

ARTICLE

Qingjin Yiqi granules for post-COVID-19 condition: A randomized clinical trial

Wentai Pang^{1,2}  | Fengwen Yang^{1,2} | Yubin Zhao³ | Erhei Dai⁴ | Jihong Feng⁵ | Yuhong Huang⁵ | Yongming Guo⁶ | Shengyuan Zhou⁵ | Ming Huang¹ | Wenke Zheng^{1,2} | Jiang Ma³ | Hong Li³ | Qing Li³ | Lijuan Hou³ | Shuo Zhang⁵ | Hui Wang^{1,2} | Qingquan Liu⁷ | Boli Zhang^{1,2} | Junhua Zhang^{1,2}

¹State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

²Evidence-Based Medicine Center, Tianjin University of Traditional Chinese Medicine, Tianjin, China

³Shijiazhuang People's Hospital, Shijiazhuang, China

⁴Shijiazhuang Fifth Hospital, Shijiazhuang, China

⁵Second Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China

⁶College of Acupuncture-moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin, China

⁷Beijing Hospital of Traditional Chinese Medicine, Beijing, China

Correspondence

Junhua Zhang and Boli Zhang, State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China. Email: zhangbolipr@163.com; zjhtcm@foxmail.com

Wentai Pang, Fengwen Yang, and Yubin Zhao contributed equally to this work.

Abstract

Objective: To evaluate the effectiveness and safety of Qingjin Yiqi granules (QJYQ) on post-COVID-19 condition (PCC).

Method: Patients who met the inclusion criteria were randomly assigned to two groups, the QJYQ group received QJYQ combined with standard rehabilitation treatments (SRTs) and the control group only received SRTs. The treatment course was 14 days. The primary outcomes were modified Medical Research Council (mMRC) scale and Borg scale, while the secondary outcomes included symptoms score and 6-minute walking distance (6MWD). The safety outcome was the incidence of adverse events.

Results: A total of 388 patients with PCC were enrolled and randomly assigned to the QJYQ group ($n = 194$) and the control group ($n = 194$). Compared to the controls, the mMRC scale was improved in the QJYQ group, which was better than that of the control group [β (95%CI): -0.626 ($-1.101, -0.151$), $p = 0.010$]. A significant improvement in Borg scale was also observed in the QJYQ group compared to the control group [β (95%CI): -0.395 ($-0.744, -0.046$), $p = 0.026$]. There was no statistically significant difference in symptoms score and 6MWD between the two groups ($p = 0.293$, $p = 0.724$). No treatment-related adverse events were observed in either group.

Conclusions: QJYQ can bring benefits to patients with PCC, mainly in the improvement of breathlessness and fatigue.

KEYWORDS

COVID-19, post-COVID-19 condition, Qingjin Yiqi granules, randomized clinical trial, rehabilitation treatment

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an acute respiratory tract disease caused by the novel severe acute respiratory syndrome coro-

navirus 2 (SARS-CoV-2),^{1,2} which is a Public Health Emergency of International Concern, posing a serious risk to human health, daily life and global economy.³ Till January 5, 2022, there were 293.75 million confirmed cases of COVID-19 and 5.45 million deaths.⁴ There were

approximately more than 200 million patients with post-COVID-19 condition (PCC),^{5,6} of which over 90% suffered from persistent symptoms, including fatigue (53.1%–80%), breathlessness (43.4%–53%), anxiety (14.6%–23%), and insomnia (26%–30.8%),^{7–11} substantially reducing the quality of life.^{12,13}

For about two years, global researchers have made great achievements in vaccines and drugs, which are powerful weapons for fighting against COVID-19.^{14, 15} However, for patients with PCC, there was lack of new treatment. In China, there were several guidelines for the rehabilitation of patients with PCC,^{16,17} where respiratory training as well as traditional Chinese therapies including herbal medicine, acupuncture, traditional exercise (e.g., Baduanjin) were recommended.¹⁸

Qingjin Yiqi granules (QJYQ) is a new prescription for patients with PCC, which comprises by 16 herbs: Renshen (*Ginseng Radix Et Rhizoma*), Maidong (*Ophiopogonis Radix*), Wuweizi (*Schisandrae Chinensis Fructus*), Fuling (*Poria*), Banxia (*Pinelliae Rhizoma*), Xuanshen (*Scrophulariae Radix*), Cangzhu (*Atractylodis Rhizoma*), Chenpi (*Citri Reticulatae Pericarpium*), Gancao (*Glycyrrhizae Radix Et Rhizoma*), Chaihu (*Bupleuri Radix*), Shengma (*Cimicifugae Rhizoma*), Yiyiren (*Coicis Semen*), Huangqin (*Scutellariae Radix*), Mabancao (*Verbenae Herba*), Lugen (*Phragmitis Rhizoma*), and Danzhuye (*Lophatheri Herba*). These herbs are initially extracted with water, followed by concentration and spray-drying to powder, after which excipients are added with the final mixture pelletized by dry granulation method. Each package contains 10 g, equivalent to 52 g of the crude drug. QJYQ has been recommended by the Rehabilitation Guidelines of Integrated Medicine for COVID-19 Patients in Hebei and Tianjin, and has been widely used in clinical practice.¹⁶ In order to provide more clinical evidence on the effectiveness and safety of QJYQ, a randomized clinical trial was carried out.

2 | METHODS

2.1 | Study design

This study was a randomized, open-label clinical trial to evaluate the effectiveness and safety of QJYQ for patients with PCC. The study was done in Shijiazhuang (Hebei, China).

Ethical approval was granted by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (TJUTCM-EC20210001). Orally informed consent was obtained from all patients or their legal representatives. The protocol of this study was registered in Chinese Clinical Trial Registry (ChiCTR2100042822).

2.2 | Participants

Participants were recruited from Shijiazhuang People's Hospital and Shijiazhuang Fifth Hospital, who were hospitalized at the two hospitals during the treatment period. Patients who met the discharge criteria were transformed into the rehabilitation ward, where the patients

were candidates for this study. Eligible participants were randomly divided into the QJYQ group and the control group in a 1:1 ratio.

2.3 | Eligibility criteria

Eligible participants were mild, ordinary, or severe COVID-19 patients who met the discharge criteria according to the Guidelines for the Diagnosis and Treatment of COVID-19 (trial version 8): normal temperature for more than 3 days; significant improvements in respiratory symptoms; substantial enhancements of acute exudative lesions on chest radiography; two consecutive negative results of RT-PCR tests with at least a 1-day interval between tests.¹⁹ Exclusion criteria were as follows: chronic lung diseases (e.g., chronic obstructive pulmonary disease, interstitial lung disease); previous history of pulmonary surgical intervention; severe clinical condition (e.g., heart failure, stroke); severe chronic disease (e.g., liver cirrhosis, malignant tumors); allergic constitution or allergic to QJYQ; pregnant or breast feeding women.

2.4 | Interventions

All participants received standard rehabilitation treatments (SRTs), which consisted of respiratory training (Lip breathing training, 20 minutes each time, 3 times daily; abdominal breathing training was performed at a rate of 7 breaths per minute for 20 minutes, twice a day; respiratory rhythm training, 20 minutes each time, 3 times per day); and Baduanjin exercise, twice a day.²⁰ Participants in the QJYQ group took QJYQ orally with a dose of 10 g twice daily for 14 days. Any other herbal medicines were prohibited in either group.

2.5 | Outcomes

The primary outcomes were the modified Medical Research Council (mMRC) scale and the Borg scale. The mMRC was used to assess breathlessness^{21,22} and the Borg scale was employed to evaluate perceived exertion and fatigue.²³ Outcomes were detected and assessed at baseline, 7 days, and 14 days after randomization.

The secondary outcomes were the 6-minute walking distance (6MWD) and the symptoms score.²⁴ The symptoms score was the sum of each symptom score, which covered cough, expectoration, pharynx ministry unwell, fatigue, breathlessness, chest distress, chest pain, body pain, palpitation, dysphoria, headache, dizziness, insomnia, hair loss, hidrosis, decreased appetite, constipation, diarrhea, smell disorder, and taste disorder. The degree of each symptoms varied from 0 to 3, 0 = no symptom, 1 = mild, 2 = ordinary, 3 = severe.

The safety outcome was treatment-related adverse events. Treatment-related adverse events involved symptoms and abnormal liver and renal function that were counted as "normal to abnormal" or "abnormal increase".^{25–27} The correlation between adverse events and treatment was assessed by clinical investigators.

2.6 | Statistical analysis

Statistical analysis was performed by R software, following the intention to treat (ITT) principle with the mean imputation applied for missing data. Exploratory subgroup analyses of each efficacy outcomes were performed according to gender, age, and comorbidities.

Continuous variables (e.g., age, height, weight) were expressed as mean \pm standard error of the mean (SEM), which were compared by the Student's *t*-test (normally distributed variables) or the Mann-Whitney test (variables without normal distribution). Categorical variables (e.g., gender, symptoms) were presented as counts and percentages, which were compared by the chi-square test. The comparison of efficacy between two groups was conducted by generalized estimating equation (GEE) analyses with the results displayed as β and 95% confidence interval (CI). Statistical tests were two-sided, and the significance level was set at $\alpha = 0.05$.

3 | RESULTS

3.1 | Participants and baseline characteristics

From January to March 2021, a total of 388 participants (194 per group) were admitted and randomly distributed into two groups. Altogether four (1.03%) participants dropped out, with one participant (0.52%) leaving the QJYQ group due to the taste of QJYQ and three participants (1.55%) withdrawing from the control group owing to their poor compliance. Mean imputation was implemented for the data missing caused by those dropouts. Eventually, all 388 participants were included in the ITT analysis (Figure 1).

The common symptoms at baseline were breathlessness and fatigue (both were 115 times, 29.64%), chest distress (94 times, 24.23%), cough (71 times, 18.30%), insomnia (70 times, 18.04%), pharynx ministry unwell (56 times, 14.43%), and expectoration (48 times, 12.37%). There was no statistically significant difference between the two groups in the baseline characteristics (Tables 1 and 2).

3.2 | Effectiveness

Participants in the QJYQ group exhibited remarkable improvements on both primary outcomes compared with the control group (Table 3). The mMRC scale was illustrated in Figure 2A. The score of mMRC scale was 1.29 ± 0.05 in the QJYQ group and 1.27 ± 0.05 in the control group at baseline. After 7 days of treatment, the score was 0.65 ± 0.04 in the QJYQ group and 0.80 ± 0.05 in the control group. After 14 days of treatment, the score was 0.20 ± 0.03 in the QJYQ group and 0.34 ± 0.04 in the control group. The GEE estimated difference of the mMRC scale was [β (95%CI) = -0.626 ($-1.101, -0.151$); $p = 0.010$].

The Borg scale was depicted in Figure 2B. At baseline, the score of Borg scale was 10.55 ± 0.16 in the QJYQ group and 10.51 ± 0.13 in the control group. After 7 days of treatment, the score decreased to 9.29 ± 0.12 and 9.51 ± 0.11 , respectively. The score, after 14 days

of treatment, appeared to be 7.89 ± 0.09 in the QJYQ group and 8.37 ± 0.10 in the control group. The GEE estimated difference of the Borg score was [β (95%CI) = -0.395 ($-0.744, -0.046$); $p = 0.026$].

The improvements of the symptoms score and the 6MWD were similar in the QJYQ group and the control group (Figure 3) with the GEE estimated difference of the symptoms score being [β (95%CI) = 0.235 ($-0.204, 0.674$); $p = 0.293$] and that of the 6MWD being [β (95%CI) = 0.006 ($-0.029, 0.041$); $p = 0.724$] (Table 4).

The subgroup analysis of mMRC scale showed that the QJYQ group performed better than the control group [β (95%CI) = -1.021 ($-1.988, 0.053$); $p = 0.039$] in the subgroup of males. Data showed that QJYQ can markedly decrease the mMRC score in the subgroup of patients younger than 65 years old [β (95%CI) = -0.725 ($-1.261, -0.189$); $p = 0.008$]. Besides, in the subgroup of patients without comorbidities, the QJYQ group was superior to the control group [β (95%CI) = -0.754 ($-1.384, -0.125$); $p = 0.019$]. As for other subgroups, no statistically significant difference between the QJYQ group and the control group was witnessed (Figure 4).

The subgroup analysis of Borg scale disclosed that the performance of the QJYQ group was greater than that of the control group in the subgroup of males [β (95%CI) = -0.765 ($-1.331, -0.198$); $p = 0.008$]. In addition, a remarkable reduction of the Borg score in the QJYQ group was observed in the subgroup of patients younger than 65 years old [β (95%CI) = -0.446 ($-0.826, -0.066$); $p = 0.021$]. In terms of other subgroups, there was no statistically significant difference between the QJYQ group and the control group (Figure 5).

In the subgroup analyses of symptoms score and 6MWD, neither the QJYQ group nor the control group showed statistically significant differences in all subgroups (Figures 6 and 7).

3.3 | Safety

There was no death or serious adverse event that occurred in either group. Besides, no "abnormal increase" of liver and renal function and no "normal to abnormal" of total bilirubin (TBIL), creatinine (Cr) and blood urea nitrogen (BUN) was observed in both groups. It was found that a total of 19 participants experienced "normal to abnormal" of alanine transaminase (ALT), 9 of them came from the QJYQ group and 10 of them belonged to the control group. Twelve participants were observed to undergo "normal to abnormal" of aspartate aminotransferase (AST), with 4 from the QJYQ group and 8 from the control group. None of the abnormalities in ALT and AST was considered to be related to QJYQ and SRTs by the assessment of clinical investigators.

4 | DISCUSSION

The results of this study provided evidence that QJYQ could bring benefit to patients with PCC. In this study, data showed the QJYQ group was superior to the control group in mMRC scale and Borg scale, improving the symptoms of breathlessness and fatigue of patients with PCC. No adverse event related to QJYQ was recorded.

TABLE 1 Demographic and clinical characteristics

Variables	QJYQ group (n = 194)	Control group (n = 194)	p Value
Age (year)	47.96 ± 1.36	44.82 ± 1.17	0.050
Gender (male/female)	72/122	77/117	0.602
Height (cm)	163.34 ± 0.54	164.30 ± 0.53	0.231
Weight (kg)	68.43 ± 1.05	66.79 ± 0.93	0.185
Temperature (°C)	36.38 ± 0.02	36.40 ± 0.03	0.672
Systolic pressure (mmHg)	132.69 ± 1.31	130.39 ± 1.19	0.362
Diastolic pressure (mmHg)	86.93 ± 1.25	85.14 ± 0.92	0.421
Respiration rate (bpm)	19.21 ± 0.53	19.20 ± 0.37	0.054
Heart rate (bpm)	81.24 ± 0.93	82.04 ± 0.90	0.734
Oxygen saturation (%)	98.14 ± 0.09	98.14 ± 0.08	0.754
White blood cell count (10 ⁹ /L)	6.30 ± 0.09	6.42 ± 0.12	0.971
Neutrophil count (10 ⁹ /L)	5.82 ± 0.63	5.25 ± 0.48	0.390
Lymphocyte count (10 ⁹ /L)	2.78 ± 0.23	2.58 ± 0.22	0.133
Hematocrit (%)	39.46 ± 1.25	37.12 ± 0.45	0.136
Hemoglobin (g/L)	130.82 ± 0.92	129.72 ± 0.91	0.156
Blood platelet (10 ⁹ /L)	232.34 ± 3.38	233.30 ± 3.63	0.942

Note: Data are mean ± SEM.

QJYQ = Qingjin Yiqi granules.

TABLE 2 Persistent symptoms

Variables	Total (n = 388)	QJYQ group (n = 194)	Control group (n = 194)	p Value
Breathlessness	115 (29.64)	61 (31.44)	54 (27.84)	0.436
Fatigue	115 (29.64)	59 (30.41)	56 (28.87)	0.739
Chest distress	94 (24.23)	46 (23.71)	48 (24.74)	0.813
Cough	71 (18.30)	35 (18.04)	36 (18.56)	0.896
Insomnia	70 (18.04)	36 (18.56)	34 (17.53)	0.792
Pharynx ministry unwell	56 (14.43)	27 (13.92)	29 (14.95)	0.773
Expectoration	48 (12.37)	27 (13.92)	21 (10.82)	0.355
Hair loss	30 (7.73)	17 (8.76)	13 (6.70)	0.447
Palpitation	18 (4.64)	10 (5.15)	8 (4.12)	0.629
Constipation	17 (4.38)	9 (4.64)	8 (4.12)	0.804
Decreased appetite	16 (4.12)	8 (4.12)	8 (4.12)	1
Dizziness	12 (3.09)	6 (3.09)	6 (3.09)	1
Hidrosis	12 (3.09)	7 (3.61)	5 (2.58)	0.558
Body pain	9 (2.32)	6 (3.09)	3 (1.55)	0.312
Dysphoria	8 (2.06)	3 (1.55)	5 (2.58)	0.475
Headache	8 (2.06)	5 (2.58)	3 (1.55)	0.475
Smell disorder	8 (2.06)	6 (3.09)	2 (1.03)	0.153
Diarrhea	7 (1.80)	5 (2.58)	2 (1.03)	0.253
Taste disorder	4 (1.03)	3 (1.55)	1 (0.52)	0.315
Chest pain	3 (0.77)	2 (1.03)	1 (0.52)	0.562

Note: Data are n (%).

QJYQ = Qingjin Yiqi granules.

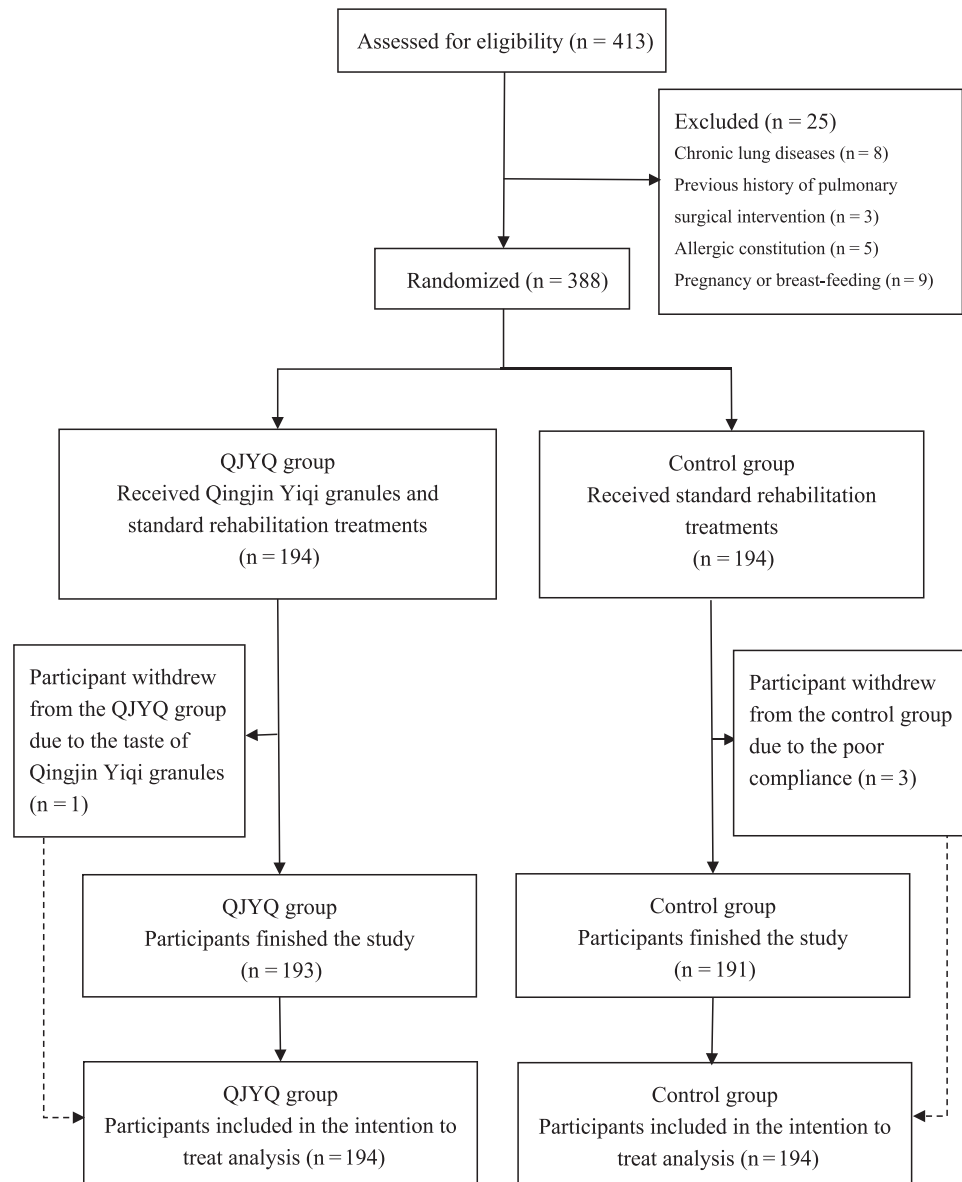


FIGURE 1 Flowchart of study

TABLE 3 Primary outcomes

Outcomes	Time	QJYQ group (n = 194)	Control group (n = 194)	β (95%CI)	p Value
mMRC scale	Baseline	1.29 ± 0.05	1.27 ± 0.05	-0.626 (-1.101, -0.151)	0.010
	7 days	0.65 ± 0.04	0.80 ± 0.05		
	14 days	0.20 ± 0.03	0.34 ± 0.04		
Borg scale	Baseline	10.55 ± 0.16	10.51 ± 0.13	-0.395 (-0.744, -0.046)	0.026
	7 days	9.29 ± 0.12	9.51 ± 0.11		
	14 days	7.89 ± 0.09	8.37 ± 0.10		

Note: Data are mean ± SEM.

QJYQ = Qingjin Yiqi granules; mMRC = modified Medical Research Council.

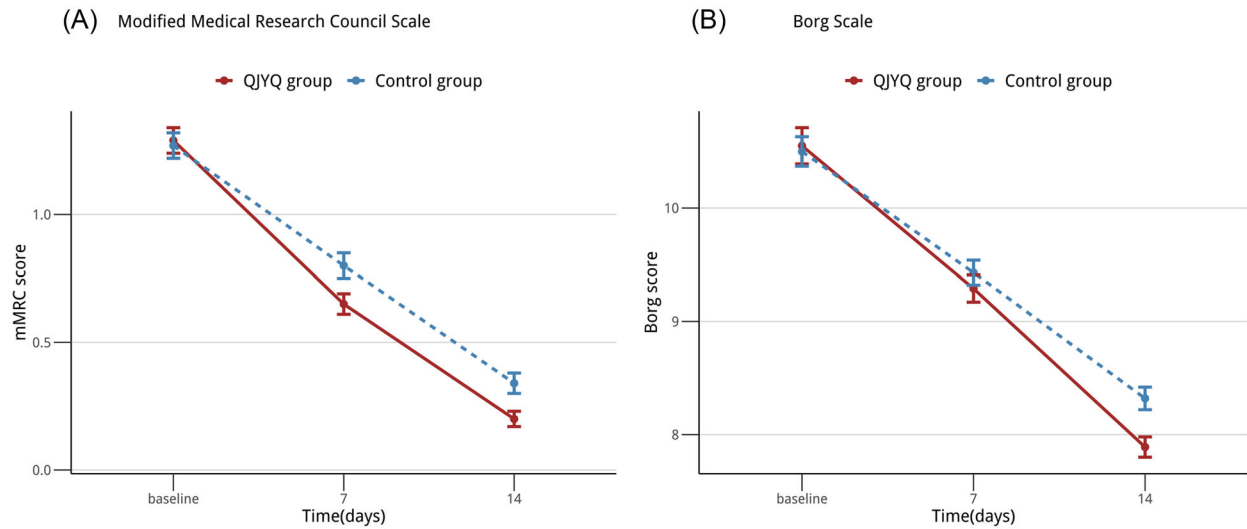


FIGURE 2 Line chart: primary outcomes. (A) The changes of modified Medical Research Council (mMRC) scale, from baseline to 14 days. (B) The changes of Borg scale, from baseline to 14 days. All data were expressed as mean \pm standard error of the mean; $n = 194$ per group

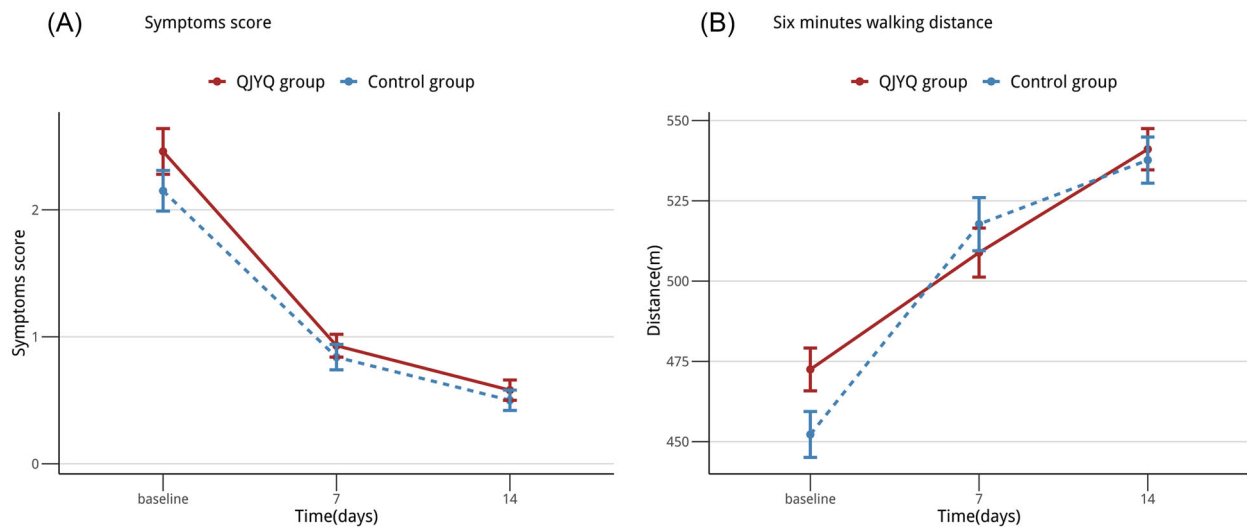


FIGURE 3 Line chart: secondary outcomes. (A) The changes of symptoms score, from baseline to 14 days. (B) The changes of 6-minute walking distance (6MWD), from baseline to 14 days. All data were expressed as means \pm standard error of the mean; $n = 194$ per group

TABLE 4 Secondary outcomes

Outcomes	Time	QJYQ group ($n = 194$)	Control group ($n = 194$)	β (95%CI)	p Value
Symptoms score	Baseline	2.46 \pm 0.18	2.15 \pm 0.16	0.235 (−0.204, 0.674)	0.293
	7 days	0.93 \pm 0.09	0.84 \pm 0.10		
	14 days	0.58 \pm 0.08	0.50 \pm 0.08		
6MWD	Baseline	472.50 \pm 6.67	452.23 \pm 7.15	0.006 (−0.029, 0.041)	0.724
	7 days	508.88 \pm 7.64	517.74 \pm 8.27		
	14 days	541.07 \pm 6.43	537.68 \pm 7.18		

Note: Data are mean \pm SEM.

QJYQ = Qingjin Yiqi granules; 6MWD = 6-minute walking distance.

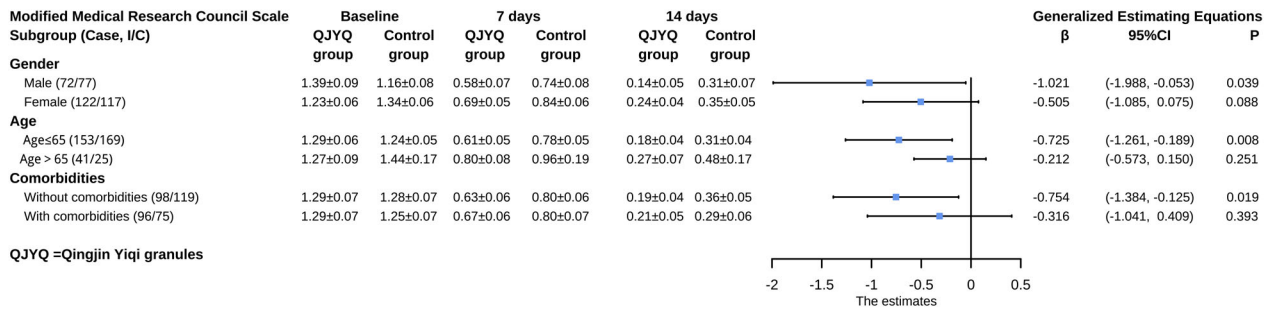


FIGURE 4 Subgroup analyses of modified Medical Research Council (mMRC) scale. Subgroup analyses were performed on the basis of gender, age, and comorbidities. Data of mMRC scale at baseline, 7 days, and 14 days after randomization were expressed as mean ± standard error of the mean; the effect estimates were represented as β and 95% confidence interval

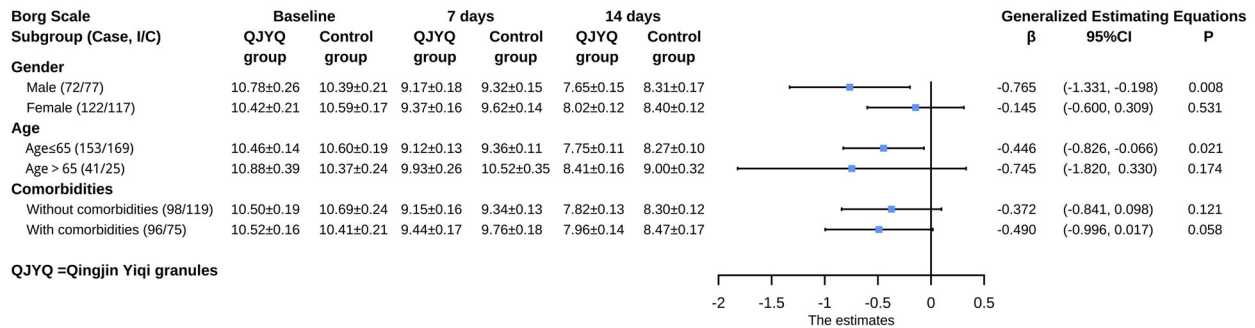


FIGURE 5 Subgroup analyses of Borg scale. Subgroup analyses were performed on the basis of gender, age, and comorbidities. Data of Borg scale at baseline, 7 days, and 14 days after randomization are expressed as mean ± standard error of the mean; the effect estimates were represented as β and 95% confidence interval

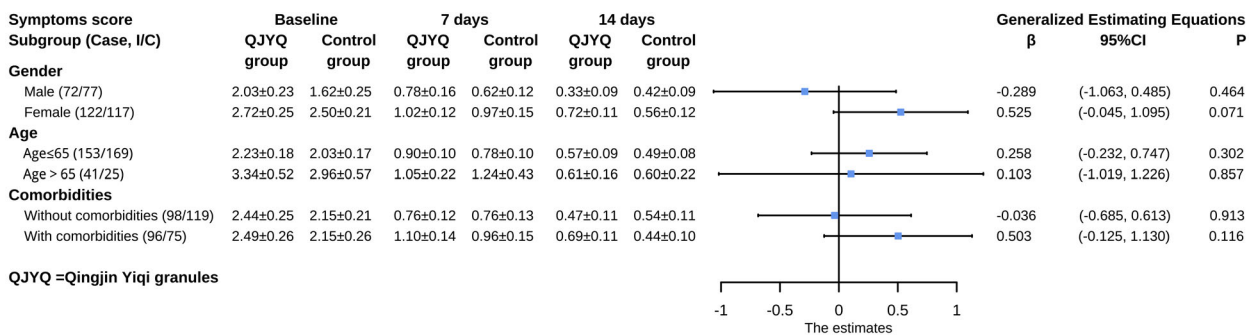


FIGURE 6 Subgroup analyses of symptoms score. Subgroup analyses were performed on the basis of gender, age, and comorbidities. Data of symptoms score at baseline, 7 days, and 14 days after randomization were expressed as mean ± standard error of the mean; the effect estimates were represented as β and 95% confidence interval

In terms of symptoms score and Δ MWD, there was no significant difference between the two groups. The participants in this study, whose conditions were predominantly mild instead of serious. Therefore, the symptoms score and Δ MWD in this study were close to normal at baseline. SRTs incorporate respiratory training and Baduanjin had been proven to exert the effects of improving the symptoms and pulmonary function by prior studies.²⁸⁻³⁰ So, it was difficult to detect

the specific add-on effect of QJYQ, especially in a small sample clinical trial.

In this study, common symptoms among participants were breathlessness (29.64%), fatigue (29.64%), chest distress (24.23%), cough (18.30%), and insomnia (18.04%). The percentages of other symptoms were under 15%. Compared with other studies, some similarities and differences were found.

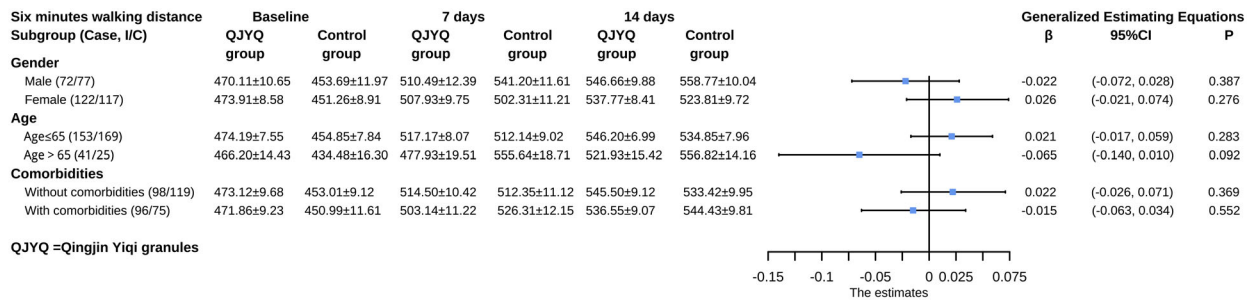


FIGURE 7 Subgroup analyses of 6-minute walking distance (6MWD). Subgroup analyses were performed on the basis of gender, age, and comorbidities. Data of 6MWD at baseline, 7 days, and 14 days after randomization are expressed as mean \pm standard error of the mean; the effect estimates were represented as β and 95% confidence interval

First, the types of symptoms observed in this study were similar to those reported in other studies. Swapna Mandal et al. conducted a study in Britain from April to June 2020 with 384 patients and found that the most common symptoms in patients with PCC included fatigue (69%), breathlessness (53%), and cough (34%).⁸ Moreover, Chaolin Huang et al. reported a cohort study conducted in China from January to May 2020 with 1733 patients, in which fatigue (63%) and insomnia (26%) were the most prevalent symptoms.⁹

Second, the proportion of symptoms in this study was notably lower than that in studies from other countries. Aleksander Och et al. reported a study carried out in Europe from October 2020 to February 2021, including 79 patients, with 60.76% fatigue and more than 20% of 12 kinds of symptoms.³¹ Similarly, Greg Vanichkachorn et al. published a cohort study undertaken in America from June to December 2020, which included 100 patients, with 80% fatigue, 49% breathlessness, and more than 82% limitation of normal function.¹¹

Third, the symptoms ratio of this study was less than studies conducted in China at the early stage of COVID-19 pandemic. Lixue Huang et al. performed a study in China from January to May 2020, in which 1230 patients attended and the ratio of fatigue and insomnia were 52% and 27%, respectively.³² A higher symptoms ratio was reported in Chaolin Huang's study, with 63% fatigue and 26% insomnia.⁹

The reasons for the low symptoms ratios in this study can be summarized as follows: (1) mutations in SARS-CoV-2 occurred over the last 2 years with different variants causing the different ratio of symptoms;^{33,34} (2) the differences in geographic distribution and climate among each study, also influenced the symptoms; (3) the difference interventions for patients with acute COVID-19 condition is an important factor, which can influence the symptom ratio. TCM was rarely used in other countries, and the utilization rate of TCM in the early stage of COVID-19 pandemic was insufficient in China. All the patients included in this study received TCM during the acute period of COVID-19, which was an important factor in the reduction of symptoms.

There were several limitations in this study. First, it was an open-label study without placebo control, rather than the double-blind trial, which might cause selection bias and detection bias. Second, add on design was used based on ethical considerations. As a consequence, the

real efficacy of QJYQ might be underestimated. Third, the treatment course was no more than 14 days. So, the data of this study could not find the long-time effectiveness of QJYQ. Trials with long-time follow-up were warranted.

5 | CONCLUSIONS

The results of this study provided evidence that QJYQ is a safe Chinese herbal medicine which can bring benefits to patients with PCC. Large sample, strictly designed, randomized clinical trials are still needed to provide more high-quality evidence for the long-term effect of QJYQ for PCC.

ACKNOWLEDGMENTS

This work is supported by National Natural Science Foundation of China: (82004505), (82074583); National Key Research and Development Program of China: (2021YFC0863200).

ORCID

Wentai Pang  <https://orcid.org/0000-0001-5180-2116>

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How to cite this article: Pang W, Yang F, Zhao Y, et al. Qingjin Yiqi granules for post-COVID-19 condition: a randomized clinical trial. *J Evid Based Med*. 2022;15:30–38. <https://doi.org/10.1111/jebm.12465>