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Original Article

Long-term follow-up of the treatment for severe COVID-19 with qigong exercise and acupressure: A randomized controlled trial

Shuting Liu[a,b,c,†], Ranran Zhu[a,†], Chongjie Yao[d,e], Chao Zhan[f], Jinxiang Wang[a], Min Fang[e], Lei Fang[a,b,*]

[a] School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[b] Department of Rehabilitation Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai, China
[c] Department of Rehabilitation Medicine, Suzhou Hospital of Traditional Chinese Medicine, Suzhou, China
[d] School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[e] Department of Rehabilitation Medicine, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China
[f] Department of Rehabilitation Medicine, Huangshi Hospital of Traditional Chinese Medicine, Hubei, China

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ABSTRACT

Background: Most clinical trials have reported significant short-term effects of traditional medicine therapies on COVID-19 patients. However, there is no clinical trial to determine the long-term effects of traditional medicine therapies on severe COVID-19 patients.

Methods: A total of 128 patients with severe COVID-19, who were recruited in our previous clinical trial following hospital discharge, were monitored at months 14 and 28. This trial aims to evaluate the long-term effect of an early Qigong exercise and acupressure rehabilitation program on patients with severe COVID-19.The intervention group received qigong exercise and acupressure therapy, plus standard therapies. The control group received standard therapies.The study was a single-center, parallel, randomized, prospective follow-up study. The outcomes of the study included changes in the modified Borg dyspnea scale (MBS), the modified Medical Research Council dyspnea scale (mMRC), the patient health questionnaire-9 scale (PHQ-9), the activity of daily living (ADL), the remaining clinical symptoms and any intervention related adverse events.

Results: The intervention group showed a statistically significant improvement in the mMRC scores (−0.4, 95 % CI (−0.6, 0.2), $P < 0.001$) and the MBS scores (−0.6, 95 % CI (−0.9, −0.3), $P < 0.001$) after 14 months of discharge compared with the control group. At 28 months of discharge, the intervention group, compared with the control group alone, significantly increased their MBS scores (−0.4, 95 % CI (−0.7, −0.1), $P = 0.024$) and a significantly decreased positive rate of dyspnea symptoms after 14 months of discharge ($P < 0.05$). However, ADL and PHQ-9 scores showed no significant difference between the two groups during the follow-up ($P > 0.05$).

Conclusions: QARP had long-term sustained efficacy for dyspnea, chest tightness, and cough in patients with COVID-19, especially in young and middle-aged patients, and the effect was significant at the 14th month of follow-up.

Trial registration: This trial was registered at the China Clinical Trial Registry (ChiCTR2100044572).

1. Introduction

Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), an acute infectious disease with predominantly inflammatory lung lesions, the spectrum of clinical manifestations encompasses mild upper respiratory tract symptoms that are asymptomatic and severe acute respiratory distress syndromem.[1] As of February 17, 2023, World Health Organization (WHO) reported that there had been >756 million cases of SARS-CoV-2 infections globally, including 6844,267 deaths.[2] Although most SARS-CoV-2-infected patients recover from the acute phase, the study emphasized that 43.2 % of patients had at least one COVID-19-related symptom within one year of infection and nearly a quarter of critically severe patients still had persistent symptoms at 2-year follow-up.[3] Consequently, the long-term recovery of discharged COVID-19 patients, especially those with severe COVID-19, remains in urgent need of medical intervention.

Essential elements of traditional Chinese medicine (TCM) include qigong exercise and acupressure therapy, commonly used to treat res-

* Corresponding author at: School of ReRehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China.
E-mail address: fanglei@shutcm.edu.cn (L. Fang).
† These authors have contributed equally to this work.

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piratory disorders.[4-8] Since the outbreak of the COVID-19 pandemic, qigong exercise and acupressure as complementary and alternative medicine have been used in the early treatment or rehabilitation of COVID-19. Studies have verified that they significantly enhance the respiratory function of patients with COVID-19 and are also beneficial in improving their depression and anxiety.[9-11] However, the long-term effectiveness of acupressure therapy and qigong exercise in COVID-19 remains unclear.

We previously reported the short-term safety and efficacy of the acupressure rehabilitation program and qigong exercise (QARP) in a single-center, parallel, randomized controlled trial (ChiCTR2000029994), from admission to discharge. We found that QARP significantly improved pulmonary function, symptoms of cough and dyspnea, and shortened hospital stays for patients with severe COVID-19 compared with standard therapies alone.[12] Therefore, the 28-month postdischarge follow-up results of QARP were reported for patients with severe COVID-19 in a single-center, parallel, randomized controlled trial.

2. Methods

2.1. Study design and participants

This was a single-center, parallel, randomized, prospective follow-up study. Based on previous clinical studies on the effect of respiratory symptoms after acupressure therapy plus Liu Zi Jue Qigong interventions, the mMRC Scale score in the control group is 0.52 with a standard deviation of 0.11, and the average mMRC Scale score in the treatment group is 0.95 with a standard deviation of 0.92.[13] In this study, the target sample size will be 64 participants in each group, anticipating on maximum loss to follow-up of 20 %. Total 128 eligible participants aged 20–80 years who met the severe COVID-19 diagnostic requirements were recruited in our pre-study, receiving standard therapies (n = 64) or standard therapies + QARP (n = 64). Young and middle-aged: 20–59 years, elderly: 60–80 years. Participants were assessed at baseline (on admission) and at discharge. Protocols and published articles have detailed the study design and pre-test methodology.[14] To evaluate the effectiveness of QARP in long-term follow-up, all patients were followed up 14 and 28 months after discharge from Huangshi Hospital of Traditional Chinese Medicine in Hubei Province. The study was performed in accordance with the principles of the Declaration of Helsinki. All patients signed informed consent forms and received follow-up subsidies. The ethical approval number for the follow-up study is HSZYPJ-2021–001–01, registered with the China Clinical Trial Registry (ChiCTR2100044572). The reporting of the study complies with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial protocol and CONSORT checklist can be found in Supplementary material.

2.2. Eligibility criteria

The following requirements had to be met to be included: The candidate had to be stable, ages 20–80, meet the critical diagnostic criteria for severe COVID-19,[15] be willing to sign an informed consent form, refrain from participating in other exercise programs, and give consent to finish the follow-up. Patients with problems from other significant underlying disorders, including hypertension, coronary heart disease, obstructive pulmonary disease, and chronic obstructive pulmonary disease, with severe bone and joint illnesses, with cognitive dysfunction preventing them from understanding the trial process and rehabilitation material, with serious mental illness (for example, severe osteoporosis, periarteritis, and spinal arthritis), with any of the aforementioned conditions that impair limb function and movement, with pregnancy or nursing (women), who engage in other types of exercises during the trial with respiratory failure who require mechanical ventilation, and with shock or combined organ failure requiring intensive care unit (ICU) monitoring and treatment were excluded.

2.3. Randomization, allocation concealment, and blinding

SPSS version 26.0 (IBM, Chicago, IL) was used to generate random numbers, and eligible patients were randomly selected to receive either standard therapies plus QARP or standard therapies in a 1:1 ratio. The assignment of groupings to determine random numbers was performed by a committed individual who refrained from including subjects. Hidden grouping was conducted using the envelope method. The envelope might be opened, and the participant would accept the appropriate measures if they satisfied the inclusion requirements. The specific intervention did not allow blinding of patients or the therapist administering the intervention. However, outcome assessors and data statisticians were not informed of the grouping information to reduce bias.

2.4. Interventions

Participants received standard therapy prescribed by health authorities as standard guidelines. It proceeds as follows: (1) Patients should be given enough time to rest, and medical personnel must closely monitor vital signs, oxygen saturation, and other parameters. (2) Depending on the changes in the patient's state, routine blood and urine tests, C-reactive protein, biochemical indicators, blood coagulation function, arterial blood gas analysis, chest imaging, etc., should be monitored. (3) Prompt evaluation of patients experiencing respiratory distress and/or hypoxemia is imperative. Particularly, patients with severe illnesses should be fitted with a nasal cannula or mask for oxygen inhalation. (4) If needed, doctors should provide antiviral medications along with antibiotics. (5) To preserve the stability of the internal environment, water and electrolyte balance must be checked and to reinforce supportive treatment to guarantee adequate heat. (6) These symptoms could also be relieved by applying traditional Chinese medicine.

As per the normal guidelines for therapy, the QARP group was mandated to perform a QARP that included Liu Zi Jue Qigong exercises and acupressure therapy. The program was presented At both 10 a.m. and 4 p.m. daily. On the first day, participants were shown how to perform the Liu Zi Jue Qigong exercise live by therapists with 10 years of comparable clinical experience or until they were competent. The exercise involved having participants pronounce 'Xu, He, Hu, Si, Chui, Xi' 12 times in a relaxed position. Workbooks with guidelines and videos of the Liu Zi Jue Qigong exercise were also provided to facilitate further practice. Furthermore, every treatment occurred for 20 min, making it 40 min daily. After agreeing on the participants' acupuncture spots, pressure levels, and length of therapy, a physical therapist administered the acupressure treatment daily. When the subjects were in a sitting or laying position, the therapist applied mild pressure to the acupoints, pressing perpendicular to the skin surface for 3–7 s. Lung viscera are associated with the acupoints of Feishu (BL13), Danzhong (RN17), and Zhongfu (LU1). The therapy lasted from the day of the patient's admission until discharge.The average period of hospitalization for patients with severe COVID-19 was 3 weeks.

2.5. Follow-up procedures

At discharge, patients were invited to join the COVID-19 Rehabilitation WeChat group, which was created to facilitate further follow-up. Patients in the QARP group were instructed to continue to complete QARP treatment at home, while patients in the control group completed pursed-lip breathing exercises thrice a week. Patients who continue the follow-up program received monthly subsidies. Physical therapists monitor each patient remotely by consulting on the phone about the history of training activities, including intensity, duration, and training-related issues, and motivate the patient for the next phase. Patients had in-person follow-up visits on the 14th and 28th months following discharge. During the follow-up appointment, patients who completed various questionnaires regarding depression and dyspnea were physically

examined and interviewed by a trained physician and researcher. Additionally, the patients' general information and medical history were recorded in detail. A combination of a remote telephone and a WeChat e-questionnaire was used for patients who could not come to the hospital due to some objective reasons (e.g., offsite). Electronic and paper questionnaires are the same.

2.6. Outcomes

The principal result was changes in the scores on the modified Borg dyspnea scale (MBS),the activity of daily living (ADL) and the modified Medical Research Council dyspnea scale (mMRC) between the baseline and 28-month discharge visit. mMRC is a simple and verified tool for evaluating the perceived breathlessness of patients. It is also used to assess the effect of dyspnea on daily activities.[16] Higher scores on the mMRC indicate a more severe degree of dyspnea; the score ranges from 0 to 4.[17] The MBS is a vertical scale from 0 to 10, in which patients are asked to choose the number that best describes their feeling of breathlessness, with higher numbers indicating more severe dyspnea.[18] The secondary outcomes were the patient health questionnaire-9 scale (PHQ-9) scores and the remaining clinical symptoms at 28 months of discharge (cough and breathlessness). The PHQ-9 is a questionnaire that screens for depression. The total score is 27, a higher score is indicated the greater the risk of depression.[19,20]

2.7. Statistical analysis

Data processing was performed using the statistical program SPSS 26.0. Data analysis was conducted based on the intention-to-treat principle. The linear mixed-effects model analysis method was used to analyze data on repeated measures. Time and intervention were included as fixed-effect variables. Considering that individual variability increases the variability of the data, the study participants (ID) was included as a random effect variable in the model. To increase the test efficacy, the means were adjusted by including baseline data as a covariate in the model. Symptoms (breathlessness and cough) were statistically analyzed for positivity using the chi-square test. Multiple interpolations processed the missing data. Here, a 2-tailed $P < 0.05$ threshold was used to indicate statistical significance.

3. Results

3.1. Participant characteristics

Between January 2020 and August 2022, 128 eligible participants were recruited. The mean age was 51.8 years; 55 (43 %) patients were male and 73 (57 %) were female; 43 (34 %) patients had coexisting comorbidities. The baseline attributes of both groups were similar and balanced. Additionally, the age group was divided into young, middle-aged, and elderly participants for analysis. The two groups of young and middle-aged participants were balanced, and there was a difference in the respiratory rate of the older participants (Table 1). At the 28-month follow-up at discharge, there was one death in the standard therapies group; the cause of death was an acute myocardial infarction episode, and this adverse effect was promptly reported to the ethics committee. Total 127 patients completed all the outcome measurements (Fig. 1).

3.2. Primary outcome

Table 2 shows the changes in mMRC and MBS from baseline (at admission) to discharge at 28 months. At 14 months of discharge, the standard therapies group had a mean reduction of –1.9 (95 % CI, –2.1 to –1.7) in mMRC scores and a mean reduction of –4.1 (95 % CI, –4.7 to –3.5) in MBS scores from baseline, and the QARP group had a mean reduction of –2.5 (95 % CI, –2.7 to –2.3) in mMRC scores and a mean reduction of –4.8 (95 % CI, –5.4 to –4.3) in MBS scores from baseline. The QARP group showed significantly superior efficacy for all primary outcomes compared with the standard therapies group [mMRC, –0.4 (95 % CI, –0.6 to 0.2; $P < 0.001$)] and MBS, –0.6 (95 % CI, –0.9 to –0.3; $P < 0.001$). The MBS score from baseline was reduced by –4.6 (95 % CI, –5.1 to –4.1) on average for the standard therapies group and –5.1 (95 % CI, –5.7 to –4.6) on average for the QARP group at 28 months of discharge; the QARP group demonstrated a significant between-group difference of –0.4 (95 % CI, –0.7 to –0.1; $P = 0.024$) in MBS scores when compared with the standard therapies group. Fig. 2a compares the MBS and mMRC scores between the two groups. Table 2 shows that the ADL score increased at all follow-up time points compared to baseline.

3.3. Results of age stratification analysis

At 14 months of discharge, the QARP group had statistically significant differences in mMRC and MBS scores compared with the standard therapies group for young and middle-aged patients; no significant differences were found between the two groups for any outcome at any point during the follow-up period for the older participants (Fig. 2).

3.4. Secondary outcomes

Fig. 3 shows the change in symptom positivity rates. The positive rates of cough and breathlessness symptoms were significantly decreased in both groups at all time points compared with discharge ($P < 0.05$); compared with 14 months of discharge, the positive rates of cough and breathlessness symptoms decreased significantly in the QARP group ($P < 0.05$), and the positive rates of cough symptoms decreased significantly in the standard therapies ($P < 0.05$). At 14 months of discharge, compared with the standard therapies, the QARP group had a statistically significant reduction in the positive rate of breathlessness symptoms ($P < 0.05$).

3.5. Safety results

No adverse events (include fall, dizziness, bone fracture, vital signs, etc.) related to the intervention occurred during the trial.

4. Discussion

Over 770 million people have been infected with SARS-CoV-2, with 6.97 million fatalities.[2] One study found that 19.8 % of patients with COVID-19 had multiple persistent symptoms, such as chest tightness and dyspnea, two years after infection, with 24.4 % of patients with severe disease experiencing persistent symptoms; dyspnea did not significantly subside over time.[3] Therefore, pulmonary rehabilitation is crucial for improving long-term symptoms in patients with COVID-19. However, because of the uneven development of rehabilitation services globally, meeting the demand for COVID-19 rehabilitation is challenging.[21] Enhancing the rehabilitation of chronic diseases, such as respiratory disorders, is made possible by complementary and alternative medicine, which is an affordable and easily available medical resource.[22] In the short term, liuzijue, tai chi, baduanjin, and acupressure improve dyspnea, exercise capacity, quality of life, anxiety, and depression as adjunct therapies to pulmonary rehabilitation. However, there are no reports on the long-term influence of Qigong and acupressure on the persistent symptoms of the participants.[4-7] Thus, after a 28-month follow-up trial following hospital discharge, our study confirmed that QARP can further ameliorate dyspnea, chest tightness, and cough in patients with long-term COVID-19.

In our study, the mMRC and the MBS scale were used together to monitor the improvement of dyspnea in patients with long-term COVID-19. According to the findings, during the 28-month follow-up period, the QARP group's MBS and mMRC scores dropped by 5.1 and 2.7 points, respectively, compared with those at admission. These changes were

Table 1
Demographics and baseline characteristics of patients.

Variable	QARP group, n = 64(95 % CI)	Control group, n = 64(95 % CI)	P-value
Age	50.0 (47.2, 52.8)	53.6 (50.2, 57.0)	0.104
Young and middle-aged	45.5 (43.3, 47.7)	45.0 (41.5, 48.6)	0.827
Elderly	66.3 (64.1, 68.5)	66.2(64.7, 67.7)	0.941
Sex			
Male	25 (39.1 %)	30 (46.9 %)	0.372
Female	39 (60.9 %)	34 (53.2 %)	
BMI (kg/m2)	23.8(23.1, 24.6)	23.9(23.1, 24.7)	0.945
Young and middle-aged	24.1(23.2, 25.0)	23.5(22.6, 24.5)	0.415
Elderly	23.1(21.8, 24.3)	24.4(22.9, 25.9)	0.224
Temperature, ˚C	37.5 (37.3, 37.8)	37.4 (37.2, 37.6)	0.326
Young and middle-aged	37.5 (37.3, 37.8)	37.4 (37.2, 37.7)	0.676
Elderly	37.5 (36.9, 38.1)	37.2 (36.9, 37.6)	0.401
Heart rate (bpm)	85.5 (82.7, 88.4)	85.4 (82.3, 88.5)	0.941
Young and middle-aged	85.4 (81.8, 88.9)	85.7 (82.5, 88.9)	0.886
Elderly	86.2 (81.9, 90.5)	84.9 (78.6, 91.3)	0.774
Respiration rate (times/min)	23.1 (20.6, 25.6)	22.6 (21.6, 23.6)	0.728
Young and middle-aged	23.5 (20.3, 26.7)	21.3 (20.3, 22.3)	0.250
Elderly	21.6 (20.0, 23.2)	24.5 (22.6, 26.3)	0.018*
Systolic blood pressure (mm Hg)	124.2(121.9, 126.6)	123.3 (119.9, 126.6)	0.648
Young and middle-aged	123.6(120.9, 126.3)	121.1(117.5, 124.7)	0.250
Elderly	126.3(120.9, 131.6)	126.5(120.0, 132.9)	0.970
Diastolic blood pressure (mm Hg)	73.0 (70.7, 75.3)	72.5 (70.2, 74.9)	0.799
Young and middle-aged	73.3 (70.6, 76.0)	71.3 (68.3, 74.2)	0.301
Elderly	71.6 (67.2, 76.1)	74.4 (70.3, 78.6)	0.381
Blood oxygen saturation (SaO_2 %)	92.7 (92.1, 93.2)	92.8 (92.1, 93.5)	0.778
Young and middle-aged	92.6 (92.0, 93.3)	92.9 (92.2, 93.7)	0.519
Elderly	92.9 (91.9, 93.8)	92.6 (91.2, 93.9)	0.770
MBS	5.5 (4.9, 6.1)	5.3 (4.8, 5.8)	0.663
Young and middle-aged	5.3 (4.6, 5.9)	5.2 (4.5, 5.9)	0.883
Elderly	6.1 (5.0, 7.3)	5.4 (4.6, 6.2)	0.292
mMRC	2.9 (2.7, 3.1)	2.7 (2.5, 2.8)	0.137
Young and middle-aged	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.058
Elderly	3.2 (2.8, 3.7)	3.0 (2.6, 3.3)	0.356
ADL	93.3 (91.9, 94.6)	92.9 (91.9, 93.9)	0.649
Young and middle-aged	92.9 (91.2, 94.6)	93.0 (91.4, 94.6)	0.914
Elderly	94.6 (92.5, 96.8)	92.7 (91.5, 93.9)	0.072
PHQ9	13.3 (12.0, 14.7)	13.7 (12.3, 15.0)	0.717
Young and middle-aged	13.4 (11.9, 14.9)	12.4 (10.8, 14.0)	0.352
Elderly	13.0 (9.8, 16.2)	15.5 (13.2, 17.8)	0.184
Any comorbidity			0.244
Hypertension	10 (16 %)	10 (16 %)	
Diabetes	8 (13 %)	5 (8 %)	
Chronic Hepatitis B	2 (3 %)	1 (2 %)	
Chronic gastritis	2 (3 %)	2 (3 %)	
Coronary heart disease	6 (9 %)	1 (2 %)	
Chronic bronchitis	1 (2 %)	0	
Rheumatic heart disease	0	1 (2 %)	
Symptoms and signs			0.986
Cough	62 (97 %)	61 (95 %)	
Fever	53 (83 %)	52 (81 %)	
Dyspnoea	48 (75 %)	50 (78 %)	
Diarrhea	7 (11 %)	9 (14 %)	
Fatigue	44 (69 %)	47 (73 %)	

BMI, body mass index; MBS, modified Borg dyspnea scale; mMRC, modified medical research council dyspnea scale; ADL, the activity of daily living; PHQ-9,the Patient Health Questionnaire 9; QARP, qigong exercise and acupressure rehabilitation program; SaO2, oxygen saturation; young and middle-aged: 20–59 years; elderly: 60–80 years.
* $P < 0.05$.

statistically different from those in the standard therapies group and far exceeded the clinical MCID values of –1[23] and –0.5,[24] which were clinically significant. Meanwhile, the percentage of symptoms of chest tightness and cough in the QARP group was significantly reduced by 23.44 % and 15.33 % at the 14th-month follow-up, respectively, relative to the discharge, and the percentage of the two symptoms reduced by 31.25 % and 21.88 %, respectively, following the 28th-month follow-up. The specificity of the acupoints and qigong training maneuvers may explain the superiority of improving dyspnea, chest tightness, and cough symptoms in the QARP group. Specific acupoints selected for our study included Feishu (BL13), Zhongfu (LU1), and Danzhong (RN17), which were located on the dorsal side of the lung, anterior side of the lung, and center of the chest, and are important reflex areas for respiratory diseases. Acupressure can stimulate peripheral sympathetic nerve excitation, promote bronchial smooth muscle diastole, reduce airway resistance, relieve airflow limitation, and thus alleviate the symptoms of dyspnea and wheezing.[25,26] Furthermore, Liuzijue uses a combination of pursed lip breathing and belly breathing to make six distinct sounds (xu, he, hu, si, chui, and xi) and trunk and upper limb movement, which exercises the respiratory muscle strength of the intercostal muscle, rectus abdominis muscle, and diaphragm and enlarges the volume of the pleural, increasing pulmonary ventilation, to improve the tightness and shortness of breath in the chest.[27] mMRC scores were less significant than MBS results during the 28-month follow-up period. The mMRC

Table 2
Changes in clinical scale scores from admission to discharge at 28 months.

Outcome	Scale scores, median(IQR)		Mean change from baseline(95 % CI)		QARP group vs. standard therapy group				
	QARP group (n = 64)	Standard therapy group (n = 64)	QARP group	Standard therapy group	Difference(95 % CI)	P value	Group × time interaction	Time	Group
mMRC									
T0	3(2, 3.8)	3(2, 3)	NA	NA	NA	NA	$\chi 2 = 4.1$	$\chi 2 = 113.0$	$\chi 2 = 10.7$
T1	1(1, 1)	1(1, 1)	−1.8(−2.0,−1.6)	−1.5(−1.7,−1.3)	−0.1(−0.3,−0.0)	0.121			
T2	0(0, 1)	1(0, 1)	−2.5(−2.7,−2.3)	−1.9(−2.1,−1.7)	−0.4 (−0.6,0.2)*	< 0.001	$P = 0.018$	$P < 0.001$	$P = 0.001$
T3	0(0, 0)	0(0, 0)	−2.7(−2.9,−2.5)	−2.4(−2.6,−2.2)	−0.1(−0.3,0.1)	0.220			
MBS									
T0	5(4, 7)	6(4, 7)	NA	NA	NA	NA	$\chi 2 = 0.5$	$\chi 2 = 96.0$	$\chi 2 = 20.3$
T1	2(1, 2)	2(1, 3)	−3.7(−4.2,−3.2)	−3.1(−3.5,−2.6)	−0.5 (−0.9,−0.2)*	0.002			
T2	0.5(0, 0.9)	0.8(0, 2)	−4.8(−5.4,−4.3)	−4.1(−4.7,−3.5)	−0.6 (−0.9,−0.3)*	< 0.001	$P = 0.628$	$P < 0.001$	$P < 0.001$
T3	0(0, 0.5)	0(0, 1)	−5.1(−5.7,−4.6)	−4.6(−5.1,−4.1)	−0.4 (−0.7,−0.1)*	0.024			
ADL									
T0	95(90, 100)	95(90, 95)	NA	NA	NA	NA			
T1	100(95, 100)	100(95, 100)	5.1(4.1,6.0)	5.2(4.3,6.2)	0.2(−1.7,2.0)	0.853	$\chi 2 = 0.8$	$\chi 2 = 3.6$	$\chi 2 = 1.0$
T2	100(100, 100)	100(100, 100)	6.7(5.4,8.1)	7.0(6.0,8.1)	0.0(−1.8,1.9)	0.985	$P = 0.447$	$P = 0.028$	$P = 0.326$
T3	100(100, 100)	100(100, 100)	6.7(5.4,8.1)	5.5(2.3,8.7)	1.5(−0.3,3.3)	0.110			
PHQ-9									
T0	14.5(9, 18)	14.5(9, 18)	NA	NA	NA	NA			
T1	7(4, 9)	6(3, 9)	−6.5(−7.7,−5.3)	−7.0(−8.0,−6.0)	0.5(−0.6,1.7)	0.389	$\chi 2 = 0.5$	$\chi 2 = 22.7$	$\chi 2 = 0.0$
T2	7(6, 7)	7(6, 7)	−6.7(−8.0,−5.4)	−6.6(−7.9,−5.4)	−0.1(−1.3,1.0)	0.859	$P = 0.593$	$P < 0.001$	$P = 0.908$
T3	3(1, 6.8)	4(2, 7)	−9.2(−11.1,−7.3)	−8.9(−10.5,−7.4)	−0.3(−1.4,0.9)	0.638			

T0: Admission; T1: Discharged; T2: Discharged 14 months; T3: Discharged 28 months.

* The QARP group compared with standard therapies group, $P < 0.05$. QARP, qigong exercise, and acupressure rehabilitation program; mMRC, modified medical research council dyspnea scale; MBS, modified Borg dyspnea scale; ADL, the activity of daily living; PHQ-9, patient health questionnaire-9 scale.

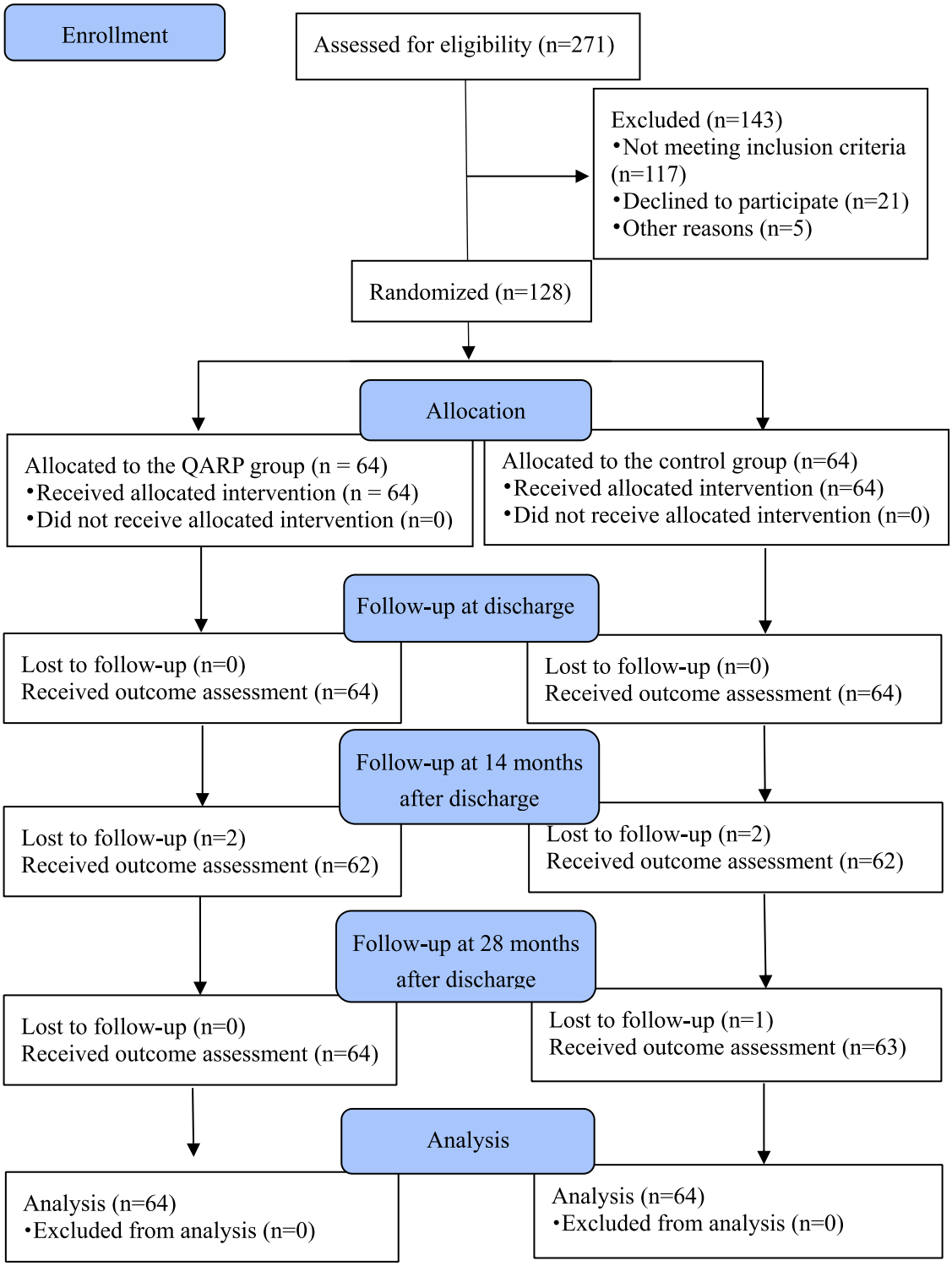

Fig. 1. CONSORT flow diagram.

scale assesses the severity of dyspnea based on the dimension of limitation of activities of daily living, with fewer grades, so it is less sensitive in detecting changes in dyspnea.[28] Moreover, the clarity of the descriptions corresponding to the five grades was poor, and there was heterogeneity in patients' understanding of the content of grades 0, 2, and 3, which resulted in limited identification of changes in dyspnea severity on the mMRC scale.[29]

Further subgroup analysis revealed that the improvement in mMRC and MBS scores of young and middle-aged people in the standard therapies group and QARP group was significantly better than those of older people at 14 months of follow-up, primarily because older people have more severe pulmonary health conditions, including pulmonary function decline (e.g., decreased respiratory muscle strength, chest wall compliance, and pulmonary elastic contractility), and chronic primary diseases (e.g., chronic obstructive pulmonary disease) with the increase in age.[30,31] Subsequently, gastrointestinal symptoms caused by chronic wasting diseases and SARS-CoV-2 attacking the mucosal epithelium cause COVID-19 in elderly patients with a worse nutritional status,

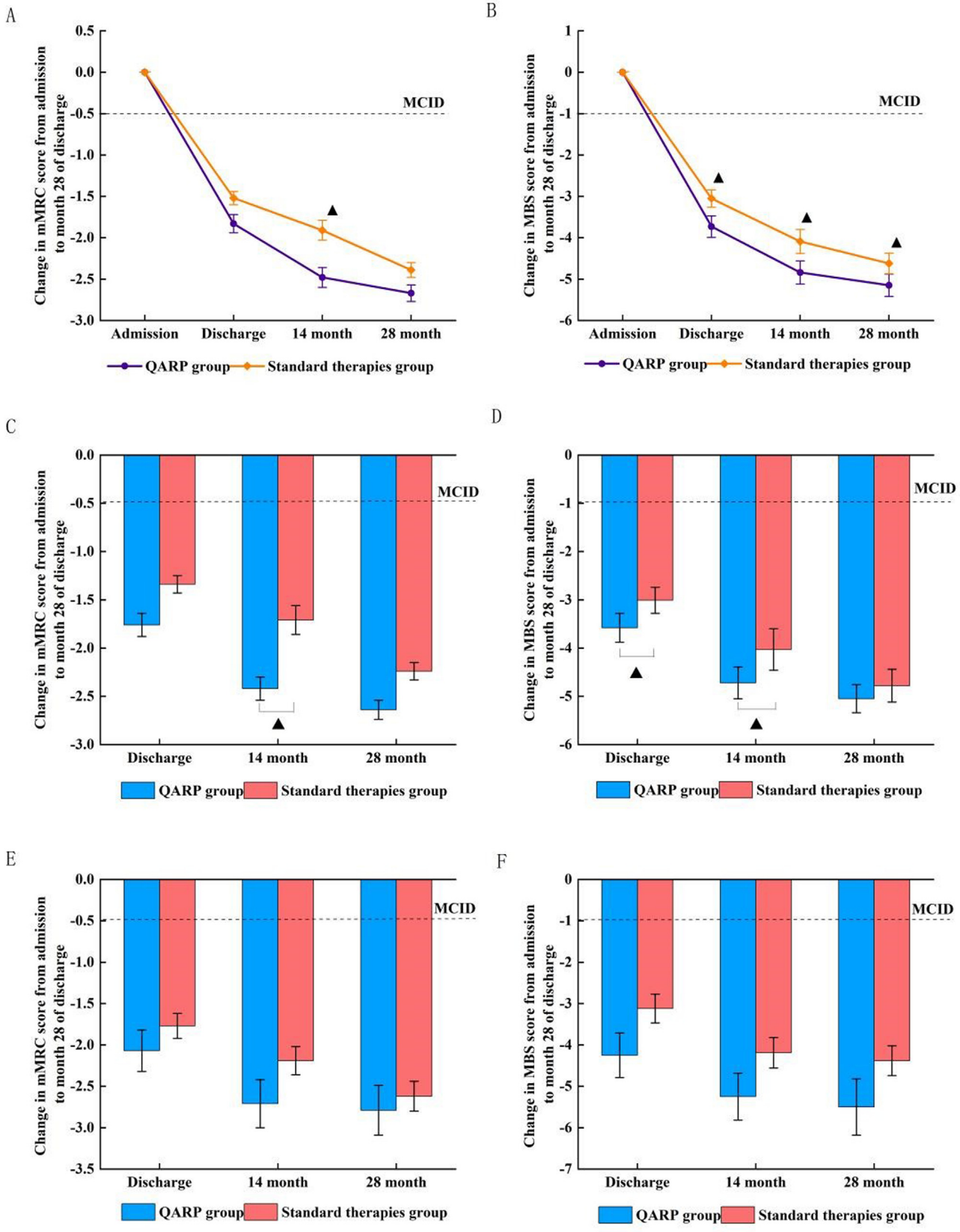

Fig. 2. Changes in primary and secondary outcomes among the groups over time.
A, B: Changes in mMRC and MBS; C, D: Changes in mMRC and MBS among young and middle-aged people; E, F: Changes in mMRC and MBS in the elderly. ▲, There was a significant difference ($P < 0.05$) between the QARP and standard therapy groups. Abbreviations: MBS, modified Borg dyspnea scale; MCID, minimal clinical important difference; mMRC, modified medical research council dyspnea scale; QARP, qigong exercise and acupressure rehabilitation program.

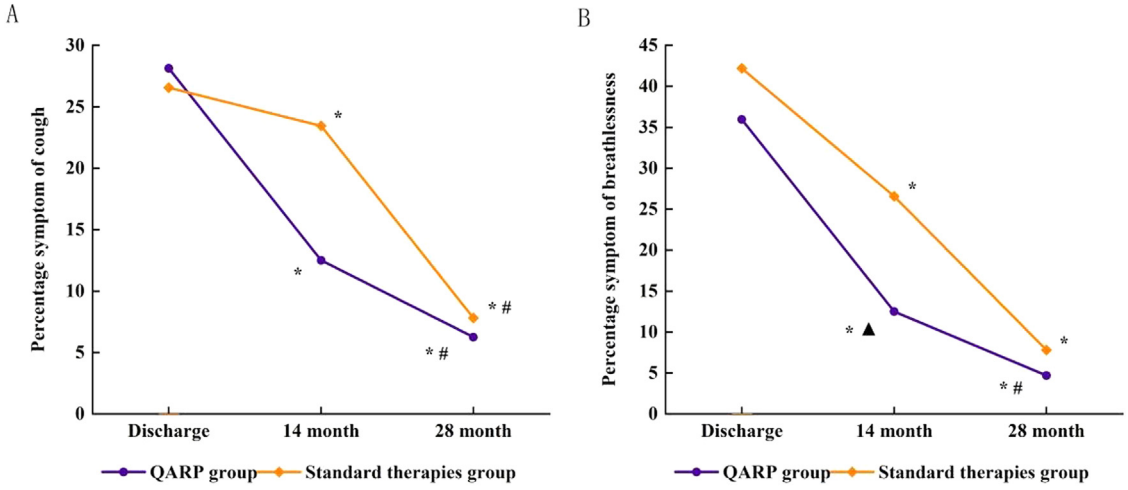

Fig. 3. Changes in clinical symptoms among groups over time.
▲, The QARP group compared with the standard therapies group, $P < 0.05$. Comparison within the group: *, compared with discharge, $P < 0.05$; #, compared with month 14 of discharge, $P < 0.05$. Abbreviations: QARP, qigong exercise, and acupressure rehabilitation program.

negatively affecting exercise capacity and cardiorespiratory fitness.[32,33] However, there were no significant differences in PHQ-9 scores between the two groups, which may be related to the relatively short duration of the QARP intervention and the absence of acupuncture points selected for their specific effects on relieving anxiety and depression after discharge. Patients in both groups achieved a perfect score on ADL competence, which means that severe COVID-19 patients had significant dysfunction in ambulating, personal hygiene, and toileting during the acute phase; on the contrary, it had little effect on ADL in the long term.

It was also found that coughing is less likely to improve and lasts longer than chest tightness and dyspnea. This may be because SARS-CoV-2 induces peripheral and central hypersensitivity through a combination of neuroinflammatory and neuroimmune effects, causing a state of laryngeal hypersensitivity, which then causes chronic refractory or unexplained cough.[34] Furthermore, patients with recurrent infections after unblocking or with other comorbidities, such as influenza A, can also cause respiratory inflammatory responses and thus cough, which may contribute to the refractory and persistent nature of cough in long-term COVID-19 patients.

WHO has declared that COVID-19 global health emergency is over. However, pandemics, such as the new omicron strain, influenza A, and mycoplasma pneumonia in the post-COVID-19 era remain a long-term health burden worldwide.[35] Our research lays the foundation for the widespread use of traditional treatments in future global, infectious, and especially unexplained major health events, thus assuring human health.

4.1. Limitations

This study has several limitations. First, patients recruited for this trial had other concurrent underlying conditions; therefore, it was challenging to assess COVID-19 patients individually; despite the random grouping method used, some bias was inevitable. Second, this trial evaluated outcomes at baseline, discharge, month 14 of discharge, and month 28 of discharge; this design was designed to obtain longer-term treatment effects and did not follow patients at multiple time points of discharge; hence, it ought to be gathered and examined in upcoming research. Third, during the follow-up period, some patients may experience other health issues, such as bacterial infections, which can also affect lung function and cannot be prevented. Additionally, even though the patients underwent strictly supervised training three times per week during the follow-up period, there is a possibility that some patients may have engaged in more frequent exercises.

5. Conclusions

QARP rapidly and significantly improved mMRC scores, MBS scores, chest tightness, and cough in COVID-19 patients at 14 months, and the efficacy was sustained up to the 28th month. QARP was also more effective in young and middle-aged patients than in older patients. Therefore, in the future, the application of QARP should be considered as a complementary therapy to conventional therapies for global public health emergencies.

Author contributions

Prof. Fang L had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Miss Liu, Zhu and Dr. Yao contributed equally to this work.
Conceptualization and Methodology: Liu, Zhu, Yao, Fang M, Fang L.
Formal Investigation and Data Analysis: All authors.
Writing - Original Draft: Liu, Zhu, Yao, Fang M, Fang L.
Writing - Review & Editing: All authors.
Funding: Fang L, Fang M.
Supervision: Yao, Fang M.

Declaration of competing interest

The authors declare no conflict of interests.

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Ethical statement

The study was performed in accordance with the principles of the Declaration of Helsinki. All patients signed informed consent forms and received follow-up subsidies. The ethical approval number for the follow-up study is HSZYPJ-2021–001–01.

Data availability

The data used in this study can be made available upon reasonable request to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101084.

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