Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial

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ABSTRACT

Background: As of September 17, 2021, coronavirus disease 2019 (COVID-19) has infected more than 226 million people in a worldwide pandemic, with conservative estimates suggesting that there are more than 204 million convalescent patients with COVID-19. Previous studies have indicated that patients in the recovery phase exhibit decreased function of multiple organs. In China, traditional Chinese medicine (TCM) treatment is recommended in the rehabilitation period of COVID-19; however, the safety and efficacy of such treatment remain to be confirmed.

Aim of study: The present study aimed to evaluate the efficacy and safety of Bufei Huoxue (BFHX) in restoring the functional status and exercise tolerance of patients recovering from COVID-19.

Methods: A total of 131 patients in the rehabilitation period of COVID-19 infection were randomly divided into a Bufei Huoxue (BFHX) group (n = 66) and a placebo group (n = 65). BFHX or placebo was given orally three times a day (1.4 g/dose) for 90 days. The primary outcomes was to evaluate improvements in exercise tolerance and imaging manifestations on chest computed tomography (CT).

Results: After the exclusion of two patients who withdrew prior to receiving any medications, 129 patients were recruited, including 64 patients in the BFHX group and 65 patients in the placebo group. After 3 months of treatment, the BFHX group exhibited greater attenuation of pneumonia lesions on chest CT than the placebo group ($P<0.05$). Improvements in 6-min walk distance (6MWD) relative to baseline were also significantly better in the BFHX group than in the placebo group ($P<0.01$). Scores on the Fatigue Assessment Inventory (FAI) were lower in the BFHX group than in the placebo group ($P<0.05$). Although the rate of adverse events was higher in the BFHX group than in the placebo group (9.38% vs. 4.62%), the difference was not significant ($P = 0.3241$).

Conclusions: BFHX may exert strong rehabilitative effects on physiological activity in patients recovering from COVID-19, which may in turn attenuate symptoms of fatigue and improve exercise tolerance.

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1. Introduction

Abbreviations

6MWD	6-min walk distance
BFHX	Bufei Huoxue capsules
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
FAI	Fatigue Assessment Inventory
FAS	full analysis set
IL6	interleukin 6
ITT	intention-to-treat
LOCF	last observation carried forward
MAPK8	mitogen-activated protein kinase 8
NCOA2	nuclear receptor coactivator 2
PPS	per protocol set
SS	safety set
PTGS	post-transcriptional gene silencing
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGRQ	St George's respiratory questionnaire
TCM	traditional Chinese medicine

Since December 2019, a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide. As of September 17th, 2021, the number of coronavirus disease 2019 (COVID-19) cases continues to increase, with 226,236,577 confirmed cases, 4,654,548 deaths, and 204,397,158 recovered individuals across 185 countries and regions (COVID-19 coronavirus pandemic, 2021). Due to worldwide efforts targeted toward rapid vaccine development, there are currently several vaccines against COVID-19 on the market, offering hope for curbing the spread of the virus. Studies are now providing greater insight into the long-term effects of COVID-19 on the human body. Researchers have reported that 63% of discharged patients still exhibit lung injury on computed tomography (CT) images 6 months after the onset of disease (Shaw et al., 2021; Sonnweber, 2020). One research study from China observed that 76% of COVID-19 survivors still had at least one clinical symptom—which commonly included fatigue, myasthenia (63%), and sleeping disorders (26%)—6 months after acute infection (Huang et al., 2021). A prospective UK cohort study from medRxiv also noted that 70% of patients with COVID-19 were not fully recovered after discharge (Rachael et al., 2021). In the meantime, Chinese researchers and doctors have investigated the convalescence of patients with COVID-19 at an earlier timepoint for better clinical outcomes (General Office of the National Health Commission, 2020). In view of this situation, Current guidelines for the diagnosis and treatment of COVID-19 (i.e., the fourth edition of COVID-19 diagnosis and treatment guidelines issued by the National Health Commission of the People's Republic of China) recommend the use of traditional Chinese medicine (TCM) during the rehabilitation period. It's been proven that the application of TCM can shorten the hospital stay of the patients who were infected by coronavirus (Huang et al., 2020). For thousands of years, TCM has been to treat infectious diseases. In TCM, patients are evaluated and treated based on its special theories and aetiologies. The prescriptions of TCM typically consists of a complex combination of components according to TCM signs (Wu et al., 2008). From TCM's point of view, the principal pathogenesis of viral pneumonia is the damage of Qi by evil toxin (also considered as pro-inflammatory factors). The COVID-19 patients are more common in the manifestations of Qi deficiency and blood stasis, for which reason they are prone to have fatigue and decreased exercise endurance. Replenishing and restoring pulmonary Qi are important approach for rehabilitation of COVID-19 (Wu et al., 2021).

The Bufei Huoxue capsule (BFHX) is a widely known Chinese patent medicine that is typically used to promote blood circulation and improve lung and kidney function in patients with cardiopulmonary diseases (Wu et al., 2012). BFHX consists of three ingredients from TCM: *Astragali radix*, *Paeoniae radix rubra,* and *Psoraleae fructus* (The Official Product Information for Bufei Huoxue Capsule). *Astragali radix* exerts broad-spectrum effects on the human body by strengthening the immune system, increasing tolerance against hypoxia, regulating organ function, and preventing microbial infection (Yao et al., 2003; Hu et al., 2018; Hong et al., 2017; Luo et al., 2020). *Paeoniae radix rubra* exerts therapeutic effects by improving microcirculation, reducing the viscosity of serum and plasma, and clearing excessive "heat" and "cold" from the blood (Liu et al., 2000; Luo et al., 2002). *Psoraleae fructus* plays a role in strengthening myocardial function, dilating the coronary arteries, and increasing blood flow (Zhao, 2002; Qu et al., 2019; Zhang et al., 2020). The polysalen polysaccharides in psoralen can also significantly enhance immunity (Zhang et al., 2017). The incorporation of these three Chinese medicinal herbs in BFHX may help to improve lung function and microcirculation, in addition to providing anti-microbial, anti--endotoxin, and anti-hypoxia benefits (Xie et al., 2019; Ma et al., 2016; Guo and Zhang, 2007; Yang et al., 2005).

Recently, some studies based on network pharmacology have indicated that BFHX exhibits therapeutic effects in those recovering from viral pneumonia by supressing inflammatory pathways (Rao et al., 2020; Guo et al., 2020). As a respiratory infectious disease, COVID-19 is considered related to qi deficiency in the lung and spleen; thus, proponents of TCM have argued that BFHX may exert a therapeutic effect in patients recovering from COVID-19. Accordingly, BFHX has been integrated into clinical guidelines in several provinces of China for the recovery management of COVID-19 (Beijing Administration of Traditional Chinese Medicine, 2020; Guizhou Administration of Traditional Chinese Medicine, 2020; Health Commission of Anhui Province, 2020). Multiple clinical trials have demonstrated that BFHX exerts beneficial effects in patients with lung diseases including chronic obstructive pulmonary disease, asthma, and pulmonary tuberculosis. These effects may be due to reductions in acute exacerbation, alleviation of inflammatory responses in the airway, and reversal of immunologic disorders (Bai et al., 2016; Yu et al., 2019; Xu et al., 2018), which have been cited as common clinical symptoms and pathogenetic mechanisms in COVID-19. Therefore, to provide evidence-based data for the use of BFHX in COVID-19 convalescence, the present randomised, double-blind, placebo-controlled clinical trial aimed to evaluate the efficacy and safety of BFHX in restoring the functional status and exercise tolerance of patients recovering from COVID-19.

2. Materials and methods

This was a multicentre, randomised, double-blind, placebo-controlled study (Chen et al., 2021). All patients were hospitalised with COVID-19 at five hospitals in China. Te study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (registration number: 2020–87).

Written informed consent was obtained from all study participants. This study was registered with the China Clinical Trial Registration Centre (registration number: ChiCTR2000032573).

2.1. Inclusion and exclusion criteria

We enrolled hospitalised patients who met the following criteria: (1) age ≥18 years; (2) diagnosis of COVID-19 in accordance with "The Diagnosis and Treatment Scheme of COVID-19 (7th Trial Version)"; (3) patient condition meeting the discharge standards stipulated in "The Diagnosis and Treatment Scheme of COVID-19 (7th Trial Version)" after treatment; (4) qi deficiency in the lung and spleen based on "The

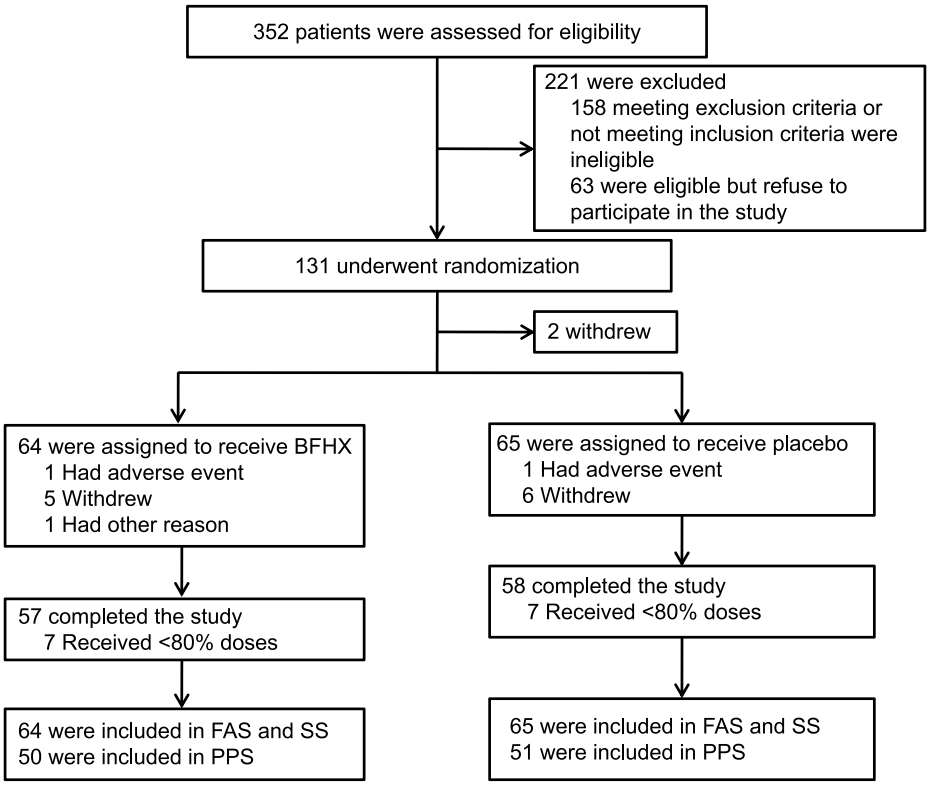

Fig. 1. Study flow chart.

Diagnosis and Treatment Scheme of COVID-19 (7th Trial Version)"; (5) patients and their dependents agreeing to participate in the study and providing written informed consent.

Exclusion criteria were as follows: (1) known or suspected allergy to the components of BFHX; (2) acute infections caused by other viruses or bacteria; (3) abnormal liver and kidney function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and serum creatinine [SCr] $\geq$1.5 times the upper limit of normal); (4) participation in other clinical drug trials; (5) pregnancy, lactation, or other conditions preventing adoption of effective contraceptive measures during the trial period; (6) severe comorbid liver disease (such as liver tumours or various types of hepatitis), history of drug-induced liver injury, or current history of/potential for the use of drugs with the potential to damage the liver during the study period (e.g., immunosuppressive agents such as cyclosporine and tacrolimus; anti-tuberculosis drugs such as rifampicin and isoniazid; chemotherapy drugs such as cyclophosphamide, methotrexate, and azathioprine; restorative medicinal herbs for liver damage such as *polygonum multiflorum*, *tusanqi*, and *tripterygium wilfordii*); and (7) any other circumstances under which the investigators considered the patient unsuitable for participation in the study.

2.2. Calculation of sample size

Based on previous research, the 6-min walk distance (6MWD) was selected as the primary efficacy indicator for estimating the sample size (Brooks et al., 2003; Fujimoto et al., 2017). Assuming that the 6MWD in the BFHX-treated group would be 60 m more than that in the control group on average, the sample size of each group was estimated as 31 (Std = 60; $\alpha = 0.05$; $\beta = 0.10$) using PASS (Version 11.0.7). We increased the sample size to 65 in each group in consideration of study risk and bias.

2.3. Study medication

BFHX (Chinese medicine Z20030063, Guangdong Lei Yun Shang Pharmaceutical Co., Ltd. (Yunfu, Guangdong Province, China); batch number 022001; specifications: 0.35 g per capsule) was obtained in the form of hard capsules containing fine brown particles/powder that is slightly fragrant, sour, and bitter. BFHX is composed of three herbs: *Psoraleae fructus* (Buguzhi) (40%), *Astragali radix* (Huangqi) (40%), and *Paeoniae radix rubra* (Chishao) (20%). The placebo capsule (Guangdong Lei Yun Shang Pharmaceutical Co., Ltd.; batch number 012007; specifications: 0.35 g capsules) was made of starch, caramel, and tartrazine, and its smell, colour, shape, and packaging were the same as those for the BFHX capsule. The drug quality standards conform to the regulations of the Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2015). The chemical construction and quality of BFHX capsules were assessed by high performance liquid chromatography (HPLC). The fingerprint of BFHX can be seen in supplemental figures and tables (Tang et al., 2018).

2.4. Intervention and efficacy evaluation

A list of 160-case random sequences was generated by computer using a randomisation scheme based on the stratified block random method. Data analysis was performed independently by professional statisticians to guarantee that all enrolled participants were evenly allocated to the BFHX or control groups. Then, 80 participants from each group were randomly selected. The allocation code was individually sealed in an opaque envelope. In this trial, all participants and researchers involved in drug distribution, outcome evaluation, and data analysis were blinded to the allocation. Urgent unblinding, under the principal investigators' permission, was permitted in instances of severe adverse events or other unpredictable situations. Every participant was offered rehabilitation options ranging from oxygen to aerosol inhalation, respiratory training, and sports exercises, depending on the actual treatment needs. Eligible patients received BFHX capsules or placebo capsules at an oral dose of 1.4 g (four capsules) thrice daily for 90 days concomitantly with rehabilitation therapy.

All patients underwent monthly follow-up for 3 months. Basic

Table 1
Comparison of patient characteristics at baseline.

Term	BFHX (N = 64)	Placebo (N = 65)	P-value [a]
Male (%)	31 (48.44)	29 (44.62)	0.7254
Age (years, $\bar{x} \pm s$)	54.16 ± 12.11	52.51 ± 12.31	0.4448
Age group (years, %)			0.7810
18–40	6 (9.38)	8 (12.31)	
41–64	47 (73.44)	44 (67.69)	
65–75	8 (12.50)	11 (16.92)	
>75	3 (4.69)	2 (3.08)	
Height (cm $\bar{x} \pm s$)	164.80 ± 7.21	163.94 ± 7.65	0.5163
Weight (kg $\bar{x} \pm s$)	68.08 ± 11.78	65.92 ± 9.80	0.2603
BMI (kg/m^2 $\bar{x} \pm s$)	24.995 ± 3.536	24.474 ± 2.894	0.3607
Han nationality (%)	64 (100.00)	65 (100.00)	–
Manual labour (%)	12 (18.75)	9 (13.85)	0.4835
Marriage			0.3800
Married	58 (90.63)	62 (95.38)	
Unmarried	5 (7.81)	3 (4.62)	
Other	1 (1.56)	0 (0.00)	
Severe/critical patients (%)	13 (20.31)	7 (10.77)	0.1516
Time from confirmation to randomisation (day)	131.2 ± 14.0	130.7 ± 14.6	0.8254
Time from discharge to randomisation (day)	94.3 ± 17.0	94.3 ± 20.5	0.9845
Comorbidities (N, %)			
Rheumatic diseases	1 (1.56)	0 (0.00)	0.4961
Respiratory diseases	2 (3.13)	1 (1.54)	0.6191
Urinary system diseases	1 (1.56)	1 (1.54)	1.0000
Endocrine and metabolic system diseases	11 (17.19)	10 (15.38)	0.8155
Nervous system diseases	1 (1.56)	0 (0.00)	0.4961
Digestive system diseases	1 (1.56)	6 (9.23)	0.1148
Cardiovascular diseases	12 (18.75)	13 (20.00)	1.0000
Ophthalmic Diseases	1 (1.56)	0 (0.00)	0.4961
Classification of concomitant medication (N, %)			
Digestive and metabolic system	10 (15.63)	5 (7.69)	0.1807
Cardiovascular system	9 (14.06)	10 (15.38)	1.0000
Chinese medicine/Chinese patent medicine	3 (4.69)	1 (1.54)	0.3652
Blood system	2 (3.13)	5 (7.69)	0.4401
Endocrine system	1 (1.56)	1 (1.54)	1.0000
Respiratory system	1 (1.56)	0 (0.00)	0.4961
Motor system	1 (1.56)	0 (0.00)	0.4961
Nervous system	1 (1.56)	0 (0.00)	0.4961
Antibiotics	1 (1.56)	0 (0.00)	0.4961
Combined	1 (1.56)	0 (0.00)	0.4961

[a] P-values were calculated for continuous outcomes with t-tests for the change from baseline to the last visit after three months of treatment; Fisher' s exact test was performed for categorical outcomes.

information, clinical symptoms, vital signs, medication status, and adverse events were recorded to evaluate the participants' exercise tolerance and degree of symptom improvement. The primary indicators included improvements in 6MWD and findings on chest computed tomography (CT) images. Secondary efficacy measurements consisted of Chinese medicine syndrome scores, St. George's Respiratory Questionnaire (SGRQ) score, Borg-Dyspnea Scale scores, and Fatigue Assessment Inventory (FAI) scores. Additionally, any side effects or adverse events during the 3-month follow-up period were recorded. Quantification of lung lesions on CT was performed using an intelligent Evaluation System of Chest CT for COVID-19 (YT-CT-Lung, YITU Healthcare Technology Co., Ltd., China), which combines a fully convolutional network with adaptive thresholding and morphological operations for the segmentation of lungs and pneumonia lesions. The automatic lesion delineation in each case was confirmed or modified based on the consensus of two chest radiologists (Liu et al., 2020).

2.5. Safety monitoring

In this study, several indices were monitored to assess safety: (1) vital signs including body temperature, heart rate, respiratory rate, and blood pressure; (2) laboratory examination results including complete blood count (white blood cells, red blood cells, haemoglobin, platelets, neutrophils, and lymphocytes); clinical urine test results (leukocytes, blood, protein, glucose); liver function (AST, ALT, total bilirubin, γ-glutamyl transpeptidase, and alkaline phosphatase levels); and renal function (blood urea nitrogen and SCr); and (3) the incidence, timing, severity, and duration of adverse events.

2.6. Statistical analysis

Based on the intention-to-treat (ITT) principle, all participants taking medicine after randomisation were included in the statistical analysis. Efficacy and safety analyses were performed using the ITT datasets. Per-protocol datasets were selected from the ITT population for efficacy analysis.

Descriptive statistics including counts, percentages, means, and standard deviations were calculated for categorical and continuous outcomes, respectively. Means and standard deviations were reported for the primary and secondary indicators. For continuous outcomes, a two-tailed Student's t-test and Wilcoxon–Mann–Whitney test were used to test for differences between groups for normally and non-normally distributed variables, respectively. Fisher's exact test was used to analyse categorical outcomes. The centre effect was considered using the generalised linear model. Two-sided tests were set at a significance level of 0.05. We did not consider type I error correction because of the exploratory nature of the research. SAS version 9.4 (SAS Institute Inc.) was used for all analyses.

Sensitivity analysis of the primary indicators was conducted using the imputed data of the last observation carried forward (LOCF). For participants who prematurely withdrew from the trial, the outcomes of the last visit were used as the final outcome.

3. Results

3.1. Patient sample and characteristics

From May 4 to June 21, 2020, 352 patients discharged following COVID-19 treatment at five subcentre university hospitals in China were screened, and 131 patients who were eligible for the trial were recruited randomly. All participants were randomly divided into the BFHX (n = 66) and placebo (control, n = 65) groups using a ratio of 1:1. Two patients did not take the test drug after randomisation. A total of 129 patients were eventually enrolled in this study, and 115 patients completed the study (Fig. 1). Patient characteristics are shown in Table 1. Both groups were comparable in terms of demographic characteristics, severity of illness, and time of discharge (P>0.05). There were also no differences in the mainstay of treatment or concomitant medications.

3.2. Primary indicators

After undergoing therapy for 3 months, patients in the BFHX group exhibited significant decreases in the volume of total lung lesions (P = 0.0243), volume of ground-glass opacities (P = 0.0444), volume of consolidations (P = 0.0188), and the percentage of consolidations in the whole lung (P = 0.0428) on chest CT when compared with the placebo group (Table 2). Improvements in pneumonia as reflected by chest CT were observed in 15.09% and 7.84% of patients in the BFHX and placebo groups, respectively (Table 3). More than 80% of patients in the two groups remained in stable condition. Notably, six patients in the placebo group developed worsening of pneumonia, whereas none in the BFHX group presented with deterioration (Table 3). Improvements in 6MWD were significantly better in the BFHX-treatment group than in the

Table 2
Changes in primary and secondary indicators from baseline to after three months of treatment [a]

Indicator	BFHX (N = 64) [b]				Placebo (N = 65) [b]				Least Squares Means Differences (95% CI)	P-value[b]
	No. of patients[c]	Baseline	After 3 months of treatment	Change	No. of patients[c]	Baseline	3 months after treatment	Change		
Primary indicator										
Chest CT Indexes										
Volume of total lung lesions (cm^3)	53	31.5 ± 120.5	14.3 ± 32.1	-19.2 ± 96.4	51	15.1 ± 39.4	29.2 ± 75.4	15.1 ± 47.5	-34.0 (-63.5 to -4.6)	0.0243
Volume of the ground-glass opacities (cm^3)	53	29.3 ± 115.4	13.2 ± 30.6	-18.3 ± 92.0	51	14.2 ± 38.2	23.9 ± 71.4	10.5 ± 42.4	-32.6 (-60.7 to -4.5)	0.0444
Volume of the consolidations (cm^3)	53	1.8 ± 34.4	1.1 ± 2.3	-0.9 ± 4.7	51	1.0 ± 1.6	2.0 ± 4.1	1.1 ± 3.4	-1.4 (-2.6 to -0.1)	0.0188
6-Min Walk Distance (m)	58	427.3 ± 73.6	475.6 ± 63.7	45.3 ± 62.4	60	435.0 ± 73.3	445.5 ± 69.1	10.1 ± 59.4	34.2 (11.7–56.8)	0.0022
Secondary indicator										
Fatigue Assessment Inventory	58	119.1 ± 26.2	85.5 ± 27.6	-31.2 ± 27.0	60	112.9 ± 31.6	100.4 ± 25.7	-12.5 ± 36.1	-17.8 (-29.5 to -6.2)	0.0019
Total SGRQ	58	16.0 ± 12.1	3.2 ± 2.9	-12.0 ± 10.9	60	14.0 ± 10.1	4.5 ± 4.2	-9.1 ± 8.6	-2.4 (-5.8 to 1.0)	0.1148
Part 1 SGRQ	58	4.0 ± 4.3	0.5 ± 0.9	-3.2 ± 4.0	60	3.8 ± 4.0	0.5 ± 1.1	-3.4 ± 4.1	0.3 (-1.2 to 1.7)	0.8310
Part 2 SGRQ	58	9.3 ± 8.0	1.4 ± 2.4	-7.5 ± 7.1	60	7.5 ± 6.5	2.3 ± 3.3	-4.9 ± 4.9	-2.2 (-4.4 to -0.1)	0.0234
Borg Dyspnea score	58	2.1 ± 1.3	0.7 ± 1.2	-1.3 ± 0.9	60	2.1 ± 1.2	0.9 ± 1.4	-1.2 ± 1.3	-0.1 (-0.5 to 0.2)	0.4801
Chinese medicine symptom complex score	58	4.3 ± 2.5	1.1 ± 1.7	-3.1 ± 2.6	60	4.5 ± 2.8	0.9 ± 1.2	-3.4 ± 2.4	0.4 (-0.4 to 1.3)	0.4723

‡ P-values were calculated for continuous outcomes with t-tests for the change from baseline to the last visit after three months of treatment; Fisher' s exact test was performed for categorical outcomes.

[a] Data are presented as the means ± standard deviations. The changes from baseline to the end of three months of treatment were arithmetic. N lrb% is the number of patients and percentage. The least squares mean difference was calculated by analysing the generalised linear regression model with site as a confounder.

[b] Total patients are allocated to the intention-to-treat population.

[c] No. of patients observed at end of three months of treatment.

Table 3
Improvement of CT severity of pneumonia N (%).

Level	BFHX (N = 64)	Placebo (N = 65)	P-value
Improved	8 (15.09)	4 (7.84)	0.0238
Stable	45 (84.91)	41 (80.39)	
Deteriorative	0 (0)	6 (11.76)	
Total	53 (100)	51 (100)	

P-value was calculated with Fisher' s exact test.

control group (FAS: 40.8 ± 57.9 m vs. 9.3 ± 72.0 m; 95% CI: 7.4–55.6 m; $P = 0.0110$). This effect was also observed after 3 months of treatment (FAS: 45.3 ± 62.4 m vs. 10.1 ± 59.4 m; 95% CI: 12.9–57.3 m; $P = 0.0022$.) (Fig. 2A and B).

3.3. Secondary indicators

No overall significant difference was found in the SGRQ scores between the two groups ($P = 0.1148$). While there was no difference in the first part of the SGRQ score ($P = 0.8310$), the two groups exhibited significant differences in the second part of the SGRQ score ($P = 0.0234$). No statistical differences in Borg-Dyspnea Scale ($P = 0.4801$) or TCM syndrome ($P = 0.4723$) scores were observed (Table 2). However, FAI scores (reflecting symptom recovery) were significantly lower in the BFHX group than in the control group (FAS: 85.5 ± 27.6 vs. 100.4 ± 25.7; $P = 0.0030$) (Fig. 2C and D).

3.4. Safety

The most common adverse event was elevated ALT and AST levels. Laboratory tests for other aberrant values were rarely performed. After drug withdrawal and symptomatic treatment, the abnormal test indices returned to normal within two weeks in patients experiencing adverse events (AEs). There was no significant difference in the incidence of adverse events between groups ($P = 0.3241$), and no serious AEs occurred during this study (Table 4).

4. Discussion

In attempting to provide in-depth insight into the damage that SARS-CoV-2 inflicts on the human body, researchers have increasingly recognised that many patients who have recovered from COVID-19 continue to live with lingering symptoms that compromise their overall quality of life (Wang et al., 2020). A clinical study found that patients with COVID-19 who had been discharged still experienced fatigue (13%), palpitations (10%), dyspnoea (9%), cough (6%), lower limb oedema (1%), chest pain (1%), and haemoptysis (0.2%) 3 months later. The incidence rates of fatigue, palpitations, and dyspnoea are also significantly higher in critically ill patients with COVID-19 than in non-critically ill patients (Qin et al., 2021). Fatigue or myasthenia, sleep difficulties, and anxiety or depression were also common among COVID-19 survivors 6 months after acute infection (Qin et al., 2021). Critically ill patients with a prolonged inpatient stay have been the main target population of long-term recovery intervention, as they are prone to develop more severe chest CT imaging manifestations and pulmonary diffusion capacity damage. Studies have reported that 63% of COVID-19 survivors experience pulmonary sequelae, including impairments in lung function and pulmonary vessel lesions (Shaw et al., 2021; Sonnweber et al., 2020; Huang et al., 2021). Thus, it is necessary to carry out interventions during the recovery period of COVID-19 to ensure that survivors can return to their previous life, occupation, and functional

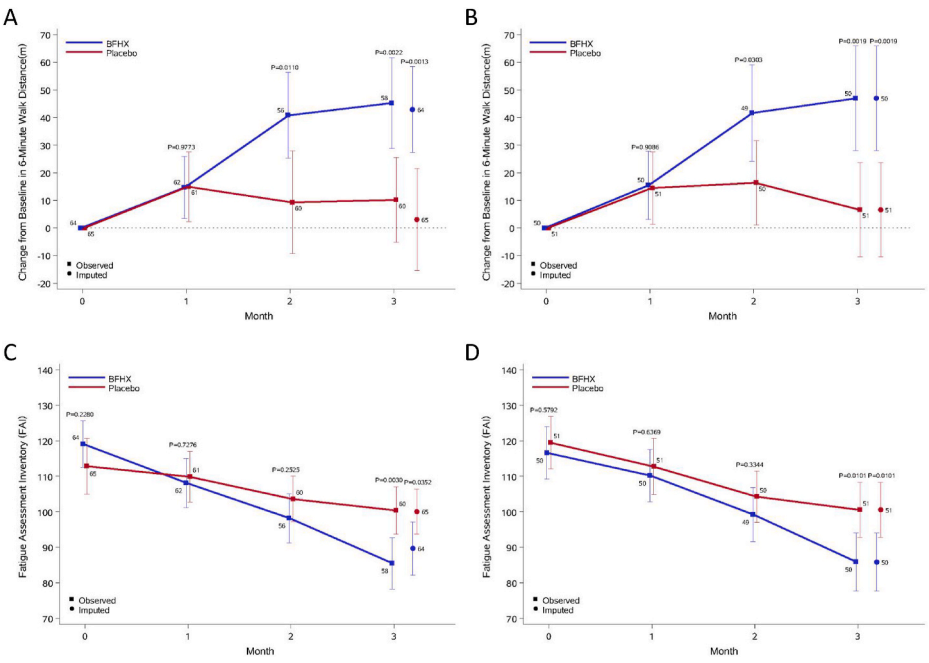

Fig. 2. Mean changes in 6-min walking distance and Fatigue Assessment Inventory results relative to baseline after three months of treatment in the placebo and BFHX Groups.
A. Mean changes from baseline in 6-min walk distance in the BFHX and control groups in the full dataset. B. Mean changes from baseline in 6-min walk distance in the BFHX and control groups in the per-protocol dataset. C. Fatigue Assessment Inventory scores in the BFHX and control groups in the full dataset. D. Fatigue Assessment Inventory scores in the BFHX and control groups in the per-protocol dataset. Data are presented as medians with 95% confidence intervals (95% CI). The last observation carried forward was imputed in the case of death or clinical worsening without a termination visit or measurement at the termination visit.
BFHX: Bufei Huoxue.

Table 4
Comparison of adverse events N (%).

Adverse	BFHX	Placebo	P-value
Total (%)	6 (9.38)	3 (4.62)	0.3241
Abnormal liver function (%)	4 (6.25)	2 (3.08)	0.4401
Liver injury (%)	1 (1.56)	0 (0.00)	0.4961
Diarrhoea (%)	1 (1.56)	0 (0.00)	0.4961
Excessive menstruation (%)	0 (0.00)	1 (1.54)	1.0000

P-value was calculated with Fisher' s exact test.

status.

In this study, we aimed to evaluate the efficacy and safety of BFHX in restoring the functional status and exercise tolerance of patients recovering from COVID-19 infection. Although a few patients in both groups received other rehabilitation interventions (aerobic exercise, breathing exercises, Baduanjin, and psychological therapy), there were no significant differences in these interventions between the two groups ($P > 0.05$), eliminating the confounding effect of other rehabilitation efforts. Our findings indicated that treatment with BFHX for 3 months resulted in an improvement in the 6MWD and imaging manifestations on chest CT. Three months of treatment also helped reduce fatigue and improve exercise tolerance.

Previous studies have reported that the major CT findings of COVID-19 include bilateral ground-glass opacities, consolidation, and peripheral and diffuse distribution (Liu et al., 2020). As BFHX was associated with better attenuation of COVID-19 manifestations on chest CT than placebo in the convalescent period, our findings suggest that BFHX promotes the absorption of lung lesions and prevents deterioration of pneumonia following COVID-19 infection.

Improvements in scores on the second part of the SGRQ, which assesses exercise capacity, were also higher in the BFHX group than in the control group. In addition, there was no statistically significant difference in the incidence of AEs between the two groups, indicating that BFHX represents a potential therapy with a favourable safety profile for the treatment of COVID-19 during convalescence.

Based on current experiences with COVID-19 treatment, TCM has already been incorporated into the Chinese rehabilitation guidelines for COVID-19, which has been beneficial for the immunity of patients recovering from COVID-19 (General Office of the National Health Commission, 2020). BFHX consists of psoralen, paeoniflorin, isopsoralen, verbasil glucoside, pentagalloyl glucose, verbasil isoflavones, tonic osteostatin, and isopsoralen (Tang et al., 2018). Previous clinical studies have shown that BFHX suppresses inflammatory injury of the lung, ameliorates lung function and pulmonary vascular haemodynamics, and through these mechanisms, relieves cough and chronic obstructive pulmonary disease (Xie et al., 2019). A network pharmacology study demonstrated that BFHX can also exert a therapeutic effect during the rehabilitation period of COVID-19 by targeting multiple cytokines and signalling pathways such as interleukin 6 (IL6), mitogen-activated protein kinase 8 (MAPK8), post-transcriptional gene silencing 1 (PTGS1), PTGS2, and nuclear receptor coactivator 2 (NCOA2) (Guo et al., 2020). These findings may provide a pharmacological basis for understanding improvements in symptoms following treatment with BFHX capsules in patients recovering from COVID-19.

There are a few limitations to this study. First, more objective evaluations are required to verify whether BFHX improves symptoms by ameliorating pulmonary diffusion function. In addition, a larger sample size is required to thoroughly verify the therapeutic effects of BFHX for all symptoms.

5. Conclusions

Neglecting rehabilitation intervention for patients with COVID-19 may result in prolonged recovery time and irreversible sequelae, which greatly deteriorate a patient's quality of life. The results of this multicentre, double-blind, randomised controlled trial suggest that BFHX reduces symptoms of fatigue and improves exercise tolerance in patients recovering from COVID-19. We believe that administration of BFHX to convalescent patients with fatigue, residual lung damage, and impaired exercise tolerance after discharge from the hospital will vastly minimise these symptoms and promote patient recovery following COVID-19 infection.

CRediT authorship contribution statement

Yuqin Chen: Conceptualization, Methodology, Writing – original draft. **Chunli Liu:** Investigation, Resources, Methodology. **Tingping Wang:** Investigation, Resources. **Jingjing Qi:** Investigation, Resources. **Xiaoqing Jia:** Investigation, Resources. **Xiansheng Zeng:** Investigation,

Resources. **Jianling Bai:** Formal analysis, Data curation, Visualization. **Wenju Lu:** Methodology, Project administration. **Yu Deng:** Formal analysis, Data curation. **Bihua Zhong:** Investigation. **Wenjun He:** Investigation. **Yue Xing:** Writing – original draft. **Zhan Lian:** Investigation. **Haohao Zhou:** Investigation. **Junping Yan:** Investigation. **Xuejiao Yang:** Investigation. **Hao Yu:** Investigation. **Jiawei Zhou:** Investigation. **Dansha Zhou:** Writing – review & editing. **Lixia Qiu:** Formal analysis, Visualization. **Nanshan Zhong:** Writing – review & editing, Project administration, Funding acquisition. **Jian Wang:** Conceptualization, Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2021.114830.

Conflicts of interest

The authors have declared no conflicts of interest. Guangdong Leiyunshang Pharmaceutical Co., Ltd. provided the medications for the study. However, they did not participate in research design, data collection, data analysis, data interpretation, or manuscript writing.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. All participants provided written informed consent.

Data availability and consent to participate

The authors declare that the data supporting the findings of this study are available from the corresponding authors upon reasonable request. Information that could compromise the privacy of research participants is not available.

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