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Clinical efficacy of Jingyin granules, a Chinese patent medicine, in treating patients infected with coronavirus disease 2019

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ABSTRACT

Background: Jingyin granules (JY), one patented Chinese herbal formula, have been advised for treating coronavirus disease 2019 (COVID-19) in China. As of now, the safety and effectiveness of JY in treating COVID-19 patients were still to be evaluated.

Purpose: To investigate the safety and clinical effectiveness of JY in treating mild COVID-19 patients.

Methods: We carried out a prospective cohort study, as the highly infectious COVID-19 omicron variant ranged in Shanghai (ClinicalTrial.gov registration number: ChiCTR2200058692).

Results: Nine hundred participants were recruited in this clinical trial study, and 830 patients met the eligibility criteria. Seven hundred and ninety-one patients, accomplished the following-up assessment, including 423 cases of JY group and 368 cases of placebo group. NCR in JY group at 7-day posttreatment was considerably greater than that in placebo group (4.9 [3.0, 6.0] vs 5.0 [4.0, 7.0] days, P < 0.001; 6.0 [4.0, 8.0] vs 7.0 [5.0, 9.0] days, P < 0.001). None of the patients with mild COVID-19 developed into severe cases. The median NCT of SARS-CoV-2 and ILOS in JY group were lesser than that in placebo group (4.9 [3.0, 6.0] vs 5.0 [4.0, 7.0] days, P < 0.001; 6.0 [4.0, 8.0] vs 7.0 [5.0, 9.0] days, P < 0.001). In both groups, the obvious improvement in clinical symptoms was observed, but the difference was not significant. In the subgroup of age ≤ 60 years, JY promoted SARS-CoV-2 RNA negative conversion (HR=1.242; 95% CI: 1.069-1.444, P < 0.001). No patients in both groups were reported as the case of serious adverse event.

Conclusion: JY maybe the potential medicine for treating mild COVID-19 patients, which had beneficial effects on increasing NCR, and shortening NCT and ILOS.

Abbreviations: BMI, Body mass index; COVID-19, Coronavirus disease 2019; CI, Confidence intervals; H1N1, Influenza A virus; HR, Hazards ratio; ILOS, Inpatient length of stay; JY, Jingyin granules; MCH, Mobile cabin hospital; NCR, Negative conversion rate; NCT, Negative conversion time; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, Standard deviation; TCM, Traditional Chinese Medicine.

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Introduction

Recent years, contagious respiratory illnesses, such as influenza, SARS, Ebola, coronavirus disease 2019 (COVID-19), caused considerable detrimental impact on human healthiness, social steadiness, and economic growth (Boretti et al., 2021; Shah et al., 2020; Stadler et al., 2003; Zitzmann and Kaderali, 2018). In late February 2022, the novel viral genomes from 129 patients were confirmed as Omicron BA.2 sub-lineage (Zhang et al., 2022) in Shanghai. The Omicron variant has raised universal concerns because it has high transmissibility and immune evasion capability (Balint et al., 2022). The Omicron variant’s transmissibility is 3 times greater than Delta variant (Long et al., 2022). It is still a severe risk to the health of the public (Ito et al., 2022) and puts enormous pressure on the healthcare system due to its high transmissibility. As of July 11, 2022, the patients infected with COVID-19 were over 552.50 million, and the deaths had reached more than 6.34 million deaths in the world (WHO, 2022).

Therefore, it is urgently needed to develop the effective drug for fighting COVID-19 pandemic. Since thousands of years ago, traditional Chinese medicine (TCM) was applied to prevent and treat contagious respiratory illnesses, which might be the potential candidate for treating COVID-19. Among these herbal remedies, Banlangen granules, Lianhua Qingwen capsules and Jingyin granules (JY) have been verified for use in China as antiviral treatment for a variety of infection disease, including influenza and COVID-19 (Wu et al., 2020; Yu T, 2020; Zhuang et al., 2020). Evidences from clinical studies have demonstrated that TCM could markedly shorten the hospitalized days and improve the medical indicators in COVID-19 patients (Hu et al., 2021).

JY originated from the classical TCM formula Yinqiao Powder, and it is composed of nine herbs [Herba Schizonpetae (Jing Jie), Flos lonicerae (Jin Yin Hua), HerbaTaraxaci (Pu Gong Ying), Lindigowoad Leaf (Da Qing Ye), Folium Llicis Purpureae (Si Ji Qing), Herba Houttuyniae (Yu Xing Cao), Arctium lappa L. (Niu Bang Zi), Saposhnikoviae Radix (Fang Feng), and Radix Glycyrrhizae (Gan Cao)]. JY has been demonstrated to be very effective for treating respiratory diseases. Further, previous researches have confirmed that JY has anti-inflammatory and antiviral effects (Wu et al., 2020; Zhang et al., 2022; Zhu et al., 2022; Zhiyang et al., 2020). JY is advised for treating COVID-19 patients by the Expert consensus on traditional Chinese medicine diagnosis and treatment of COVID-19 infection in Shanghai (Spring edition). In our study, one prospective study about JY treating mild COVID-19 patients was carried out in the mobile cabin hospital (MCH), which will provide the clinical evidence in support of TCM treating COVID-19 during the Omicron wave in Shanghai.

Material and methods

Study design

We designed one prospective cohort study, in order to assess the safety and effectiveness of JY in treating mild COVID-19 patients. In the MCH of City Footprint Hall in Shanghai, mild COVID-19 patients were enrolled. JY group was administrated with JY, and placebo group received TCM placebo. Treatment was started within 6 hours after enrollment.

TCM placebo or JY were administrated at an oral dose of 15 g or 13 g twice daily for 7 days.

Ethical Approval

The design and protocol of this study were approved by Ethics Committee of Shanghai University of Traditional Chinese Medicine (No.2022-1098-35-01). The current study was registered in the Chinese Clinical Trial Registry (No.ChCTR2200058692).

Intervention

JY was manufactured by Shanghai Shangyao Xingling Technology Pharmaceutical Co., LTD (Z20090039). JY was composed of nine herbs, which was shown in Table S1.

In the light of Guiding principles for clinical research on new drugs of TCM, TCM placebo contained herbs lower than 10% of TCM formula dose, which was similar with formula in smell and color(Zheng XY, 2002). In this study, TCM placebo was composed of Radix Glycyrrhizae 1 g and Wrinkled Gianthyssop Herb 1 g, which were similar in smell, color, shape, and packaging to the JY. Radix Glycyrrhizae and Wrinkled Gianthyssop Herb were chosen as TCM placebo for their distinct odors.

Participants

All of patients who met the following characteristics were included: (1) age ≥ 18 years; (2) diagnosed with mild COVID-19. In terms of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 9th) (National Health Commission & State Administration of Traditional Chinese Medicine, 2022), patients infected with SARS-CoV-2 who had mild symptoms and no imaging sign of pneumonia were diagnosed as mild cases; (3) all participants gave written informed consent.

Patients were excepted from this study if they met one or more characteristics: (1) complicated with other respiratory diseases, including influenza, other pneumonia, suppurative tonsillitis, acute trachea-bronchitis, tuberculosis, primary ciliated dyskinesia syndrome, and other acute onset nasal diseases; (2) suffering from severe primary diseases, such as viral hepatitis, hemophilia, diabetes with unstable control, and mental illness;(3) pregnant women, lactating females or women planning to become pregnant; (4) people with allergies; (5) enrolled in other clinical trials within the last 3 months; (6) any other conditions that the researchers deemed the patients to be unsuitable for taking part in the study.

The participants were removed from the study for any of the following reasons: (1) unwilling to take part in the research; (2) experienced a secondary infection or specific physiological changes during the trial necessitating discontinuation of the intervention; (3) experienced any allergic reactions or serious adverse events.

Study Outcomes

The primary clinical outcomes included negative conversion rate (NCR) and the rate of severe cases. The secondary clinical outcomes included negative conversion time (NCT), inpatient length of stay (ILOS), and the disappearance rates of clinical symptoms.

SARS-CoV-2 viral RNA levels were determined using the Ct values in Real-Time RT-PCR. On the basis of Diagnosis and Treatment Protocol for Novel coronavirus Pneumonia (Trial Version 9.0), if Ct values of ORF1ab and N Coronavirus genes were ≥ 35, the coronavirus was considered as negative. NCT was the time between enrollment and the earliest time of at least two sequential negative tests 24 hours apart. The cumulative NCR was the percentage of patients who tested negative for COVID-19 and was recorded every day. The disappearance of clinical symptoms was observed. The symptoms score was the sum of each symptom score, including fever, cough, fatigue, headache, snuffle, runny nose, sore throat, myalgia, chest distress, vomiting, abdominal distension, abdominal pain, and diarrhea. The score of primary symptoms (fever, sore throat, snuffle, and runny nose) was defined as 3, and the score of other symptoms was defined as 1.

Safety

The safety indicators were treatment-related adverse events. The incidence, time, seriousness, duration and relatedness of adverse events were recorded. The correlation between adverse events and treatment
was assessed by clinical investigators.

Statistical analyses

Graphpad prism 8.0 and SPSS 24.0 were used to perform statistical analyses. Continuous variables were presented as medians (No./Total cases) and data were analyzed by Chi-square test, including gender, co-morbidity, disparity rate of clinical symptoms, and NCR. Kaplan-Meier method was applied to draw survival curves, and Log-rank test was chosen to evaluate data. Risk factors for clinical outcomes were identified by the Cox analyses, and the results were presented as the hazard ratios (HR), 95% confidence intervals (CI). All of statistical tests were two-sided, and P < 0.05 was defined as statistically significant.

Results

Nine hundred mild COVID-19 patients were screened for eligibility in MCH from April 8 to May 6, 2022. Seventy patients were ineligible for diverse reasons and 830 patients were assigned to receive JY (JY group, n = 453) or TCM placebo (placebo group, n = 377). 30 eligible patients in JY group and 9 eligible patients in placebo group withdrew from this study. Finally, 423 patients in JY group and 368 patients completed this study. JY, Jingyin granules; n, number of participants.

Baseline characteristics

At baseline, the key demographic and clinical descriptions were comparable in both groups, including gender, Body-mass index (BMI), and Ct value of ORF1ab genes, (Table 1). Four hundred and four were women (51.1%). The median age of all cases combined was 47 years. In addition, a total of 129 (16.3%) patients had comorbidities in both groups. In JY group, the rates of comorbidities, including hypertension, chronic bronchitis and chronic liver disease, were greater than that in placebo group (12.5% vs 3.8 %, P < 0.001; 2.8% vs 0.0%, P = 0.01; 5.4% vs 1.1%, P < 0.001). Compared with placebo group, the interval-time from the first positive record of SARS-CoV2 to admission in JY group was longer (M [Q1, Q3]: 3.0 [2.0, 4.0] vs 3.0 [2.0, 4.0]; Mean [SD]: 3.4[1.9] vs 2.8[1.7], both P < 0.001). Non-statistics difference was shown in the median Ct value of ORF1ab gene between two groups on

Cross-sectional analysis of baseline demographic and key clinical characteristics

| Variables               | Total (N = 791) | Placebo group (N = 368) | JY group (N = 423) | P value |
|-------------------------|-----------------|------------------------|-------------------|---------|
| Age (yr), Median (Q1, Q3) | 47 (32, 56)     | 48 (34, 57)             | 46 (30, 55)       | 0.025*  |
| Gender, No./Total (%)    |                 |                        |                   | 0.942   |
| Male                    | 388/791 (49.1)  | 180/368 (49.8)          | 208/423 (49.2)    |         |
| Female                  | 404/791 (51.1)  | 188/368 (51.1)          | 215/423 (50.8)    |         |
| BMI** Median (Q1, Q3)    | 23.4            | 23,23(21.0, 25.4)       | 23.2(21.4, 26.0)  | 0.127   |
| Interval-time (d), Median (Q1, Q3) | 3 (2, 4)       | 3 (2, 4)                | 3 (2, 4)          | <0.001*** |
| Mean (SD)               | 3.1(1.8)        | 2.8(1.7)                | 3.4(1.9)          |         |
| Ct value of ORF1ab, Median (Q1, Q3) | 25.6           | 25.3(21.3, 29.8)        | 26.0(21.6, 30.0)  | 0.681   |
| Symptom, No./Total (%)   |                 |                        |                   |         |
| Fever                   | 72/791 (9.1)    | 35/368 (9.5)            | 37/423 (8.7)      | 0.710   |
| Gough                   | 485/791 (61.3)  | 217/368 (59.0)          | 268/423 (63.4)    | 0.206   |
| Fatigue                 | 135/791 (17.1)  | 69/368 (18.8)           | 66/423 (15.6)     | 0.241   |
| Headache                | 98/791 (12.4)   | 54/368 (14.7)           | 44/423 (10.4)     | 0.069   |
| Snuffle                 | 195/791 (24.7)  | 84/368 (22.8)           | 111/423 (26.2)    | 0.266   |
| Runny nose              | 157/791 (19.8)  | 75/368 (20.4)           | 82/423 (19.4)     | 0.726   |
| Sore throat             | 240/791 (30.3)  | 116/368 (31.5)          | 124/423 (29.3)    | 0.501   |
| Myalgia                 | 59/791 (7.5)    | 28/368 (7.6)            | 31/423 (7.3)      | 0.881   |
| Chest distress          | 55/791 (7.0)    | 27/368 (7.3)            | 28/423 (6.6)      | 0.692   |
| Vomiting                | 14/791 (1.8)    | 9/368 (2.4)             | 5/423 (1.2)       | 0.179   |
| Abdominal distention     | 12/791 (1.5)    | 5/368 (1.4)             | 7/423 (1.7)       | 0.734   |
| Abdominal pain           | 8/791 (1.0)     | 7/368 (1.9)             | 1/423 (0.2)       | 0.020*** |
| Diarrhea                 | 34/791 (4.3)    | 18/368 (4.9)            | 16/423 (3.8)      | 0.443   |
| Comorbidity, No./Total (%) | 129/791 (16.3) | 26/368 (7.1)            | 103/423 (24.3)    | <0.001*** |
| Hypertension             | 71/791 (9.0)    | 14/368 (3.8)            | 57/423 (13.5)     | <0.001*** |
| Diabetes                 | 22/791 (2.8)    | 9/368 (2.4)             | 13/423 (3.1)      | 0.592   |
| Coronary heart disease/arhythmia | 9/791 (1.1) | 4/368 (1.1)             | 5/423 (1.2)       | 0.900   |
| Chronic bronchitis        | 12/791 (1.5)    | 0/368 (0.0)             | 12/423 (2.8)      | 0.001**  |
| Chronic liver diseases    | 27/791 (3.4)    | 4/368 (1.1)             | 23/423 (5.4)      | <0.001*** |
| Othersd                  | 28/791 (3.5)    | 3/368 (0.8)             | 25/423 (5.9)      | <0.001*** |

BMI, Body mass index; JY, Jingyin granules; MCH, mobile cabin hospital; n, number of participants; SD, standard deviation.

a Data of 8 patients in JY group and 21 in the placebo group were missing.

b The interval-time was defined as the time from the positive record of SARS-CoV-2 test to enrollment. Data of 70 patients in JY group and 29 in the placebo group were missing.

c The Ct values were the first test record of SARS-CoV-2 RNA in MCH.

Fig. 1. Flowchart of study Nine hundred participants were screened for eligibility in MCH. Seventy patients were ineligible for diverse reasons and 830 patients were assigned to receive JY (JY group, n = 453) or TCM placebo (placebo group, n = 377). 30 eligible patients in JY group and 9 eligible patients in placebo group withdrew from this study. Finally, 423 patients in JY group and 368 patients completed this study. JY, Jingyin granules; n, number of participants.
the first test in MCH (26.0 [21.6, 30.0] vs 25.3 [21.3, 29.8], \( P = 0.681 \)). The median Ct value of \( N \) gene in JY group was bigger than that in placebo group (25.5 [21.3, 29.8] vs 24.5 [20.3, 28.8], \( P = 0.044 \)). In both group, the differences of clinical symptoms except abdominal pain were not statistically significant (\( P > 0.05 \)).

Clinical outcomes

Primary indicators

A significantly greater increase in NCR than placebo group was shown in JY group (HR = 1.374; 95% CI, 1.162 - 1.624, \( P < 0.001 \)), indicating an improvement of NCRs after JY treatment compared with TCM placebo treatment (Fig. 2A). Further analysis showed that, compared with placebo group, NCRs in JY group were higher at 2 days (74/423 [17.5%] vs 34/368 [9.2%], \( P < 0.001 \), 3 days (145/423 [34.3%] vs 61/368 [16.6%] \( P < 0.001 \), 4 days (215/423 [50.8%] vs 133/368 [36.1%], \( P < 0.001 \), 6 days (323/423 [76.4%] vs 257/368 [69.8%], \( P = 0.039 \)) and 7 days (380/423 [89.8%] vs 304/368 [82.6%], \( P = 0.003 \)) (Table 2). In addition, there were no mild COVID-19 patients who turned into severe cases in both groups.

Secondary indicators

After treatment of 7 days, the median NCT of JY group was decreased compared with that of placebo group (4.0 [3.0, 6.0] days vs 5.0 [4.0, 7.0] days, \( P < 0.001 \) (Fig. 2B). The ILOS were shortened by one day in JY group compared with placebo group (4.0 [3.0, 6.0] days vs 5.0 [4.0, 7.0] days, \( P < 0.001 \)\( \star \), 6 days (215/423 [50.8%] vs 133/368 [36.1%], \( P < 0.001 \), 7 days (323/423 [76.4%] vs 257/368 [69.8%], \( P = 0.039 \)) and 7 days (380/423 [89.8%] vs 304/368 [82.6%], \( P = 0.003 \)) (Table 2).

Related factors contributing to RNA negative conversion

In this study, the related factors affecting RNA negative conversion were determined by univariate Cox regression analysis. The results showed that medication of JY (HR = 1.248; 95% CI, 1.085 - 1.436, \( P = 0.002 \)), age (HR = 0.992; 95% CI, 0.988 - 0.997, \( P = 0.002 \)), interval-time (HR = 1.229; 95% CI, 1.178-1.282, \( P < 0.001 \)), and the Ct value of \( ORF1ab \) gene (HR = 1.101; 95% CI, 1.086 - 1.117, \( P < 0.001 \)) were involved in contributing to RNA negative conversion (Fig. 3A). Based on the above results, the multivariate Cox analyses was performed, and we found that the medication of JY (HR = 1.316; 95% CI, 1.129 - 1.534, \( P < 0.001 \), age (HR = 0.990; 95% CI, 0.984 - 0.995, \( P < 0.001 \), interval-time (HR=1.142 [95% CI, 1.091 - 1.196, \( P < 0.001 \), Ct value of \( ORF1ab \) gene (HR = 1.090; 95% CI, 1.072 - 1.108, \( P < 0.001 \)) were the relevant factors (Fig. 3B). These results showed that JY treatment contributed most to RNA negative conversion.

Clinical outcomes in age-subgroups

To explore the differences of clinical effectiveness in age-subgroups, patients were categorized into two subgroups. In patients aged \( \leq 60 \) years, JY treatment markedly increased NCR at 7 days compared with TCM placebo treatment (339/372 [91.1%] vs 259/308 [84.1%], \( P = 0.005 \)) (Table 4). In addition, the Kaplan-Meier analysis revealed that JY contributed to RNA negative conversion (HR = 1.242, 95% CI, 1.069 - 1.444, \( P < 0.001 \) (Fig. 4A). However, in patients aged > 60 years, no obvious differences were shown in NCR between JY group and placebo group at 7 days (41/51 [80.4%] vs 45/60[75.0%], \( P = 0.498 \)) and Kaplan-Meier analysis (HR = 1.158; 95% CI, 0.795 - 1.688, \( P = 0.355 \)).

**Table 2**

Analysis of the cumulative NCR.

| During treatment | Placebo group (\( n = 368 \)) | JY group (\( n = 423 \)) | \( P \) value |
|-----------------|-------------------------------|--------------------------|-------------|
| **Cumulative negative conversion rates, No./Total** | | | |
| (\%) | | | |
| At Day-2 | 34/368 (9.2) | 74/423 | < 0.003 ** |
| At Day-3 | 61/368 (16.6) | 145/423 | < 0.001 *** |
| At Day-4 | 133/368 (36.1) | 215/423 | < 0.001 *** |
| At Day-5 | 223/368 (60.6) | 276/423 | 0.176 |
| At Day-6 | 257/368 (69.8) | 323/423 | 0.039 * |
| At Day-7 | 304/368 (82.6) | 380/423 | 0.003 ** |

\( \star \) \( P < 0.01 \)
\( \star \) \( P < 0.001 \)
\( \star \) \( P < 0.001 \)

\( \star \) \( P < 0.05 \)

Fig. 2. Clinical outcomes in all patients. A) Kaplan-Meier analysis of all patients. B) NCT of SARS-CoV-2 in two groups and expressed as median (Q1-Q3). C) ILOS in both groups, which was expressed as median(Q1-Q3). \( \star \star \) \( P < 0.001 \). JY, Jingyin granules; n, number of participants; NCR, Negative conversion rate. NCT, Negative conversion time; ILOS, Inpatient length of stay.
Discussion

The rapidly spread of SAR-CoV-2 around the world has made enormous pressure on medical system. The antivirals approved by FDA such as Paxlovid can increase the mortality and improve adverse events in COVID-19 patients (Wen et al., 2022). Paxlovid could be used in mild to moderate COVID-19 patients with high risk for progression to severe disease, but it is more suitable for immunosuppressed patients, old patients and COVID-19 patients with comorbidity, (Ganatra et al., 2022; Huang et al., 2022; Najjar-Debbiny et al., 2022). Recent RCT study demonstrated that treating COVID-19 with Paxlovid led to an 89% decreased risk of progress to severe COVID-19 than the risk with placebo (Hammond et al., 2022). An analysis of 5287 persons from California revealed that <1% of all patients identified with emergency department encounter and hospitalization associated to COVID-19 between 5 and 15 days after receiving Paxlovid (Malden et al., 2022). Adversely, recent studies have revealed that COVID-19 rebound after Paxlovid treatment in some cases (Malden et al., 2022; Wang et al., 2022; Wang et al., 2022). Therefore, there was no definite evidence to show that Paxlovid can get used to treating mild COVID-19 patients.

However, there were no specific drugs to treat mild COVID-19 patients during Omicron wave. Several treatment strategies, including TCM especially in China, have been applied to fight against COVID-19. In this clinical trial study, we tried to explore clinical effects of JY treatment on mild COVID-19 in Shanghai. Our results suggested the

### Safety profile and adverse events

Three patients were occurring with diarrhea and one patient was occurring with vomiting in each group after treatment in the MCH. However, the above events were not directly associated with the treatment of JY and TCM placebo, which was assessed by clinical investigations. There was no death or serious adverse event occurred in either group.

### Clinical outcomes in interval-time subgroups

According to the median interval-time (3 days) in patients, all of patients were further classified into two subgroups, including the interval-time ≤ 3 days group and the interval-time > 3 days group. In both of subgroups, more patients treated by JY got RNA negative conversion compared with patients treated by TCM placebo (HR = 1.393; 95% CI, 1.122 - 1.730, *P* = 0.003; HR = 1.668; 95% CI, 1.180 - 2.357, *P* = 0.004) (Fig. 5A and B).

In addition, in the interval-time ≤ 3 days group, JY group performed the higher NCRs at 2 days, 3 days, 4 days, 7 days posttreatment than placebo group (36/242 [14.9%] vs 14/245 [5.7%], *P* = 0.001; 61/242 [25.2%] vs 28/245 [11.4%], *P* = 0.001; 108/242 [44.6%] vs 71/245 [29.0%], *P* < 0.001; 216/242 [89.3%] vs 200/245 [81.6%], *P* = 0.017). In the interval-time > 3 days group, patients in JY group got the higher NCRs at 3 days, 6 day, 7 days posttreatment (66/111 [59.5%] vs 32/94 [34.0%], *P* < 0.001; 104/111 [93.7%] vs 78/94 [83.0%], *P* = 0.015; 109/111 [98.2 %] vs 86/94 [91.5%], *P* = 0.026) (Table 5).

In the interval-time ≤ 3 days group, NCT and ILOS in JY group were shorter than that in placebo group (5.0 [3.0, 7.0] days vs 5.0 [4.0, 7.0] days, *P* = 0.001) (7.0 [5.0, 8.0] days vs 7.0 [6.0, 9.0] days, *P* = 0.004), as shown in Fig. 5C and E. In the group of interval-time > 3 days, compared with placebo group, NCT and ILOS were shortened in JY group (3.0 [2.0, 5.0] vs 4.0 [3.0, 5.0] days, *P* = 0.007; 5.0 [4.0, 7.0] vs 6.0 [5.0, 8.0] days, *P* < 0.001) (Fig. 5D and F).

### Table 3

The rate of disappearance of symptoms.

| Variables, No./Total of patients with the specific symptom (%) | Total (n=791) | Placebo group (n=368) | JY group (n=423) | *P* value |
|---------------------------------------------------------------|--------------|----------------------|-----------------|-----------|
| Fever                                                         | 69/72 (91.2) | 33/35 (94.3)         | 36/37           | 0.523     |
|                                                              | (95.8)       | (97.3)               |                 |           |
| Gough                                                         | 350/485 (72.2) | 154/217 (71.0)     | 196/268         | 0.597     |
|                                                              | (79.3)       | (73.1)               |                 |           |
| Fatigue                                                       | 117/135 (86.7) | 59/69 (85.5)       | 58/66           | 0.685     |
|                                                              | (96.9)       | (87.9)               |                 |           |
| Headache                                                      | 95/98 (94.9)  | 52/54 (96.3)        | 43/44           | 0.683     |
|                                                              | (96.9)       | (97.7)               |                 |           |
| Snuffle                                                       | 185/195 (94.9) | 79/84 (94.0)       | 106/111         | 0.650     |
|                                                              | (96.9)       | (95.5)               |                 |           |
| Runny nose                                                    | 147/157 (93.6) | 71/75 (94.7)      | 76/82           | 0.611     |
|                                                              | (96.9)       | (92.7)               |                 |           |
| Sore throat                                                   | 220/240 (91.7) | 105/116 (90.5)     | 115/124         | 0.533     |
|                                                              | (97.7)       | (92.7)               |                 |           |
| Myalgia                                                       | 54/59 (91.5)  | 26/28 (92.9)       | 28/31           | 0.727     |
|                                                              | (90.9)       | (90.3)               |                 |           |
| Chest distress                                                | 50/55 (90.9)  | 26/27 (96.3)       | 24/28           | 0.172     |
|                                                              | (90.9)       | (85.7)               |                 |           |
| Vomiting                                                      | 13/14 (92.9)  | 9/9 (100.0)        | 4/5 (80.0)      | 0.164     |
|                                                              | (100.0)      | (90.0)               |                 |           |
| Abdominal distension                                         | 12/12 (100.0) | 5/5 (100.0)       | 7/7 (100.0)     | NA        |
|                                                              |              |                     |                 |           |
| Abdominal pain                                                | 7/8 (87.5)   | 7/7 (100.0)        | 0/1 (0.0)       | 0.005**   |
|                                                              | (91.2)       | (95.5)               |                 |           |
| Diarrhea                                                      | 31/34 (91.2)  | 15/18 (83.3)       | 16/16           | 0.087     |

JY, Jingyin granules; n, number of participants. ** *P* < 0.01

as shown in Table 4 and Fig. 4B.

In patients aged ≤ 60 years, NCT and ILOS in JY group were shorter than that in placebo group (4.0 [3.0, 6.0] days vs 5.0 [4.0, 7.0] days, *P* < 0.001; 6.0 [4.0, 8.0] days vs 7.0 [5.0, 9.0], *P* < 0.001) (Fig. 4C and E). In patients aged > 60 years, NCT and ILOS in JY group were also shorter than that in placebo group (4.0 [3.0, 7.0] vs 5.0 [4.3, 7.8] days, *P* = 0.034; 6.0 [4.0, 9.0] vs 8.0 [6.0, 9.0] days, *P* = 0.016) (Fig. 4D and F). The above results showed that JY treatment played much better roles in contributing to RNA negative conversion in the patients aged ≤ 60 years.

### Table 4

Analysis of the related factors affecting the RNA negative conversion. A) Univariate Cox regression analysis of medication, gender, age, BMI, symptoms, comorbidity, interval time, and CT values of ORF1ab genes. B) Multivariate Cox analysis of medication, age, comorbidity, interval time, and CT values of ORF1ab genes. ** *P* < 0.001; *** *P* < 0.01.
Table 4
Cumulative NCR in age-subgroups

| During treatment | Age ≤ 60 | Age > 60 |
|------------------|----------|----------|
|                   | Placebo group (n = 308) | JY group (n = 372) | P value | Placebo group (n = 60) | JY group (n = 51) | P value |
| Cumulative negative conversion rates, No./Total (%) | | | | | | |
| At Day-2         | 30/308 (9.7) | 63/372 (16.9) | 0.007*** | 4/60 (6.7) | 11/51 (21.6) | 0.022*** |
| At Day-3         | 54/308 (17.5) | 126/372 (33.9) | < | 7/60 (11.7) | 19/51 (37.3) | 0.002** |
| At Day-4         | 118/308 (38.3) | 188/372 (50.5) | 0.001*** | 15/60 (25.0) | 27/51 (52.9) | 0.002** |
| At Day-5         | 192/308 (62.3) | 246/372 (66.1) | 0.304 | 31/60 (51.7) | 30/51 (58.8) | 0.450 |
| At Day-6         | 225/308 (72.4) | 289/372 (77.7) | 1.112 | 34/60 (56.7) | 34/51 (66.7) | 0.281 |
| At Day-7         | 259/308 (84.1) | 339/372 (91.1) | 0.005** | 45/60 (75.0) | 41/51 (80.4) | 0.498 |

JY, Jingyin granules; n, number of participants; NCR, Negative conversion rate.

** P < 0.01
* P < 0.05

Fig. 4. Clinical outcomes in age subgroups. A, Kaplan-Meier analysis among patients aged ≤ 60 years. B, Kaplan-Meier analysis among patients aged > 60 years. C, NCT among patients aged ≤ 60 years. D, NCT among patients aged > 60 years. E, ILOS among patients aged ≤ 60 years. F, ILOS among patients aged > 60 years. *** P < 0.01; ** P < 0.001; * P < 0.05. JY, Jingyin granules; n, number of participants; NCR, Negative conversion rate; NCT, negative conversion time; ILOS, inpatient length of stay.
Fig. 5. Clinical outcomes in interval-time subgroups. A, Kaplan-Meier analysis among patients with interval-time ≤ 3 days. B, Kaplan-Meier analysis among patients with interval-time > 3 days. C, NCT among patients with interval-time ≤ 3 days. D, NCT among patients with interval-time > 3 days. E, ILOS among patients with interval-time ≤ 3 days. F, ILOS among patients with interval-time > 3 days. ***, P < 0.001; **, P < 0.01. JY, Jingyin granules; n, number of participants; NCR, Negative conversion rate; NCT, negative conversion time; ILOS, inpatient length of stay.

Table 5
Cumulative NCR in interval-time subgroups

|                | Interval time ≤ 3 days | Interval time > 3 days |
|----------------|------------------------|------------------------|
|                | Placebo group (n=245)  | JY group (n=242)       | Placebo group (n=94) | JY group (n=111) |
| Cumulative negative conversion rates, No./Total (%) |                        |                        |                        |                        |
| At Day-2       | 14/245 (5.7)           | 36/242 (14.9)          | <                       | 19/94 (20.2)          | 30/111 (27.0)          | 0.254                   |
|                | < 0.001***             |                        |                        |                        |                        |                        |
| At Day-3       | 28/245 (11.4)          | 61/242 (25.2)          | <                       | 32/94 (34.0)          | 66/111 (59.5)          | <                       |
|                | < 0.001***             |                        |                        |                        |                        |                        |
| At Day-4       | 71/245 (29.0)          | 108/242 (44.6)         | <                       | 57/94 (60.6)          | 80/111 (72.1)          | 0.083                   |
|                | < 0.001***             |                        |                        |                        |                        |                        |
| At Day-5       | 140/245 (57.1)         | 148/242 (61.2)         | 0.368                   | 73/94 (77.7)          | 92/111 (82.9)          | 0.347                   |
| At Day-6       | 166/245 (67.8)         | 175/242 (72.3)         | 0.272                   | 78/94 (83.0)          | 104/111 (93.7)         | 0.015*                  |
| At Day-7       | 200/245 (81.6)         | 216/242 (89.3)         | 0.017*                  | 86/94 (91.5)          | 109/111 (98.2)         | 0.026*                  |

JY, Jingyin granules; n, number of participants; NCR, Negative conversion rate.
***, P < 0.001
**, P < 0.01
* P < 0.05
beneficial effects of JY on contributing to RNA negative conversion, which confirmed the beneficial effectiveness of TCM for treating mild COVID-19.

JY derived from the hospital preparation of Shuguang Hospital (Shanghai, China) has been applied to cure infectious illnesses for more than 40 years. Clinical applications have confirmed the efficacy of JY in antiviral and anti-inflammation therapy. (Yong-Li et al., 2022). In this study, it was the first time to determine the clinical effects of JY treating mild COVID-19 patients. The main advantages of JY lie in shortening NCT of SARS-CoV-2 increasing NCR, and shortening ILOS in mild COVID-19 patients.

Further, our previous studies focused on Network pharmacologic analysis revealed that JY might target the ACE gene, which was a target assisting SARS-CoV-2 to enter cells (Wang et al., 2021). Forty-five components of JY were detected in the lung tissue of rats after intra-gastric administration. Exposure to certain components in lung tissue peaked 1h after gavage. The herbal extracts of JY, such as licoriceal B, glycyrrhizin, could deactivate CYP3A to modulate the pharmacokinetics of CYP substrate-drugs (Zhang et al., 2022). These researches offered pharmacokinetic data and guidance for the clinical application of JY. Recent research revealed that many components of JY could inhibit SARS-CoV-2. Radix Glycyrrhiza could directly act on IL-6/STAT3, and suppress SARS-CoV-2 by preventing the amplifier of SARS-CoV-2 (Luo et al., 2022). The active components of Radix Glycyrrhiza, such as licoriceal B, glycyrrhizin, triterpenoids licorice-saponin A3, glycyrrhetic acid etc., either inhibit the activity of viral main protease or interact with nsp7 protein or bind to spike protein RBD to anti–SARS-CoV-2 (Hu et al., 2021; van de Sand et al., 2021; Yi et al., 2022).

Additionally, Flos lonicerae and its effective ingredients could also reduce the main protease activity of the novel coronavirus (Gu et al., 2022). The above researches will provide the relevant pharmacological basis for JY in treating COVID-19 patients. Although the clinical symptoms in both JY group and placebo group were improved, non-statistics differences were observed in the disappearance rates after treatment. Because of the limited conditions in MCH, the clinical symptoms were only recorded at admission and discharge. Therefore, the disappearance time of clinical symptoms can’t be presented, which affect the evaluation of the improvement of clinical symptoms. Follow-up observation of the improvement of clinical symptoms everyday should be performed in future clinical studies.

Among COVID-19 patients, the age and underlying diseases have a direct impact on the clinical outcomes and hospitalized days. Age is strongly implicated as one of the major risk factors for severe COVID-19 disease and its adverse events (Chen et al., 2021). Data reported by the US Center for Disease Control and Prevention showed that older persons (> 65 years) had much greater rates of hospitalizations, ICU admissions, and deaths related to COVID-19 than any younger age groups. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 9.0) pointed out that patients with COVID-19 who are over 60 years old are considered to be in the high risk group for developing severe disease. In our study, in the subgroup of age ≤ 60, higher number of patients treated by JY got RNA negative compared with the placebo group, which was not shown in patients over 60 years old. In the one hand, JY treatment may play more effective roles on patients aged ≤ 60. In another hand, the sample size was small in the group aged >60, which may be difficult to determine the efficacy of TCM. Therefore, more patients should be enrolled to analyze the effectiveness of JY treatment.

SARS-CoV-2 affected globally a large population with pneumonia-like symptoms. According to reports from COVID-19 cases, it has been found that comorbidities raise the likelihood of infection. COVID-19 patients with diabetes, malignancies, hypertension, HIV, cardiocirculatory diseases, chronic obstructive pulmonary disease, and other comorbidities are more likely to develop a life-threatening situation (Ejaz et al., 2020). In this clinical trial, although the baseline rates of comorbidities were higher in JY group compared to placebo group, the results from Univariate Cox regression analysis revealed that the comorbidities in mild COVID-19 patients did not affect the clinical effectiveness of JY.

However, there are some limitations to this study. In this study, the course of treatment was only seven days, and the patients should be followed up for long term. Furthermore, due to the heavy medical burden in the MCH, we collected information through a structured questionnaire, which resulted in the limited baseline information. Finally, the rigorous randomized clinical trials with larger samples should be designed and performed, which will provide the strong evidence for the clinical effectiveness of TCM in treating COVID-19 patients.

Conclusion
In summary, the results of our study indicated that JY might be the potential effective TCM for mild COVID-19 patients by increasing NCR and shortening NCT and ILOS.

Competing Interests
None declared.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2022.154496.

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