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ORIGINAL RESEARCH

Efficacy and Safety of Longyizhengqi Granule in Treatment of Mild COVID-19 Patients Caused by SARS-CoV-2 Omicron Variant: A Prospective Study

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Purpose: This study aimed to evaluate the clinical efficacy of Longyizhengqi granule, a traditional Chinese medicine, in patients with mild COVID-19.

Patients and Methods: We conducted a prospective study including mild COVID-19 participants conducted at Mobile Cabin Hospital in Shanghai, China. Participants were assigned to receive Longyizhengqi granule or conventional treatment. The primary outcome was the time for nucleic acid to turn negative and the secondary outcomes are hospital stay and changes in cycle threshold (Ct) values for N gene and Orf gene. Multilevel random-intercept model was performed to analyze the effects of treatment.

Results: A total of 3243 patients were included in this study (Longyizhengqi granule 667 patients; conventional treatment 2576 patients). Age (43.5 vs 42.1, p<0.01) and vaccination doses (not vaccinated: 15.8% vs 21.7%, 1 dose: 3.5% vs 2.9%, 2 doses: 27.9% vs 25.6%, 3 doses: 52.8% vs 49.8%. p<0.01) show statistical difference between Conventional treatment group and LYZQ granules group. The use of Longyizhengqi granule could significantly reduce the time for nucleic acid to turn negative (14.2 days vs 10.7 days, p<0.01), shorten hospital stay (12.5 days vs 9.9 days, p<0.01), and increase the changes in Ct value for N gene (8.44 vs 10.33, p<0.01) and Orf gene (7.31 vs 8.44, p<0.01) to approximately 1.5. Moreover, the difference in the changes of Ct values on the 4th, 6th, 8th, and 10th days seem to increase between two groups. No serious adverse events were reported.

Conclusion: Longyizhengqi granule might be a promising drug for the treatment of mild COVID-19, and it might be beneficial to effectively shorten the negative transition time of nucleic acid, the total days of hospitalization, and increase the changes of Ct values. Long-term randomized controlled trials with follow-up evaluations are required to confirm its long-term efficacy.

Keywords: COVID-19, Omicron variant, traditional Chinese medicine, prospective study

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become the most serious major global infectious disease of the twenty-first century. According to the data of the World Health Organization (WHO), as of June 20, 2022, more than 536 million confirmed cases and 6.3 million deaths have been reported globally.[1] SARS-COV-2 is mutating rapidly, with Alpha, Beta, Delta, Omicron, and other variants emerging. The Omicron variant was originally reported in South Africa in November 2021 and infected approximately 300 million people worldwide in just a few months, becoming the dominant variant in the fourth wave of the global COVID-19 pandemic.[2] The Omicron variant was first detected in China in December 2021 and rapidly spread since the end of

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February 2022, causing the largest outbreak in recent years.[3] The Omicron variant has high infectivity, fast transmission speed, strong immune evasion ability, and high concealment, but the virulence is relatively weakened, so the clinical symptoms are relatively mild.[4–7] More than 600,000 positive infections have been found in Shanghai, China, of which < 5% are severe cases.[8]

According to the Diagnosis and Treatment Guideline for COVID-19 (Trial 9th Edition)[9] released by the National Health Commission of the People's Republic of China (simplified as "Guideline" in our study), antiviral drugs not only are expensive but also have strict indications and cannot be widely used. For example, Paxlovid has been authorized for emergency use by the Food and Drug Administration (FDA) under an Emergency Use Authorization. Moreover, the "Guideline" also recommends the use of traditional Chinese medicine (TCM) during the process of treating COVID-19 cases. In previous studies, some TCM, such as Qingfei Paidutang[10] and Lianhua Qingwen,[11,12] have achieved good therapies in the treatment of confirmed COVID-19 cases, and the positive effect of TCM was accepted to a large degree. On April 6, 2022, the WHO clearly affirmed the efficacy and safety of TCM in the treatment of COVID-19 and encouraged WHO Member States to consider the possibility of using TCM in the treatment of COVID-19 within their healthcare systems and regulatory frameworks.[13] The Longyizhengqi granule (LYZQ granule, Wanshicheng Pharmaceutical Co., Ltd, Shanghai, China, Batch), a classical TCM with long history in Longhua hospital, has been previously used to treat mild influenza virus. At present, no research on the clinical efficacy of LYZQ granule has been published, but on March 30, 2022, at the 138th press conference on the prevention and control of COVID-19 in Shanghai, LYZQ granule was recommended for the treatment and prevention of COVID-19.[14] LYZQ granule was hypothesized to be effective in the treatment of COVID-19, also as a respiratory disease with clinical symptoms of the mild Omicron variant like a "big flu"; hence, it was recommended in the treatment of mild COVID-19 cases during the Omicron outbreak in China. However, clinical evidence on its efficacy and safety is lacking.

Therefore, this prospective study was conducted to confirm the efficacy and safety of LYZQ granule in the treatment of patients with mild COVID-19 caused by the Omicron variant and provide clinical evidence for future treatment of COVID-19 using the LYZQ granule.

Materials and Methods

Study Design and Patients

The open, non-blind, cluster-randomized, prospective study was conducted at mobile cabin hospitals in Tianhua road, Jinshan District, Shanghai municipality, China from April 16 to May 15, 2022 (please see the SPIRIT Checklist). It included four mobile cabin hospitals (A, B, C, D), in which A and D were managed by Tongji Hospital, affiliated with Shanghai University of Tongji and B and C were managed by Longhua Hospital, affiliated with Shanghai University of Traditional Chinese Medicine.

Patients who had a diagnosis of clinically definite diagnosis of mild COVID-19 and aged at least 14 years at the time of diagnosis were included in this study. The diagnostic criteria for suspected and diagnosed COVID-19 cases were based on the "Guideline". A positive nucleic acid test of the COVID-19 was the primary criterion for diagnosis. Viral load was measured using cycle threshold (Ct) values. Mild cases were defined as a positive nucleic acid test (Ct<35) and mild clinical symptoms with no signs of pneumonia on imaging. Moreover, patients with clinical manifestations, such as fever and/or respiratory symptoms and imaging findings of pneumonia, were considered moderate cases. Adults who meet any of the following criteria were considered as severe cases: 1) shortness of breath, respiratory rate ≥30 times/min; 2) oxygen saturation ≤93% at rest on room air; 3) arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0. 133 kPa); and 4) progressively aggravating clinical symptoms and lung imaging showing significant lesion progression > 50% within 24–48h. Patients who had one of the conditions of respiratory failure and requiring mechanical ventilation, shock, and other organ failure requiring ICU care were considered fatal cases. In our study, patients who did not meet the inclusion criteria were excluded.

The treatment was in accordance with the "Guideline". In the entire hospital stay, patients from Mobile Cabin Hospitals A and D received conventional treatment, while patients from Mobile Cabin Hospitals B and C received LYZQ granule (5g, b.i.d) (see Figure S1, Table S1 for the detailed introduction on the components and production of LYZQ

granule) besides conventional treatment. The drugs were uniformly distributed by the nurses in the mobile cabin hospitals. If the patient is allergic or intolerant to the drugs, the test would be stopped immediately. Conventional treatment included rest in bed, strengthening supportive treatment, close monitoring of vital signs, and specified effective oxygenation measures. Based on the attending physician's judgment, participants would be allowed to use Tylenol (Johnson& Johnson Pharmaceutical Co., Ltd, Shanghai, China, one table, every 4–6 hours) or Lianhuaqingwen capsule (YiLing Pharmaceutical Co. Ltd., Shijiazhuang, China, four tables, t.i.d) if their body temperature was > 38.5°C. Nucleic acid tests, including throat and nose swabs, were performed on the second day of admission for each patient and repeated every other day.

The discharge criterion of patients was as follows: the Ct values of N gene and ORF gene (test kit: Siludi, Shanghai, China; testing instrument: Bioer Technology Co., Ltd, Hangzhou, China) detected by novel coronavirus nucleic acid for two consecutive times were ≥ 35 (the sampling time interval should be at least 24h).

The study was approved by the Ethics Committee of Longhua Hospital for TCM (approval number 2022LCSY020) and registered with the China Clinical Trial Registration Center (registration number, ChiCTR2200059738).

Data Collection

Routinely collected data of hospitalized patients were retrieved from existing electronic health records (integrated electronic medical record of the Shanghai centralized admission center), including epidemiological, demographic, clinical, laboratory, and medical records. All data were double checked by two physicians (WM and SJ) who are in charge of treatment.

Outcomes

The primary outcome of this study was the time for nucleic acid to turn negative, defined as the duration from the day a patient first showed positive nucleic acid test to the day of negative nucleic acid test. Secondary outcomes included hospital days (defined as the total time of stay in the mobile cabin hospital) and changes in Ct values (defined as Day 8 Ct values minus Day 2 Ct values). Adverse events would be considered during the trial.

Statistical Analysis

We described the demographic characteristics of patients in the LYZQ granule group and conventional treatment group in the beginning, including age, sex, ethnicity, and underlying diseases. Continuous variables were reported as mean ± standard deviation, and categorical variables were presented as numbers with percentages. Two independent samples *t*-test or chi-square test were used for comparisons between groups.

Multilevel random-intercept models were used to assess the effect of treatments by considering the group effect of different mobile cabin hospital and potential confounding factors. Models for the time for nucleic acid to turn negative were adjusted for age and vaccination dose, while for hospital days and changes in Ct values, age, vaccination dose, and positive days before admission were adjusted.

All statistical analyses were performed using SAS software (v.9.4; SAS Institute, Cary, NC, USA), and a p-value < 0.05 was considered statistically significant.

Results

Data at Baseline

3243 confirmed patients were eligible, covering all districts of Shanghai. Of the enrolled population, 667 patients were classified in the LYZQ granule group, and 2576 patients were classified in the conventional treatment group. Most participants are male and ethnic Han and had hypertension and diabetes. Age (43.5 vs 42.1, p<0.01) and vaccination doses (not vaccinated: 15.8% vs 21.7%, 1 dose: 3.5% vs 2.9%, 2 doses: 27.9% vs 25.6%, 3 doses (52.8% vs 49.8%, p<0.01) seem to show statistical difference between groups (Table 1).

Table 1 Baseline Demographic and Clinical Characteristics of the Mobile Cabin Hospital Patients

	All Patients (N =3243)	Conventional Treatment Group (N = 2576)	LYZQ Granules Group (N =667)	Statistics	*P* value
Characteristics					
Age – year	43.2 ± 12.6	43.5 ± 12.4	42.1 ± 13.1	2.51	0.01
Gender – no. (%)				1.43	0.23
Male	2337 (72.1)	1844 (71.6)	493 (73.9)		
Female	906 (27.9)	732 (28.4)	174 (26.1)		
Ethnicity – no. (%)				0.01	0.91
Han	3172 (97.8)	2520 (97.8)	652 (97.7)		
Minority	71 (2.2)	56 (2.2)	15 (2.3)		
Underlying diseases – no. (%)					
Hypertension	203 (6.3)	166 (6.4)	37 (5.6)	0.73	0.39
Diabetes	78 (2.4)	69 (2.7)	9 (1.4)	3.99	0.05
Food allergy – no. (%)				2.77	0.10
No	3203 (98.8)	2540 (98.6)	663 (99.4)		
Yes	40 (1.2)	36 (1.4)	4 (0.6)		
Vaccination doses – no. (%)				13.32	<0.01
Not vaccinated	553 (17.1)	408 (15.8)	145 (21.7)		
1 dose	108 (3.3)	89 (3.5)	19 (2.9)		
2 doses	889 (27.4)	718 (27.9)	171 (25.6)		
3 doses	1693 (52.2)	1361 (52.8)	332 (49.8)		

Outcomes

The time for nucleic acid to turn negative was shorter in the LYZQ granule group compared with that in the conventional treatment group, approximately 3.5 days, which was still statistically significant after adjusting for age and vaccination dose (Table 2).

The LYZQ granule can significantly reduce the total days of hospitalization to approximately 2.5 days (Figure 1, Table 2) and increase the changes in Ct values for both Orf gene and N gene, even after adjusting for potential

Table 2 Univariate and Multivariate Analysis of Primary and Secondary Therapeutic Efficacy Outcomes

Outcome/Covariates	Value	Univariate Analysis		Multivariate Analysis		
		Statistics	*P* value	*β*(95% CI)	Statistics	*P* value
Nucleic acid turning negative time– day[a]						
Treatments		19.19	<0.01		9.12	<0.01
Conventional treatment group*	14.2 ± 4.26					
LYZQ granules group	10.70 ± 3.54			−4.14 (−6.83, −1.45)	−3.02	<0.01
Hospitalization days – day[b]						
Treatments		17.95	<0.01		21.73	<0.01
Conventional treatment group*	12.51 ± 3.49					
LYZQ granules group	9.90 ± 2.00			−2.91 (−4.14, −1.68)	−4.66	<0.01
Changes of Ct values (N)[c]						
Treatments		−4.79	<0.01		15.37	<0.01
Conventional treatment group*	8.44 ± 6.88					
LYZQ granules group	10.33 ± 6.44			0.85 (0.76, 2.29)	3.92	0.01
Changes of Ct values (O)[c]						
Treatments		−2.91	<0.01		4.76	0.03
Conventional treatment group*	7.31 ± 6.90					
LYZQ granules group	8.44 ±5.84			0.85 (0.09, 1.61)	2.18	0.03

Notes: *Represents reference group. [a]Models were adjusted for age, vaccination dose and effect. [b]Models were adjusted for age, vaccination dose, effect and positive days before admission. [c]Models were adjusted for age, vaccination dose and positive days before admission.

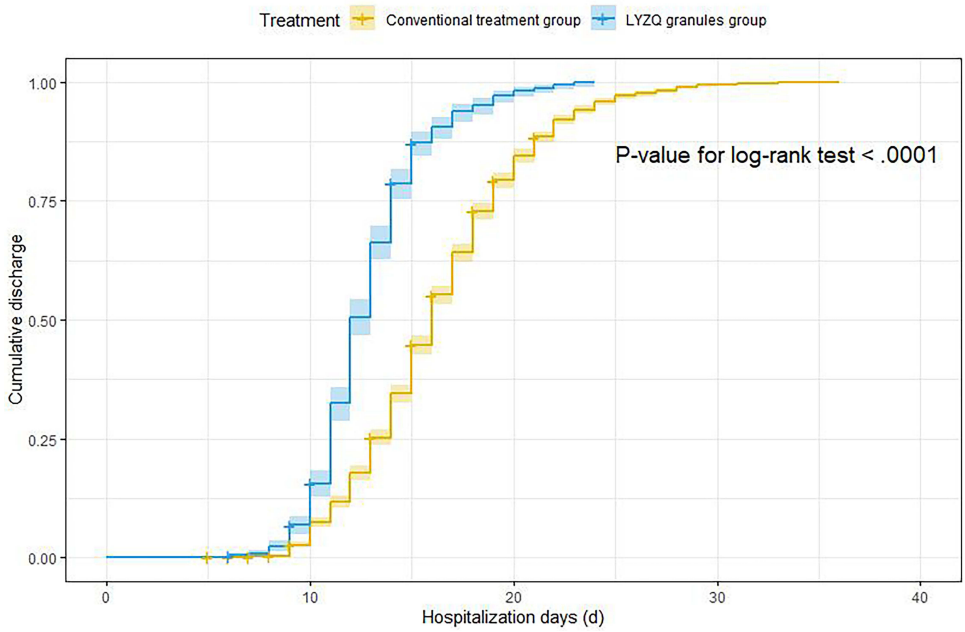

Figure 1 Kaplan–Meier curves for the cumulative discharge rate of different treatment groups. The yellow curve shows the conventional treatment group, and the blue curve shows the LYZQ granule group. In the same hospital days, the cumulative discharge rate of the LYZQ granule group was higher than that of the conventional treatment group, suggesting a positive effect of LYZQ granule.

confounding factors (Table 2). The difference in the changes of Ct values (Orf gene and N gene) on the 4th, 6th, 8th, and 10th days seem to increase over time between the two groups (Figure 2), and the difference was approximately 1.5 on the 8th day (Table 2).

Adverse Event

Seventeen patients had diarrhea symptoms after using LYZQ granule, and the symptoms were relieved after treatment with berberine or probiotics. There was no obvious side effect of diarrhea in the conventional treatment group. No serious adverse events were reported.

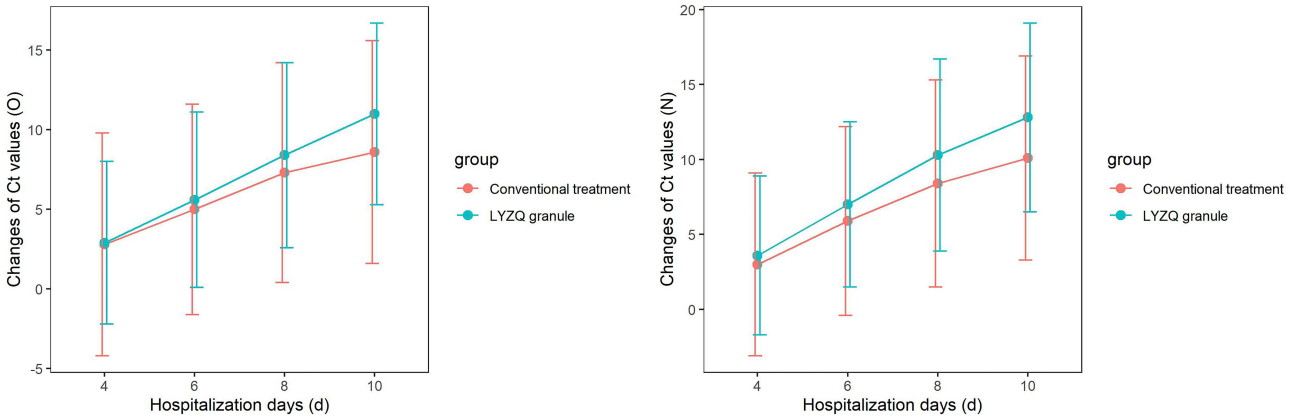

Figure 2 Error bar for changes in Ct value with different treatment groups. The red curve shows the conventional treatment group, and the blue curve shows the LYZQ granule group. The difference for the changes in Ct values on the 4th, 6th, 8th, and 10th days seem to increase between the two groups as the hospital days increase, indicating that the effect of LYZQ granule began to appear over time.

Discussion

LYZQ granule is the prescribed TCM for the treatment of influenza that was historically used for a long time in Longhua Hospital. It was tried in the treatment of COVID-19 during the Wuhan epidemic in 2020 and showed some curative effect to a certain degree, which is only described by the doctors but lacks quantitative clinical evidence. However, evidence on its clinical effectiveness and safety is still lacking. This is the first clinical study to evaluate the effectiveness of LYZQ granule in the treatment of patients with mild COVID-19 caused by SARS-CoV-2 Omicron variant in mobile cabin hospitals in Shanghai, China. We found that LYZQ granule might be a promising drug for the treatment of mild COVID-19, which might be beneficial to effectively shorten the negative transition time of nucleic acid, the total days of hospitalization, and increase the changes of Ct values.

The results showed that the LYZQ granule can effectively shorten the negative transition time of nucleic acid, approximately 3.5 days. The shortened total hospital days also supported this. Because the clinical characteristics of the Omicron variant are mainly mild and the rate of severe cases is low,[15,16] the nucleic acid negative transition time was used as the main curative indicator to evaluate the efficacy rather than the relief of symptoms in previous research.[17] For the diagnosis, treatment, and prevention and control of COVID-19, shortening the negative transition time for nucleic acid can accelerate the utilization rate of beds in mobile cabin hospitals, avoid crowding out of medical resources, and reduce medical pressure. This is important in the Omicron outbreak in Shanghai.

Ct value is an indicator of viral load, and the change in Ct value during hospitalization is one of the secondary efficacy indicators in this study. Previous studies have shown the highest viral load in the early stages of COVID-19.[18] During this period, patients are most infectious and most likely to develop antiviral resistance.[17,19,20] Therefore, a high viral load may be associated with strong infectivity. If the viral load in patients can be effectively reduced in a shorter time, the high transmissibility of COVID-19 can be successfully controlled, and further immune escape of the virus can be prevented. Our study showed that, compared with the traditional treatment group, the LYZQ granule group can consistently change the Ct value to approximately 10.3 (N gene) and 8.4 (Orf gene), indicating that the LYZQ granule can effectively reduce the viral load in patients with COVID-19 so that weaken its infectivity and effectively curb its transmission. The reason may be related to the constituents of Atractylodes in LYZQ granule. Atractylodes has immunomodulatory effects because it is rich in polysaccharides, saponins, volatile oil, amino acids, and other effective components, which regulate specific and nonspecific immunity and speed up virus elimination in the body,[21–24] which may be related to the increase of Ct values. However, the mechanism is unclear. Future studies are warranted to specifically clarify the correlation between Atractylodes and viral load reduction.

For the adverse reactions, only diarrhea was recorded, which was relieved with symptomatic treatment. It may be related to the constituents of Patchouli and Atractylodes in the LYZQ granule since it promotes gastrointestinal motility[22,24,25] but the explicit reason is unknown and further research is needed.

There are several limitations that deserved a discussion. First, due to the large number of patients infected with the Omicron variant in Shanghai and the wide range of coverage, only Ct value was measured, which can only reflect viral load to a certain extent. For exactly reflecting the viral load, other detection methods such as virus replication number may be more accurate. Second, there was a certain delay between the positive test outcome and intervention in the mobile cabin hospital. Timely intervention may better respond to drug effects. During the analysis, the positive days before admission was adjusted as a confounder, so this might have a large impact on our conclusion. Moreover, this study lacked consideration of long-term effects. After two consecutive negative nucleic acid exits, patients were not followed, so it is not possible to observe whether the patients catch the COVID-19 again after stopping the treatment, which is also important for drug efficacy.

Conclusion

We confirm that LYZQ granule might be a promising drug for the treatment of mild COVID-19. Long-term randomized controlled trials with follow-up evaluations are required to confirm its long-term efficacy.

Data Sharing Statement

Data sharing is not applicable to this article.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Longhua Hospital (Ethical Approval No.2022KCSY020) and complied with our national laws and the Helsinki Declaration, and written informed consent was obtained from all patients.

Consent for Publication

We give our consent for information about our article and the details of any images, videos, recordings, etc to be published in Infection and Drug Resistance.

Acknowledgments

LYZQ granule is a hospital preparation of Longhua Hospital, which is developed by the respiratory doctors of our hospital for the treatment of COVID-19's mild diseases. The joint team from Fudan University and Longhua Hospital conducted this study and analyzed the efficacy and safety of this drug at Mobile Cabin Hospital.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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