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A Subgroup Reanalysis of the Efficacy of Bufei Huoxue Capsules in Patients With "Long-Covid-19"

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Keywords: bufei huoxue capsules | post-acute COVID-19 syndrome | subgroup reanalysis | symptom recovery | traditional Chinese medicine

ABSTRACT

Bufei huoxue capsules (BFHX), manufactured products of traditional Chinese medicine, have demonstrated anti-inflammatory properties and efficacy against chronic pulmonary diseases and COVID-19. This study was designed to further determine the clinical efficacy of BFHX in diverse patient subgroups during the convalescent phase of COVID-19, extending upon previously reported findings from a multicenter randomized controlled trial. Patients who had clinically recovered from COVID-19 were blindly assigned to BFHX or placebo groups. All enrolled patients underwent chest computed tomography (CT) imaging, 6-min walking distance (6MWD) test, and fatigue assessment inventory (FAI) at monthly follow-up for 3 months. A post hoc subgroup reanalysis was performed on subgroups of sex, age, severity of acute illness, and positive/negative IgG antibody against S antigen variants. A total of 129 patients were enrolled in BFHX ($N = 64$) and placebo groups ($N = 65$). The 6MWD and FAI scores were more significantly improved in females and mild patients than in males and severe patients after BFHX treatment. Lung CT image evaluated by the change in whole lung volume and mean CT value showed that the patients below 60 years gained more therapeutic effects after 3 months of BFHX treatment ($p = 0.0008$; $p = 0.017$; $p = 0.0313$, respectively). The subgroup reanalysis implies that the therapeutic effectiveness of BFHX in managing COVID-19 convalescence could potentially be influenced by factors including gender, age, and disease severity.

Abbreviations: 6MWD, 6-min walk distance; BFHX, bufei huoxue capsules; COVID-19, coronavirus disease 2019; CT, computed tomography; FAI, fatigue assessment inventory; FAS, full analysis set; PACS, post-acute COVID-19 syndrome; TCM, traditional Chinese medicine.

Chi Hou, Yue Xing, and Yuqin Chen contributed equally to this study and share the first authorship.

Chunli Liu and Jian Wang contributed equally to this study and share the senior authorship.

Trial registration: This study was registered with the China Clinical Trial Registration Center (registration number: ChiCTR2000032573).

1 | Introduction

The ongoing COVID-19 pandemic continues to pose significant challenges to global public health. Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this highly contagious viral infection has resulted in millions of confirmed cases and a substantial number of deaths worldwide. As the pandemic continues to persist, it has become increasingly evident that a substantial proportion of individuals who have recovered from the acute phase of COVID-19 continue to experience a wide range of persistent symptoms and complications [1]. Studies have provided greater insights into the long-term effects of COVID-19 on the human body. Those who continued to experience several symptoms even weeks or months after the initial infection with SARS-CoV-2 were classified as "long COVID-19" [2], also termed post-acute COVID-19 syndrome (PACS) [3, 4]. Observational clinical studies found that almost three-quarters of the patients who were diagnosed with critical or noncritical disease, recovered from COVID-19, and were discharged from the hospital had lung injury on computed tomography (CT) images [5, 6] and described more than several symptoms including fatigue, upper respiratory complaints, muscle weakness, and sleep difficulties [7–9]. However, the mechanisms underlying PACS remain unclear. Currently, SARS-CoV-2 is likely to live with humans for an extended time, and the number of infections is bound to increase annually, with an increasing number of people experiencing recovery from the virus. Although supportive therapies are the cornerstone of the management of COVID-19, clinical management during the rehabilitation period of PACS warrants further study.

In the early stages of the occurrence of COVID-19 in China, traditional Chinese medicine (TCM) was repurposed for the clinical management of COVID-19 in the guidelines issued by the National Health Commission of China, based on its history of development and efficacy as a treatment for infectious diseases, such as influenza [10]. It has been reported that therapy with TCM reduces the duration of hospital stay for patients infected with coronavirus [11]. Multiple studies have shown that some oral or intravenous TCM preparations exert protective effects against COVID-19, including Lianhuaqingwen capsules, Liushen capsules, ReDuNing injections, and Xuebijing injections [12–14]. Therefore, it is necessary to exploit TCM, which has evident benefits in the treatment of the new virus and in the improvement of recovery.

Bufei huoxue capsules (BFHX), approved by the Chinese Food and Drug Administration in 2003, were extracted from the dried ripe fruit of *Psoralea corylifolia* L. (Psoraleae Fructus, bu gu zhi) and the dried roots of *Paeonia lactiflora* Pall. (Paeoniae Radix Rubra, chi shao) and *Astragalus membranaceus var. mongholicus* (Bunge) P.K. Hsiao (Astragali Radix, huang qi). Ultrahigh-performance liquid chromatography-mass spectrometry analysis revealed that BFHX contains eight main bioactive compounds [15], which generally demonstrate a wide spectrum of pharmacological properties, including anti-inflammatory, antiviral, antibacterial, and immunomodulatory activities [16, 17]. Additionally, BFHX may help improve lung function and microcirculation in patients with chronic obstructive pulmonary disease and asthma [18]. Network pharmacology analysis also indicated that BFHX exhibits therapeutic effects in patients recovering from viral pneumonia by suppressing inflammatory pathways [19, 20]. In a recent publication, we provided evidence-based data suggesting that BFHX, a widely known Chinese patent medicine, could significantly help attenuate fatigue symptoms and improve exercise intolerance, thus facilitating recovery from COVID-19 [21]. In this study, a further subgroup analysis of the data was performed to identify the potential effect of sex, age, disease severity, and the presence of antibodies against SARS-CoV-2 on the efficacy of BFHX.

2 | Methods

The present study was a post hoc subgroup analysis of patients who participated in our previous randomized controlled trial (Chen et al., 2022). All patients with COVID-19 from five hospitals in four provinces throughout mainland China were recruited immediately after discharge. The study protocol was designed according to the *Good Clinical Practice* guidelines and *the Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (registration number: 2020-87). This study was registered with the China Clinical Trial Registration Center (registration number: ChiCTR2000032573). Written informed consent was obtained from all patients. BFHX (approval number: Z20030063, batch number: 022001) was obtained from Guangdong Leiyunshang Pharmaceutical Co. Ltd. The study procedure, including inclusion and exclusion criteria, randomization and blinding, intervention and efficacy evaluation, and safety monitoring, has been described in detail previously [22]. The evaluation indicators included measurements of chest CT, 6-min walk distance (6-MWD), and fatigue assessment inventory (FAI). Whole lung volume assessment was performed using the 3D Slicer software, a widely used open-source platform for medical image analysis. Specifically, the Lung CT Analyzer extension was employed to segment and quantify lung volumes from CT images. This tool enables the segmentation of different lung regions, including normal, infiltrated, collapsed, and emphysematous areas, providing detailed volumetric analysis. The segmentation process involves both automated algorithms and manual adjustments to ensure accuracy. The total lung volume and regional lung volumes were calculated based on the segmented images, and the results were validated using 3D visualization to ensure consistency. The mean CT value (Mean Hounsfield Unit, HU) is a quantitative measure used to assess tissue density in CT imaging. In this study, the mean CT value was calculated by averaging the CT values within the regions of interest (ROIs) selected in the pulmonary

lesions of COVID-19 patients. This metric reflects the extent of absorption in the lung parenchyma following infection.

2.1 | Subgroups

In a previous study, 129 patients were enrolled in the cohort and were divided into a BFHX-treatment group and a placebo control group; each group of patients was followed up for 3 months after BFHX or placebo administration. In this study, we divided the BFHX and placebo groups into eight subgroups according to sex (including male and female subgroups), age (including subgroups of age < 60 years and age ≥ 60 years), severity (including subgroups of critical and noncritical cases), and the result of IgG-neutralizing antibodies in plasma against SARS-CoV-2 (including subgroups of antibody-positive and antibody-negative).

2.2 | Statistical Analysis

Full analysis set (FAS) were used for the statistical analysis. Data entry was performed using SAS software (SAS Institute Inc., version 9.4). Two-tailed Student's *t*-test or Wilcoxon Mann–Whitney test was used to compare continuous outcomes between the groups. The data were shown by mean ± standard deviation. Statistical significance was set at $p < 0.05$. Participants who prematurely withdrew from the trial were compared to the outcome of the last visit.

3 | Results

3.1 | The Improvement of 6-MWD Between the Subgroups

Basic demographic characteristics of the whole population are shown in Table 1; detailed information has been provided in our previous study [21]. The patients' numbers included in the analysis were shown beside the mean point. By the second month of treatment, the 6-MWD improved significantly in the female BFHX-treatment group than in the control group (FAS: 49.70 ± 42.68 m vs. 7.63 ± 81.91 m, $p = 0.0138$) (Figure 1A). It improved even more by the end of the third month (FAS: 53.81 ± 52.51 m vs. 13.18 ± 57.71 m, $p = 0.0046$) (Figure 1A). However, there was no significant difference in male patients between the BFHX and placebo groups after 3 months of treatment.

In subgroups of ages, significant improvement was seen in BFHX-treated patients older than 60 years in the second month (FAS: 58.79 ± 56.16 m vs. -5.8 ± 101.36 m, $p = 0.0195$) and the third month (FAS: 67.00 ± 47.43 m vs. 13.33 ± 54.52 m, $p = 0.0025$) (Figure 1B) compared to the placebo group. Patients younger than 60 years in the BFHX group showed no difference compared with those in the placebo group.

BFHX effectively improved 6-MWD in both mild and severe COVID-19 patients, as opposed to the placebo group, whose 6-MWD declined over time. A statistically significant difference was observed in mild patients by the second month in

TABLE 1 | Comparison of patient characteristics at baseline.

Term	BFHX ($N = 64$)	Placebo ($N = 65$)	*p* value[†]
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 labor (%)	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 randomization (day)	131.2 ± 14.0	130.7 ± 14.6	0.8254
Time from discharge to randomization (day)	94.3 ± 17.0	94.3 ± 20.5	0.9845

[†] *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.

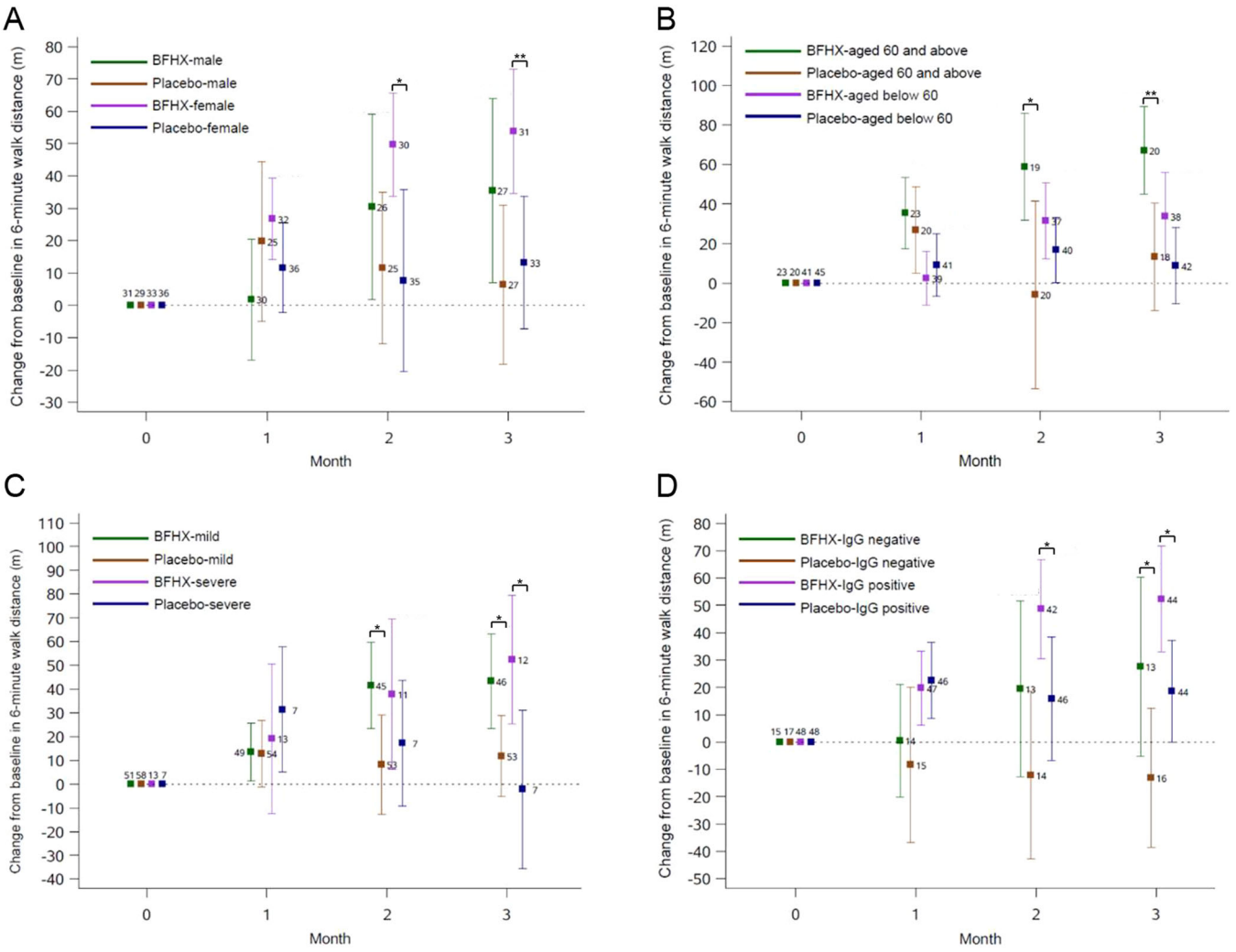

FIGURE 1 | Changes in 6-min walking distance in subgroups at different follow-up time points. The data were shown by mean ± 95% CI. The patients' number in each subgroup was shown beside the mean point. (A) Subgroups of sex. (B) Subgroups of age. (C) Subgroups of COVID-19 severity at on set. (D) Subgroups of positive/negative IgG-neutralizing antibody. *$p < 0.05$, **$p < 0.01$, significantly different as indicated.

those treated with BFHX (FAS: 41.49 ± 60.72 m vs. 8.23 ± 75.97 m, $p = 0.0201$) (Figure 1C). Also, those patients with severe illness showed an improvement after 3 months of treatment (FAS: 52.42 ± 42.46 m vs. -2.14 ± 36.11 m, $p = 0.0112$) (Figure 1C).

The results are similar in the subgroups of plasma-neutralizing antibodies; BFHX showed a therapeutic effect in both antibody-positive patients and antibody-negative patients. In the patients with positive neutralizing antibodies, the BFHX-treatment group showed a significant difference after the second month (FAS: 48.71 ± 58.21 m vs. 15.80 ± 76.07 m, $p = 0.0262$) and the third month (FAS: 52.27 ± 63.71 m vs. 18.57 ± 61.36 m, $p = 0.0133$) (Figure 1D). In the patients with negative neutralizing antibodies, the BFHX-treatment group showed a significant difference after the third month (FAS: 27.62 ± 54.18 m vs. -13.06 ± 47.84 m, $p = 0.0410$) (Figure 1D). Taken together, these results indicated that BFHX was more effective in females and patients older than 60 years and had therapeutic effects regardless of COVID-19 severity and whether neutralizing antibodies were generated.

3.2 | Differences of FAI Between the Subgroups

We performed FAI to evaluate the recovery of subjective symptoms. FAI scores were significantly lower in female patients in the BFHX group than in the female control group after 2 months (FAS: 98.6 ± 25.1 vs. 109.9 ± 21.3, $p = 0.0369$) and 3 months (FAS: 82.3 ± 28.8 vs. 105.9 ± 23.1, $p = 0.0007$) of treatment (Figure 2A). Although the FAI scores were lower in the male patients treated with BFHX than those in the placebo group, the difference was not statistically significant. In contrast to the 6-MWD, the FAI scores indicated that BFHX was more effective in patients younger than 60 years at the third month of treatment (FAS: 87.1 ± 32.3 vs. 102.0 ± 24.5, $p = 0.0008$) (Figure 2B). The FAI scores were significantly lower in patients with mild illness treated with BFHX than in those treated with placebo in the third month (FAS: 84.63 ± 27.98 vs. 102.17 ± 25.10, $p = 0.0014$) (Figure 2C). No overall significant difference was found in the FAI scores between severe illness of COVID-19 patients treated with BFHX and placebo. In addition, patients with either positive or negative neutralizing antibodies showed statistical differences in reaction to BFHX treatment. A

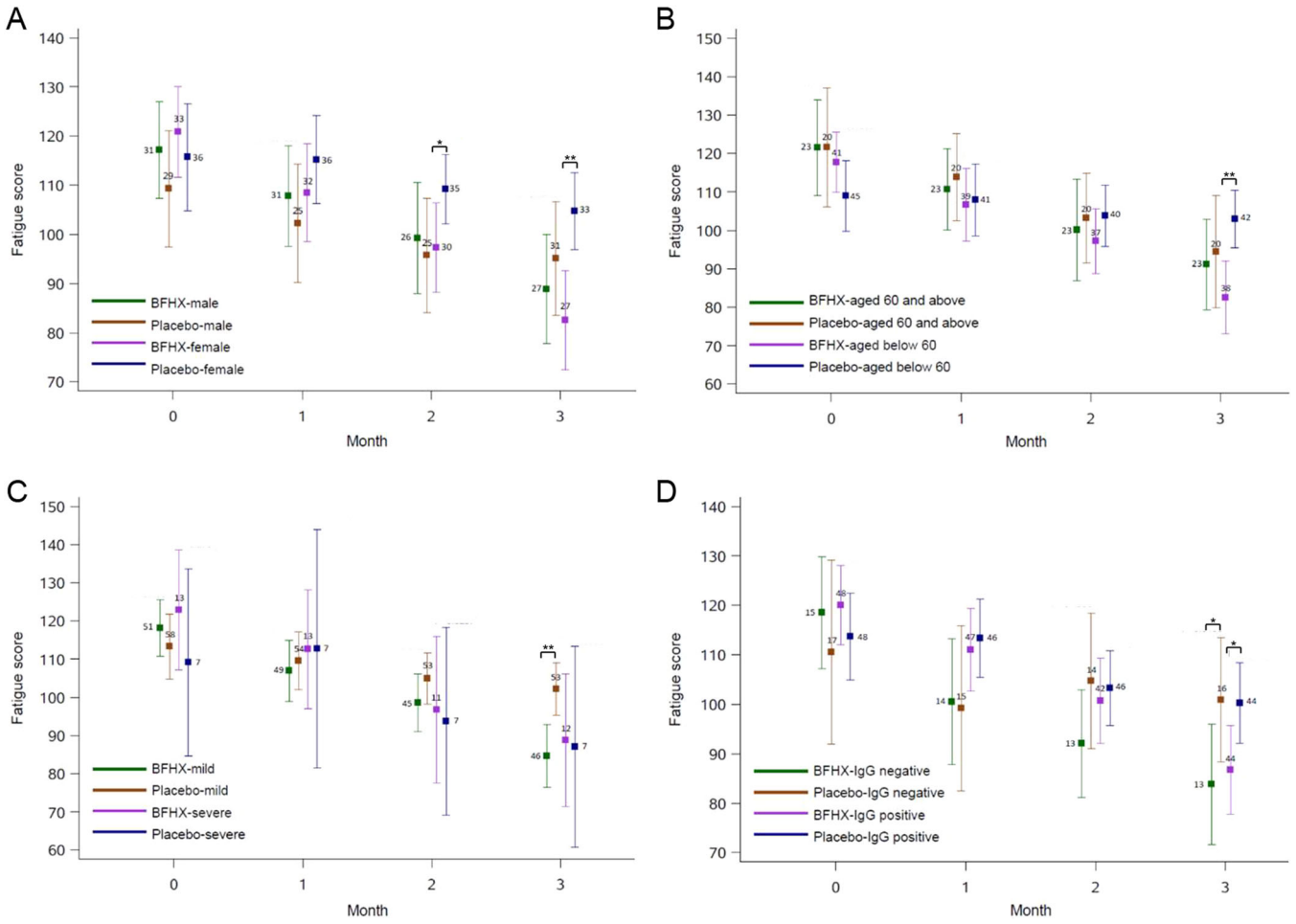

FIGURE 2 | Fatigue assessment inventory scores in subgroups at different follow-up time points. The data were shown by mean ± 95% CI. The patients' number in each subgroup was shown beside the mean point. (A) Subgroups of sex. (B) Subgroups of age. (C) Subgroups of COVID-19 severity at on set. (D) Subgroups of positive/negative IgG-neutralizing antibody. *$p < 0.05$, **$p < 0.01$, significantly different as indicated.

significant reduction in FAI score was observed in the patients treated with BFHX for 3 months (IgG-negative-BFHX vs. placebo: 83.85 ± 20.09 vs. 100.88 ± 23.56, $p = 0.0486$; IgG-positive-BFHX vs. placebo: 86.75 ± 29.49 vs. 100.23 ± 26.72, $p = 0.0272$) (Figure 2D). The evaluation of the subgroups' FAI scores indicated that females, patients younger than 60 years, and patients with mild illness could obtain more subjective symptomatic relief from rehabilitation intervention.

3.3 | The Improvement of Chest CT Image Between Subgroups

Next, the CT morphologic features were evaluated by quantitative parameters, including the changes in whole lung volume and mean CT value. After 3 months of BFHX treatment, the change in whole lung volume in the subgroup aged below 60 years (FAS: 334.07 ± 800.80 cm^3 vs. −83.54 ± 611.11 cm^3, $p = 0.0170$) (Figure 3B) and the subgroup of severe patients (FAS: 916.30 ± 1045.93 cm^3 vs. −52.98 ± 512.35 cm^3, $p = 0.0376$) (Figure 3C) both showed a notable increase. Although a more significant increase could be seen in the subgroups of male (Figure 3A) and antibody-positive patients (Figure 3D), no statistical differences were found between these subgroups. Meanwhile, treatment with BFHX was associated with decreased mean CT value in male patients (FAS: −9.14 ± 46.44 HU vs. 17.39 ± 41.00 HU, $p = 0.0405$) (Figure 4A) and those aged below 60 years (FAS: −15.84 ± 48.39 HU vs. 7.53 ± 39.75 HU, $p = 0.0313$) (Figure 4B). Whereas, in the subgroups of illness severity and anti-S antigen IgG expression, treatment of BFHX did not result in an improvement in mean CT value (Figure 4C,D).

4 | Discussion

Since the outbreak of SARS-CoV-2, there has been increased concern regarding the risk of post-acute or long-term sequelae of COVID-19. Researchers have become increasingly aware that COVID-19 patients, even after recovering, experience lingering symptoms that prohibit them from living normal lives. There have been attempts to understand the damage caused by SARS-CoV-2 at a deeper level. The most common symptoms in patients with COVID-19 are profound fatigue, headache, respiratory complaints (breathlessness, cough, chest pain, and loss of smell), and multisystem complaints (joint pain, palpitations, neurocognitive issues, and memory problems) [23–25]. In addition to somatic symptoms, organ dysfunction was also found during the recovery stage of COVID-19. Follow-up studies on rehabilitating patients with SARS-CoV-2 have

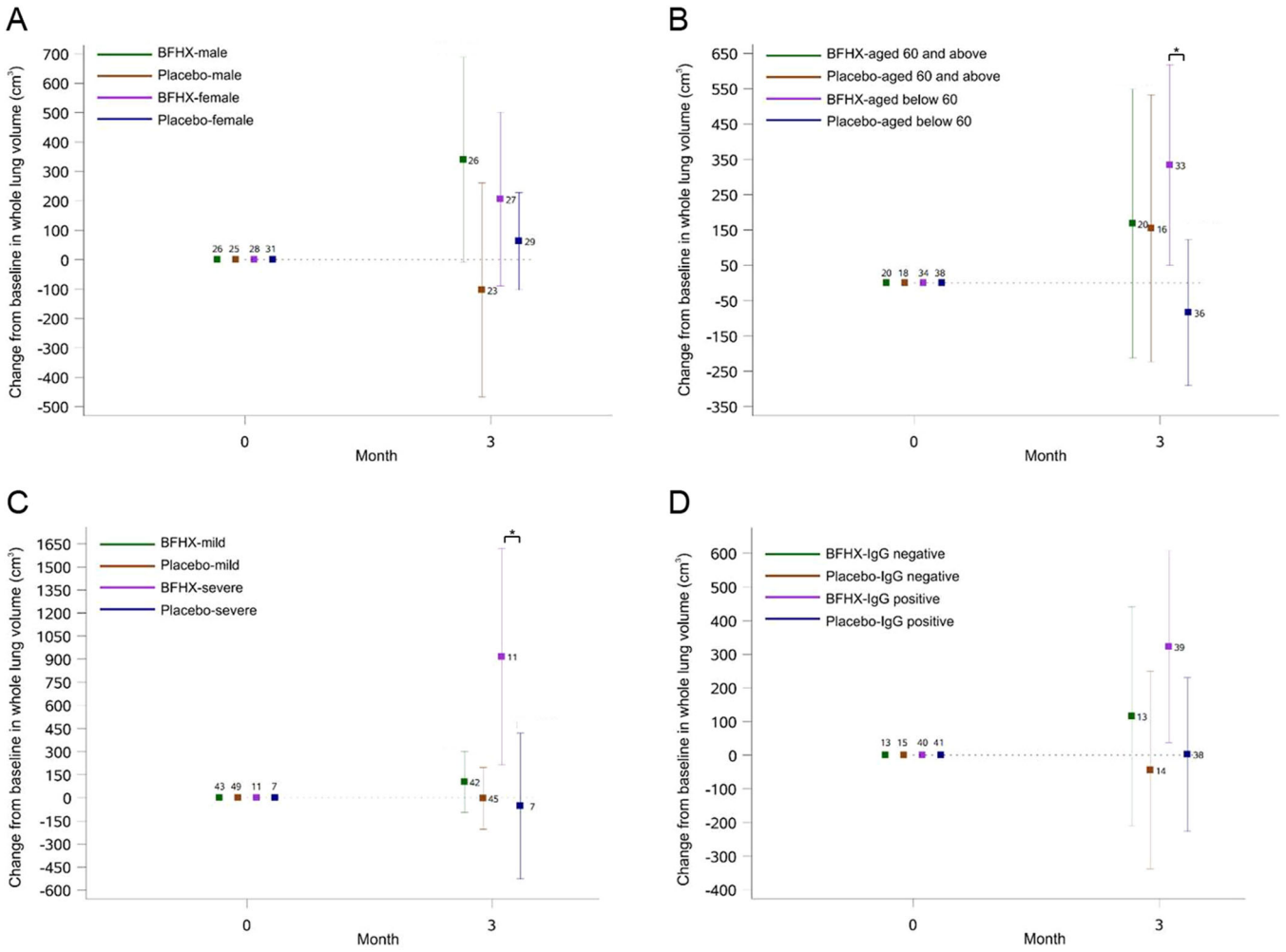

FIGURE 3 | Changes in whole lung volume of CT images at the end of follow-up. The data were shown by mean ± 95% CI. The patients' number in each subgroup was shown beside the mean point. (A) Subgroups of sex. (B) Subgroups of age. (C) Subgroups of COVID-19 severity at on set. (D) Subgroups of positive/negative IgG-neutralizing antibody. $*p < 0.05$, $**p < 0.01$, significantly different as indicated.

described impaired pulmonary function in patients at the time of discharge, regardless of the severity of COVID-19 [26–28]. This clinical evidence suggests that interventions are crucial in the recovery period from COVID-19 to help survivors return to their normal lives. Presently, there are several recommendations for managing long-term COVID-19, mainly focusing on epidemiological monitoring and physical medicine [29], yet effective and precise medication recommendations for the management of convalescent COVID-19 are lacking.

Historically, TCM has been used for millennia to fight viruses and has been shown to have evident therapeutic effects in improving clinical symptoms, chest CT, and infection indicators in COVID-19 patients [30, 31]. Biologically, many of the effective components of TCM have been proven to be anti-inflammatory and immunomodulatory in anti-COVID-19 [32]. As a patent TCM, BFHX has multiple pharmacological activities, including the promotion of blood circulation and improvement of lung and kidney function in patients with cardiopulmonary diseases [19, 20]. Animal experiments in rodent models have confirmed that BFHX can significantly reduce inflammatory factors [17, 33] and alleviate pulmonary fibrosis, probably through regulating gut microbiota [34]. The pharmacological effects of BFHX and the findings of evidence-based medicine in critical fields suggest that it can be used to foster recovery from COVID-19.

In our previous study, we found that a certain percentage of the recovered remained symptomatic and experienced radiologic dysfunction 3 months post-discharge for COVID-19, which is consistent with previous reports [35–37]. BFHX reduces fatigue symptoms and improves exercise tolerance in patients recovering from COVID-19 [21]. We observed a greater clinical benefit in female patients treated with BFHX than in those not treated with BFHX, based on both objective (6-MWD) and subjective (FAI) measures. According to a prospective cohort study of long-term COVID-19 in the United Kingdom, female sex, comorbidities, having received mechanical ventilation for critical illness, and middle age (40–59 years old) were risk factors for not fully recovering from pneumonia (Evans et al., 2021). The prevalence of prolonged COVID-19 in female patients is twice as common as that in male patients [38]. Women tend to feel fatigued to a greater extent than men, which may be associated with stress-related factors [39]. The potential mechanism underlying sex and age differences in persistent symptoms has not yet been identified. One possibility is that a wide

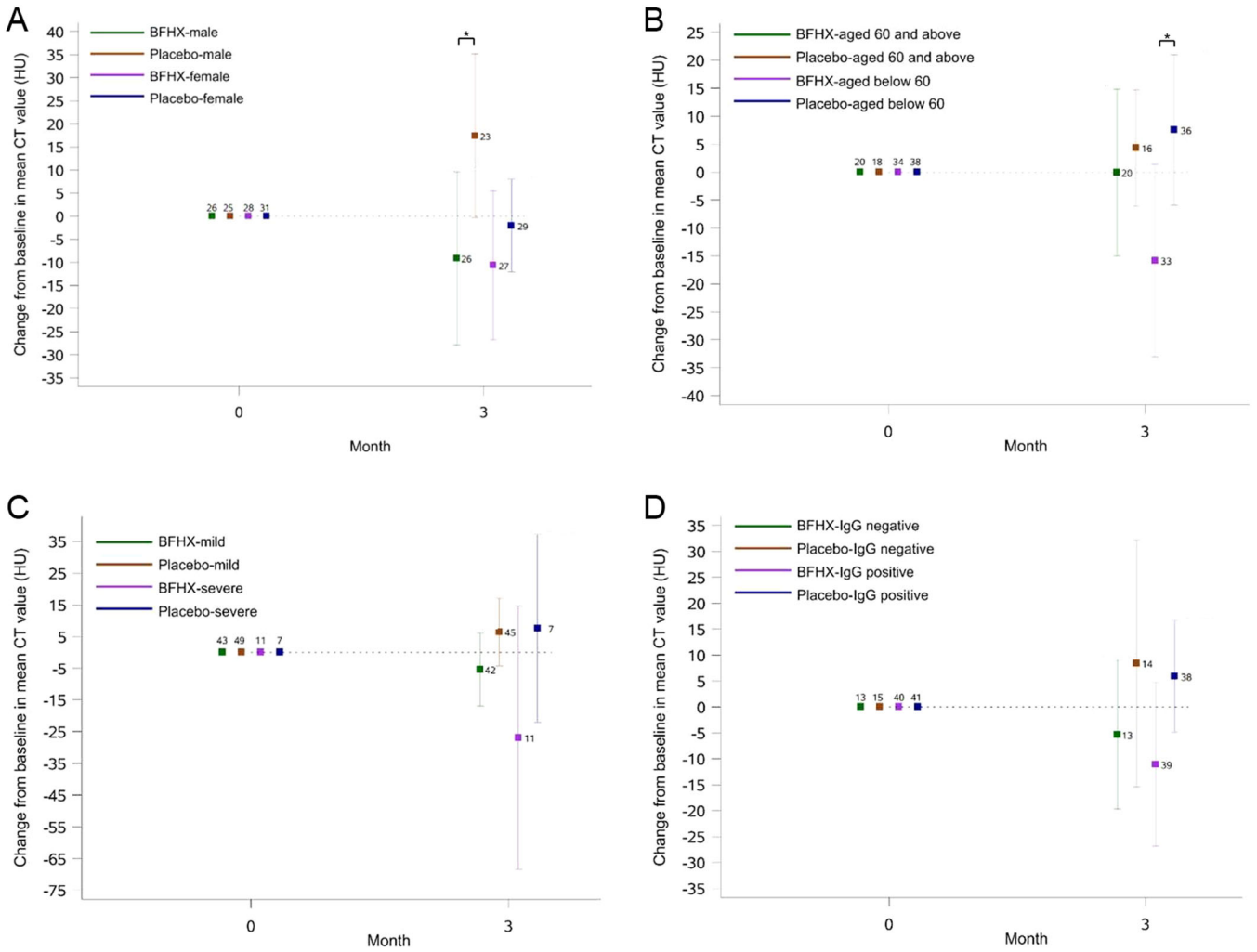

FIGURE 4 | Changes in mean CT value at the end of follow-up. The data were shown by mean ± 95% CI. The patients' number in each subgroup was shown beside the mean point. (A) Subgroups of sex. (B) Subgroups of age. (C) Subgroups of COVID-19 severity at on set. (D) Subgroups of positive/negative IgG-neutralizing antibody. *$p < 0.05$, **$p < 0.01$, significantly different as indicated.

immune response triggered by the initial infection may generate tissue-specific antibodies and other immunological reactions [40], which is more common among women over 40 years of age, similar to autoimmune diseases. Interestingly, subgroup analysis of chest CT features showed a CT recovery, reflected by the increase of whole lung volume, in both the male and female groups treated with BFHX, while a significant improvement was only seen in the male BFHX group compared to the female patients. Backtracking the baseline data, a possible explanation is that patients in the control group of men not treated with BFHX experienced worsening based on chest CT findings.

A prospective cohort study indicated that 6-MWD showed no statistically significant difference among patients with different severities 60 days after the onset of COVID-19, although the severe group had a higher rate of abnormal pulmonary function and chest radiology than patients with mild symptoms and non-severe pneumonia [41]. Our study showed that BFHX resulted in greater symptom relief and exercise tolerance reflected by longer walking distance in patients with mild pneumonia than in those with severe pneumonia at 3 months after hospital discharge, suggesting that patients with severe pneumonia may need a longer recovery time. Results from CT images indicated that the severe patients recovered more with the treatment of BFHX. Notably, whether 6MWD or FAI or the evaluation of CT images, there was more benefit in patients with positive IgG-neutralizing antibodies.

The exploration of repurposed TCM products would be valuable for use in advanced recovery from COVID-19 because no other medications with proven efficacy exist. Our findings indicated that BFHX capsules could be recommended for patients with prolonged COVID-19 to reduce the symptom burden and improve clinical outcomes, especially in women and patients with IgG-positive plasma.

However, this study had some limitations. First, this study included a small number of patients; therefore, the results should be interpreted with caution. The limited sample size of severe disease and losses of follow-up could cause a possible selection bias. Second, limited by the epidemic prevention policy, pulmonary function tests for patients were not performed. At the time we planned this study, there was deep concern about the potential transmission of the virus via pulmonary function testing. Moreover, this study was a post hoc subgroup analysis. The presence of confounding factors and

limitations in statistical power inherent to post hoc analyses restrict the generalizability of the results and the ability to draw robust conclusions.

5 | Conclusions

BFHX have potential clinical advantages for COVID-19 patients by showing improvement in clinical symptoms, exercise intolerance, and lung CT recovery. In our setting, COVID-19 was often accompanied by long-term complications, and women recovered more extensively than men with BFHX treatment. This effect was also seen in young and middle-aged patients and those who recovered from a mild disease, suggesting that patients with the aforementioned features should be given early attention during the convalescence of COVID-19. Therefore, the evaluation of patients' clinical features and follow-up for recovering outpatients are necessary for precise management strategy during the convalescent period.

Author Contributions

Chi Hou, Yue Xing, and Yuqin Chen wrote and revised the manuscript. Yuqin Chen, Tingping Wang, Jingjing Qi, Xiaoqing Jia, Xiansheng Zeng, Bihua Zhong, Yilin Chen, Yue Xing, Zhan Lian, Haohao Zhou, Junping Yan, Xuejiao Yang, and Wenju Lu followed up patients and contributed to acquisition and the accuracy of the data. Jianling Bai, Hao Yu, and Jiawei Zhou contributed to create the dataset and performed statistical analyses. Yu Deng, Yongxia Lei, and Lixia Qiu performed chest CT scanning and contributed to analyses and interpretation of data. Chi Hou, Yuqin Chen, Chunli Liu, and Jian Wang contributed to the planning and designing of the study. Yunliang Zhai and Wanli Geng contributed to the quality control of the drugs. Nanshan Zhong initiated and designed the study. Jian Wang and Chunli Liu initiated and designed the study and revised the whole manuscript. All authors have critically revised the manuscript and gave final approval for the publication of this manuscript.

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Disclosure

Guangdong Leiyunshang Pharmaceutical Co. Ltd. provided the medications for the study and did not participate in research design, data collection, data analysis, data interpretation, or manuscript writing.

Ethics Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

Consent

All participants provided written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data supporting the findings of this study will be provided by the corresponding authors upon reasonable request. Information that could compromise the privacy of research participants is not available.

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