Q1–Q3	1.358–2.183	1.823–2.650	1.420–2.315	1.808–2.670
	Median	1.67	2.125	1.775	2.125
Neutrophil count	Mean ± SD	2.749 ± 1.228	3.538 ± 1.114	2.634 ± 1.100	3.256 ± 1.226
	95% CI	2.432–3.066	3.250–3.826	2.350–2.918	2.939–3.572
	Min–Max	0.790–6.480	1.560–7.090	0.720–6.180	0.800–6.840
	Q1–Q3	1.798–3.388	2.788–4.243	1.800–3.133	2.448–4.103
	Median	2.6	3.455	2.45	2.965

SD = standard deviation.

Table 4

Seven-day nucleic acid negative rate of the participants

	Jieji Xuanfei Chuyi granules group (60)		Lianhua Qingwen granules group (57)		*P*
Nucleic acid negative rate	Negative 41/60	Positive 19/60	Negative 35/57	Positive 22/57	0.432

Table 5

Seven-day nucleic acid negative rate of the participants after correction.

	Jieji Xuanfei Chuyi granules group (60)		Lianhua Qingwen granules group (57)		*P*
Nucleic acid negative rate	Negative 39/60	Positive 19/60	Negative 32/57	Positive 22/57	.381

the LHQW granules group. There was no significant difference in other lasting clinical symptoms ($P > .05$). Both drugs have significant therapeutic effects on COVID-19.

Analysis of the continuation of clinical symptoms revealed no statistically significant difference between the 2 groups ($P > .05$). This indicates that JJXFCY granules have a therapeutic effect in the treatment of mild and common cases of COVID-19, effectively reducing the persistence of symptoms. Furthermore, the effect of JJXFCY granules on cough and sputum may be more effective than that of LHQW granules (Table 10).

3.3. Safety

Evaluation of the laboratory test results of liver and renal function of the 2 groups showed that the creatinine expression of 1 participant in the JJXFCY granules group was abnormal. This participant's creatinine index was normal before entering the group but decreased after the end of the medication.

In terms of liver function, alanine aminotransferase (ALT) of 4 cases in the JJXFCY granules group was higher than the normal value before and after admission; aspartate aminotransferase was abnormal in 1 case, which was normal before entering the group and showed a slight increase after leaving the group. γ-glutamyl transpeptidase expression of 2 participants was higher than the normal value before and after enrollment; indirect bilirubin level in 2 participants was high before and after enrollment; and total bilirubin was abnormal in 3 participants, with 2 showing a higher level both before and after enrollment and one having a slight increase. In the LHQW granules group, there were 4 cases with abnormal ALT, with 3 cases higher than the normal value and 1 case being normal before entering the group, but with an increase in ALT after leaving. The γ-glutamyl transpeptidase of 1 participant was higher than the normal value, and the other participant showed an increase after leaving the group. One participant showed high expression of indirect bilirubin before and after enrollment; total bilirubin was abnormal in 2 participants, with one having a higher level before and after enrollment and the other having a small increase after taking the drug.

During the observation period, there were no reported deaths or other adverse reactions in either group (Table 11).

4. Discussion

4.1. Analysis of research results

The COVID-19 (Omicron BA.2) pandemic in Jilin has seen a significantly greater total number of people infected but a much lower severity and mortality rate in comparison with previous outbreaks of the Delta virus strain.[29] This phenomenon has also been observed in various other regions. Numerous studies and data indicate that Omicron has caused more widespread infections yet fewer critical cases or fatalities. The ongoing outbreak and large population base have put a strain on the healthcare system. TCM may be a viable option to reduce the duration of the disease and prevent the disease from progressing to a severe stage.

In this study, 120 patients with COVID-19 (Omicron BA.2) were enrolled, with 117 completing the clinical trial. Three subjects in the control group withdrew from the trial due to refusal of medication. Data analysis revealed that the median age of patients with Omicron BA.2 in the Jilin area was 40 years, mainly consisting of young and middle-aged individuals. Clinical classification of patients with Omicron BA.2 was a mild and common disease, with many patients presenting asymptomatic or mild symptoms, such as cough, phlegm, fatigue, sore throat, nasal congestion, and runny nose. A previous study noted that the 2 most prevalent symptoms in Delta cases (regardless of vaccination status) were sore throat and hoarseness, suggesting that the symptoms of Omicron infection are different from those of

Table 6

Time-to-event analysis of hospitalization days and prehospital waiting time.

	N	Jieji Xuanfei Chuyi granules group (60)	Lianhua Qingwen granules group (57)	*P*
Hospital day	Mean ± SD	9.583 ± 2.670	9.579 ± 1.841	.429
	95% CI	8.894–10.273	9.090–10.068	
	Min–Max	7.000–23.000	7.000–14.000	
	Q1–Q3	8.000–10.000	8.000–10.000	
	Median	9	10	
Prehospital waiting time	Mean ± SD	1.900 ± 1.374	2.105 ± 1.277	.391
	95% CI	1.545–2.255	1.766–2.444	
	Min–Max	0.000–8.000	0.000–5.000	
	Q1–Q3	1.000–2.000	1.000–3.000	
	Median	2	2	

SD = standard deviation.

the Delta SARS-CoV-2 variant.[30] Other studies using[31] sample matching found that the prevalence of other symptoms, such as olfactory disorders and taste disorders, was significantly lower during the Omicron epidemic than during the Delta epidemic, with the median number of symptoms in the Omicron epidemic group being lower than that in the Delta epidemic group. This indicates that the most significant difference between the 2 virus strains is anosmia. Cough, sputum, and fatigue were prominent features of early Omicron BA.2 infection, while olfactory disturbances were a feature of the early SARS-CoV-2 infection, occurring in <20% of cases during the Omicron BA.2 epidemic. Symptoms such as burning eyes, dizziness, fever, and headache were no longer common in Omicron Ba.2.

In this study, we assessed changes in white blood cell count, lymphocyte count, and neutrophil count before and after treatment and found that both groups had values within the normal range before and after treatment, with a small degree of increase after treatment. This indicated that both treatments had a statistically significant effect on the 3 counts, without leading to an increase in severity. Lymphocyte count and percentage of lymphocytes and/or neutrophils are common indicators used to evaluate severe cases. Our results indicate that this epidemic is largely comprised of common and mild cases.

After 7 days of treatment, the 4 symptoms of fever, nausea, vomiting, and sticky stool in the JJXFCY group all disappeared on the seventh day, indicating that JJXFCY granules have a similar therapeutic effect as LHQW granules when treating mild and common cases of COVID-19. Furthermore, the time to achieve a negative test on day 7 was faster in the JJXFCY group compared with the LHQW group. This suggests that the JJXFCY granule treatment has a faster effect than the LHQW granule treatment; this trend was also observed in the comparison of hospital days.

Analysis of the 7-day symptom disappearance between the 2 groups revealed that the difference was relatively small and not statistically significant. However, the symptoms of diarrhea and muscle soreness in the JJXFCY granules group vanished by the seventh day of application. In addition, the number of cases with cough, sore throat, phlegm, nasal congestion, runny nose, cold, dry stool, and poor sleep was significantly lower in the JJXFCY granules group than in the LHQW granules group. This may imply that JJXFCY granules may have a better therapeutic effect on the above symptoms compared with LHQW granules.

We examined the presence of any positive symptoms after 15 days of treatment and found that the majority of symptoms of the 2 groups of patients were relieved or cured. The number of patients with persistent symptoms was significantly reduced compared, and the remaining symptoms were mainly cough, phlegm, and nasal congestion. This confirms that COVID-19 mainly affects the lungs and respiratory organs and has a significant and prolonged impact on respiratory function. On the 15th day of follow-up, the symptoms of dry stool in the JJXFCY group also disappeared.

At the follow-up on the 28th day after treatment, some patients still had symptoms such as coughing, shortness of breath, phlegm, a runny nose, and poor sleep. The poor sleep symptoms were all relieved in the JJXFCY granules group, suggesting that JJXFCY granules can effectively reduce the persistence of COVID-19 symptoms and significantly improve patient outcomes. After the experiment, we conducted telephone follow-up on 2 groups of patients, The nucleic acid repositive rate of JJXFCY granules was 6.67%, and the nucleic acid repositive rate of JJXFCY granules was 7.02%. No aggravation or mortality was observed, further verifying the virus-eliminating ability of the Omicron BA-2 variant strain by JJXFCY granules.

LHQW granules have the effects of clearing plague and detoxifying, promoting lung circulation and relieving heat, and are widely used to treat patients with heat toxins attacking the lungs during influenza virus colds. In combination with the drug composition and composition analysis of JJXFCY granules, we believe that JJXFCY granules have the effects of relieving muscle and fever, clearing lungs and resolving phlegm, and resisting epidemic toxin. It can also be used in mild and medium-sized patients with COVID-19, and JJXFCY granules may have a better therapeutic effect on the symptoms as relieving patients' cough, sore throat, phlegm, nasal congestion, runny nose, cold, dry stool, and poor sleep. Therefore, we recommend that patients with the above symptoms consider using JJXFCY granules.

By comparing the clinical efficacy of JJXFCY granules and LHQW granules in the treatment of mild and medium-sized patients with COVID-19, exploring the effectiveness and safety of JJXFCY granules will help guide clinical prescription drug use, increase the proportion of TCM in guiding the treatment of novel coronavirus pneumonia, increase multiple drug use choices for patients, and also provide a certain demonstration for domestic similar research.

4.2. Clinical research on the treatment of COVID-19 with TCM

Highly pathogenic and fatal infectious diseases were called "plagues" or "Wen diseases" in ancient China. TCM has been successful in treating pandemics, endemic diseases, and other infectious diseases throughout history, and a complete theoretical system for the prevention and treatment of "plague" has been established.[32]

The direct cause of the COVID-19 epidemic is the SARS-CoV-2 (Omicron variant BA.2) virus. COVID-19 is classified as a "cold and dampness epidemic" according to the climatic characteristics and symptoms of lung and spleen qi deficiency and excessive cold and dampness. Clinical manifestations of COVID-19 include fever, fatigue, unproductive cough, sore throat, dyspnea, myalgia, fatigue, normal or decreased white blood cell count, and radiation changes of pneumonia. It can also cause multiple organ dysfunction, such as shock, acute respiratory distress syndrome, acute heart injury, and acute kidney injury, leading to death.[33–35]

Studies have confirmed the role of TCM in preventing and treating COVID-19. A female patient in Guizhou Province, China, was discharged after 12 days of combined Western antiviral drugs and oral Chinese herbal treatment.[36] A family of 3 recovered quickly with antiviral/antibiotic Western medicine and Shuanghuanglian oral liquid.[37] In a study of 160 severe COVID-19 cases, the combination of TCM and Western medicine resulted in quicker absorption of lung lesions, shorter intervals from admission to negative RT-PCR (acute tubular necrosis) test results, and lower medical costs. The combined

Table 7

Comparison of days of symptom disappearance in the participants on day 7.

		Jieji Xuanfei Chuyi granules (60)	Lianhua Qingwen granules (57)	*P*
Fever	N	14	8	.153
	Mean ± SD	2.500 ± 0.855	2.000 ± 1.414	
	95% CI	2.006–2.994	0.818–3.182	
	Min–Max	1.000–4.000	1.000–5.000	
	Q1–Q3	2.000–3.000	1.000–2.250	
	Median	3	1.5	
Cough	N	29	21	.801
	Mean ± SD	4.276 ± 1.251	4.095 ± 1.729	
	95% CI	3.800–4.752	3.308–4.882	
	Min–Max	1.000–6.000	1.000–6.000	
	Q1–Q3	4.000–5.000	3.000–6.000	
	Median	4	4	
Fatigue	N	23	17	.560
	Mean ± SD	3.739 ± 1.630	3.412 ± 1.734	
	95% CI	3.034–4.444	2.520–4.303	
	Min–Max	1.000–6.000	1.000–6.000	
	Q1–Q3	3.000–5.000	2.000–5.000	
	Median	4	3	
Shortness of breath	N	16	13	.346
	Mean ± SD	3.563 ± 1.548	3.000 ± 1.528	
	95% CI	2.738–4.387	2.077–3.923	
	Min–Max	1.000–6.000	1.000–5.000	
	Q1–Q3	2.750–5.000	2.000–4.000	
	Median	3.5	3	
Diarrhea	N	10	5	.329
	Mean ± SD	2.800 ± 1.229	2.200 ± 0.837	
	95% CI	1.921–3.679	1.161–3.239	
	Min–Max	1.000–5.000	1.000–3.000	
	Q1–Q3	2.250–3.000	2.000–3.000	
	Median	3	2	
Muscle soreness	N	22	16	1.000
	Mean ± SD	2.864 ± 1.125	3.000 ± 1.414	
	95% CI	2.365–3.363	2.246–3.754	
	Min–Max	1.000–5.000	1.000–6.000	
	Q1–Q3	2.000–4.000	2.000–4.000	
	Median	3	2.5	
Expectoration	N	25	21	.671
	Mean ± SD	3.480 ± 1.806	3.238 ± 1.758	
	95% CI	2.735–4.225	2.438–4.038	
	Min–Max	1.000–7.000	1.000–6.000	
	Q1–Q3	2.000–5.000	2.000–5.000	
	Median	3	3	
Sore throat	N	20	19	.677
	Mean ± SD	3.200 ± 1.609	3.000 ± 1.333	
	95% CI	2.447–3.953	2.357–3.643	
	Min–Max	1.000–6.000	1.000–5.000	
	Q1–Q3	1.750–4.250	2.000–4.000	
	Median	3	3	
Nasal congestion	N	20	21	.979
	Mean ± SD	3.350 ± 1.461	3.381 ± 1.465	
	95% CI	2.666–4.034	2.714–4.048	
	Min–Max	1.000–6.000	1.000–6.000	
	Q1–Q3	2.750–4.250	2.000–4.000	
	Median	3	3	
Runny nose	N	19	13	1.000
	Mean ± SD	2.947 ± 1.079	3.077 ± 1.847	
	95% CI	2.427–3.467	1.961–4.193	
	Min–Max	1.000–5.000	1.000–6.000	
	Q1–Q3	2.000–4.000	1.000–4.000	
	Median	3	3	
Chest tightness	N	14	5	.154
	Mean ± SD	3.071 ± 1.639	4.000 ± 0.707	
	95% CI	2.125–4.018	3.122–4.878	
	Min–Max	1.000–6.000	3.000–5.000	
	Q1–Q3	2.000–4.000	4.000–4.000	
	Median	3	4	
Emotional tension	N	7	12	.409
	Mean ± SD	3.143 ± 1.215	2.583 ± 1.782	
	95% CI	2.019–4.267	1.451–3.715	
	Min–Max	1.000–5.000	1.000–6.000	
	Q1–Q3	3.000–3.500	1.000–4.000	
	Median	3	2	
Olfactory disorder	N	8	3	.906
	Mean ± SD	3.500 ± 1.309	3.333 ± 0.577	
	95% CI	2.405–4.595	1.899–4.768	
	Min–Max	2.000–6.000	3.000–4.000	
	Q1–Q3	3.000–3.500	3.000–3.500	
	Median	3	3	
Dysgeusia	N	8	7	.556
	Mean ± SD	3.375 ± 0.744	3.000 ± 1.291	
	95% CI	2.753–3.997	1.806–4.194	
	Min–Max	3.000–5.000	1.000–5.000	
	Q1–Q3	3.000–3.250	2.500–3.500	
	Median	3	3	
Chills	N	8	7	.172
	Mean ± SD	3.250 ± 1.389	2.143 ± 1.676	
	95% CI	2.089–4.411	0.593–3.693	
	Min–Max	1.000–5.000	1.000–5.000	
	Q1–Q3	2.750–4.250	1.000–3.000	
	Median	3	1	
Loss of appetite	N	13	5	.225
	Mean ± SD	3.154 ± 1.405	4.000 ± 1.871	
	95% CI	2.305–4.003	1.677–6.323	
	Min–Max	1.000–6.000	1.000–6.000	
	Q1–Q3	3.000–4.000	4.000–5.000	
	Median	3	4	
Nausea	N	2	1	.540
	Mean ± SD	3.500 ± 0.000	1.000 ± 0.000	
	95% CI	0.000–0.000	0.000–0.000	
	Min–Max	2.000–5.000	1.000–1.000	
	Q1–Q3	2.750–4.250	1.000–1.000	
	Median	3.5	1	
Vomit	N	4	1	.468
	Mean ± SD	3.500 ± 1.291	5.000 ± 0.000	
	95% CI	1.446–5.554	0.000–0.000	
	Min–Max	2.000–5.000	5.000–5.000	
	Q1–Q3	2.750–4.250	5.000–5.000	
	Median	3.5	5	
Sticky stool	N	4	1	.468
	Mean ± SD	3.500 ± 1.291	5.000 ± 0.000	
	95% CI	1.446–5.554	0.000–0.000	
	Min–Max	2.000–5.000	5.000–5.000	
	Q1–Q3	2.750–4.250	5.000–5.000	
	Median	3.5	5	
Dry stool	N	5	4	.526
	Mean ± SD	2.400 ± 1.517	3.250 ± 1.708	
	95% CI	0.517–4.283	0.532–5.968	
	Min–Max	1.000–4.000	1.000–5.000	
	Q1–Q3	1.000–4.000	2.500–4.250	
	Median	2	3.5	
Poor sleep	N	12	10	.866
	Mean ± SD	3.333 ± 1.435	3.400 ± 1.578	
	95% CI	2.421–4.245	2.271–4.529	
	Min–Max	1.000–5.000	1.000–5.000	
	Q1–Q3	2.750–4.250	2.250–4.750	
	Median	3.5	4	

treatment proved helpful in recovery and reduced the economic burden on patients.[38]

Studies have shown that TCM can effectively guide the treatment of COVID-19. A clinical study on 214 confirmed cases treated with Qingfei Jiedu decoction revealed a 90% overall response rate, with over 60% of symptoms improving and

Table 8

Analysis of clinical symptom improvement on day 7.

Symptom		Jieji Xuanfei Chuyi granules group (60)	Lianhua Qingwen granules group (57)	*P*
Cough	Disappear	41	30	.234
	Relief	17	25	
	Remain	0	1	
	Worsening	2	1	
Fatigue	Disappear	55	54	1.000
	Relief	5	3	
	Remain	0	0	
	Worsening	0	0	
Shortness of breath	Disappear	56	55	.597
	Relief	3	1	
	Remain	0	0	
	Worsening	0	1	
Diarrhea	Disappear	60	56	1.000
	Relief	0	0	
	Remain	0	1	
	Worsening	0	0	
Muscle soreness	Disappear	60	56	1.000
	Relief	0	1	
	Remain	0	0	
	Worsening	0	0	
Expectoration	Disappear	37	31	.741
	Relief	20	23	
	Remain	0	2	
	Worsening	3	1	
Sore throat	Disappear	57	49	.099
	Relief	2	5	
	Remain	1	2	
	Worsening	0	1	
Nasal congestion	Disappear	53	47	.740
	Relief	5	10	
	Remain	2	0	
	Worsening	0	0	
Runny nose	Disappear	58	52	.132
	Relief	2	3	
	Remain	0	1	
	Worsening	0	1	
Chest tightness	Disappear	53	55	.061
	Relief	4	2	
	Remain	1	0	
	Worsening	2	0	
Emotional tension	Disappear	57	56	.739
	Relief	3	0	
	Remain	0	1	
	Worsening	0	0	
Olfactory disorder	Disappear	55	54	.304
	Relief	3	3	
	Remain	2	0	
	Worsening	0	0	
Dysgeusia	Disappear	55	53	.848
	Relief	4	3	
	Remain	1	1	
	Worsening	0	0	
Chills	Disappear	59	56	1.000
	Relief	1	1	
	Remain	0	0	
	Worsening	0	0	
Loss of appetite	Disappear	56	56	.507
	Relief	4	0	
	Remain	0	0	
	Worsening	0	1	
Dry stool	Disappear	59	56	1.000
	Relief	1	1	
	Remain	0	0	
	Worsening	0	0	
Poor sleep	Disappear	55	53	.680
	Relief	4	1	
	Remain	0	1	
	Worsening	1	2	

Table 9

Analysis of lasting clinical symptoms on day 15.

	Jieji Xuanfei Chuyi granules group (60)	Lianhua Qingwen granules group (57)	*P*
Cough	10/60	13/57	.404
Fatigue	1/60	2/57	.612
Shortness of breath	1/60	2/57	.612
Muscle soreness	0/60	1/57	.487
Expectoration	12/60	9/57	.553
Sore throat	3/60	2/57	1.000
Stuffy nose	5/60	1/57	.207
Runny nose	1/60	2/57	.612
Chest tightness	1/60	1/57	1.000
Emotional tension	1/60	0/57	1.000
Olfactory disorder	1/60	0/57	1.000
Dysgeusia	1/60	1/57	1.000
Loss of appetite	1/60	1/57	1.000
Dry stool	0/60	1/57	.487
Poor sleep	1/60	2/57	.612

Table 10

Analysis of lasting clinical symptoms on day 28.

	Jieji Xuanfei Chuyi granules group (60)	Lianhua Qingwen granules group (57)	*P*
Cough	2/60	3/57	.677
Shortness of breath	1/60	1/57	1.000
Expectoration	1/60	3/57	.356
Runny nose	1/60	0/57	1.000
Poor sleep	0/60	1/57	.487

30% remaining stable without worsening.[39] Cold-Dampness Epidemic Prescription was applied to 2 groups of mild-to-moderate COVID-19 cases and resulted in a significant decrease in the number of severe cases.[40] Another study reported a female diabetic and hepatitis B carrier who, after 7 days of Western medicine treatment, had negative nucleic acid tests but large sheets of glass shadows in her lungs. With TCM treatment for 6 days, reexamination of chest computed tomography showed that most of the bilateral lung lesions had been resolved.[35]

TCM intervention is beneficial for the prevention and rehabilitation of patients with COVID-19. A clinical study randomly assigned 22,065 community residents to an intervention and nonintervention group.[41] The intervention group received TCM prophylaxis (Huoxiang Zhengqi Oral Liquid and Jinhao Jiere granules), and the results showed that the cold incidence of the intervention group (91.8%) was significantly lower than that of the nonintervention group. This was especially true for those aged 16 to 60 years (95.0%). TCM intervention effectively protects community residents from respiratory diseases such as colds, with a low rate of adverse events and reactions.

A comparison of patients with COVID-19 treated with TCM in Jiangxi Mobile Cabin Hospital and those treated with Western medicine in Bridgekou Mobile Cabin Hospital showed no deterioration in the former group, while 10% of the latter group had repeated and worsened conditions.[42] This suggests that TCM can effectively prevent the deterioration of COVID-19.[43] A total of 300 patients with mild-to-moderate COVID-19 were randomly divided into a Jin Yin Hua KouFuYe group and a Western medicine treatment group. The serious disease rate for the Jin Yin Hua KouFuYe group was 0% compared with 4.22% for the Western medicine treatment group, indicating that TCM can block the progression of COVID-19 and reduce severe COVID-19 incidence.[44] Meta-analysis has also supported these conclusions.[45]

Table 11

Incidence of adverse events in the safety population.

	Renal function	Liver function				
	CREA	ALT	AST	GGT	IBIL	TBIL
Jieji Xuanfei Chuyi granules group (60)	1 (1.67%)	4 (6.67%)	1 (1.67%)	2 (3.33%)	2 (3.33%)	3 (5%)
Lianhua Qingwen granules group (57)	0	4 (7.02%)	0	2 (3.51%)	1 (1.75%)	2 (3.51%)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CREA = creatinine, GGT = γ-glutamyl transpeptidase, IBIL = indirect bilirubin, TBIL = total bilirubin.

4.3. Advantages/limitations

The effective time of drug intervention and safety are 2 key parameters of drug selection and application.[46] JJXFCY granules, an oral drug, have shown significant anti-SARS-COV-2 efficacy, tolerance, and safety in clinical application. In this study, clinical symptoms were relieved 7 days after early application of JJXFCY granules, with fever, nausea, vomiting, and stool sticky symptoms disappearing. The 7-day conversion rate was 68.3%, while the nucleic acid repositive rate was 6.67%. This indicates that JJXFCY granules may shorten the time of virus clearance.

This randomized, open-label, positive-drug parallel control study explored the effectiveness and safety of JJXFCY granules compared with LHQW granules in the treatment of mild and common cases of COVID-19. Our findings may guide clinical prescription medication, improve the application of TCM in treating COVID-19, and provide evidence for similar research in China.

This study has several limitations. First, due to the large number of patients and the severe shortage of medical staff, laboratory tests (e.g., blood tests and radiology) were not done on all patients, and C-reactive protein and computed tomography data of some patients were missing. Therefore, this study mainly summarized the diagnosis and treatment of patients with COVID-19 (Omicron variant BA.2) in mobile cabin hospitals and evaluated the effectiveness and safety of JJXFCY granules in this regard. Second, the sample size was relatively small; most of the patients had mild-to-common clinical presentation, and there were no deteriorations or deaths. Thus, further large-scale multicenter research is needed to evaluate the effects and safety of JJXFCY granules in treating severe cases. Third, there was little difference between the results of the 2 granules after statistical analysis. It is important to establish a solid theoretical system of scientific knowledge to verify the effectiveness of TCM treatment.

5. Conclusion

JJXFCY granules have the same efficacy as LHQW granules in treating patients with mild and common COVID-19, with no adverse reactions. JJXFCY intervention not only effectively reduces the persistence of COVID-19 symptoms and significantly improves patient prognoses but also reduces the risk of hospitalization or death in adults with COVID-19.

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