

Xuanfei Baidu decoction, a Chinese herbal medicine for coronavirus disease 2019 (COVID-19): a randomized clinical trial

Tao Li¹, Min Zhao^{1,*}, Mingjun Zhu¹, Shixi Zhang², Jiarong He³, He Pan⁴, Mingyi Shao¹, Zhen Wang¹, Yu Fu¹, Ning Li¹, Long Zhao⁵, Xinyao Jin⁶, Fengwen Yang⁶, Wentai Pang^{6,*}

Abstract

Objective: To evaluate the efficacy and safety of Xuanfei Baidu decoction for treating coronavirus disease 2019 (COVID-19).

Methods: Patients with COVID-19 were enrolled, and eligible patients were randomly allocated to three groups: group A (Xuanfei Baidu decoction combined with conventional treatment), group B (Ganlu Xiaodu decoction combined with conventional treatment), and group C (conventional treatment only). The duration of treatment was 14 days. The primary outcomes were the duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid testing from positive to negative and hospitalization days. The secondary outcome was the rate of symptom resolution. The safety outcome was drug-related adverse events.

Results: In total, 103 patients with ordinary-type COVID-19 were included and randomly allocated to groups A (34 cases), B (35 cases), and C (34 cases). Duration for SARS-CoV-2 nucleic acid testing from positive to negative was shortest in group A [(9.88 ± 3.62) days], followed by groups C [(11.20 ± 2.93) days] and B [(12.69 ± 4.11) days]; differences between the three groups were statistically significant ($P = 0.010$). The number of hospitalization days was the least in group A [(14.00 ± 6.55) days], followed by groups B [(15.40 ± 4.02) days] and C [(16.38 ± 5.73) days], and differences between groups were statistically significant ($P = 0.019$). There was no statistically significant difference in the rate of symptom resolution between groups ($P > 0.05$). No deaths or serious adverse events occurred in either of the groups.

Conclusion: Considering the treatment of ordinary-type COVID-19, Xuanfei Baidu decoction can shorten the duration from a positive to negative SARS-CoV-2 nucleic acid test, as well as the duration of hospitalization. Moreover, there were no Xuanfei Baidu decoction-induced adverse reactions.

Keywords: COVID-19, Ordinary type, Randomized clinical trial, Traditional Chinese medicine, Xuanfei Baidu decoction

Graphical abstract: <http://links.lww.com/AHM/A44>.

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^[1-2]. As of April 14, 2022, 500.19 million confirmed cases and 6.19

million deaths had been documented^[3]. Accordingly, COVID-19 seriously impacts human health and social development^[4].

China has made substantial progress in the fight against COVID-19 using combination therapies incorporating Chinese and Western medicines^[5]. Several traditional Chinese medicines, especially the “three drugs and three prescriptions,” were recommended for clinical use during the early stage of the COVID-19 outbreak in “Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8)” issued by the National Health Commission of the People’s Republic of China^[6]. Xuanfei Baidu decoction (XFBD), developed by Professor Boli Zhang and Qingquan Liu, is one of the three prescriptions and comprises 13 Chinese medicinal herbs, including Ephedrae Herba (Mahuang), Gypsum Fibrosum (Shigao), Atractylodis Rhizoma (Cangzhu) (stir-baked with bran), Pogostemonis Herba (Guanghuoxiang), Artemisiae Annuae Herba (Qinghao), Polygoni Cuspidati Rhizoma et Radix (Huzhang), Verbenae Herba (Mabiancao), Coix Seed (Yiyiren), Phragmitis Rhizoma (Lugen), Descurainiae Semen Lepidii Semen (Tinglizi), Armeniacae Semen Amarum (Kuxingren), Citri Grandis Exocarpium (Huaajuhong), and Glycyrrhizae Radix et Rhizoma (Gancao)^[7]. Several pharmacological studies have attempted to elucidate the effective mechanism of XFBD, reporting that XFBD

¹ The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China; ² Shangqiu Municipal Hospital, Shangqiu, China; ³ The Fifth People’s Hospital of Xinyang, Xinyang, China; ⁴ Xinyang Traditional Chinese Medicine Hospital, Xinyang, China; ⁵ Nanyang First People’s Hospital, Nanyang, China; ⁶ Tianjin University of Traditional Chinese Medicine, Tianjin, China

*Corresponding author. Min Zhao, The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450008, China, E-mail: byts1969@126.com; Wentai Pang, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China, E-mail: pwtctm@tjutcm.edu.cn.

Copyright © 2023 Tianjin University of Traditional Chinese Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Acupuncture and Herbal Medicine (2023) 3:3

Received 2 November 2022 / Accepted 15 January 2023

<http://dx.doi.org/10.1097/HM9.0000000000000056>

can inhibit virus replication, control inflammatory factors, condition body immunity, and other activities^[8].

Several clinical trials have been conducted with the support of the National Key Research and Development Program of China. In the present study, we evaluated the efficacy and safety of XFBD when compared with that of ancient classical prescriptions and conventional treatments.

Methods

Study design

The present study was a three-arm, open-label, randomized controlled clinical trial. Random numbers were generated using SAS software. The study protocol was reviewed and approved by the Clinical Trials Ethics Committee of Hubei Provincial Hospital of Integrative Medicine (2020-003) and was registered with the China Clinical Trials Center (ChiCTR2000029439). The study was reported according to the CONSORT checklist^[9].

Patients

We recruited patients diagnosed with COVID-19 and admitted to designated hospitals in Henan Province, including Shangqiu Municipal Hospital, Xinyang Fifth People's Hospital, and Nanyang First People's Hospital.

The study referred to the diagnostic criteria established by the "COVID-19 Diagnosis and Treatment Plan (Trial Fifth Edition)" issued by the National Health Commission of China on February 8, 2020.

Patients who met the diagnostic criteria for ordinary-type COVID-19 and were older than 18 years were deemed eligible for study participation after obtaining oral informed consent. Patients with chronic respiratory diseases, allergic diseases (such as allergic rhinitis and allergic asthma), test drug allergies, pregnant women, and those participating in other clinical trials were excluded.

Interventions

Eligible patients were randomly allocated to three groups.

Group A: XFBD combined with conventional treatment. XFBD was prepared from herbal granules by Sichuan New Green Pharmaceutical Technology Development Co. Ltd., taken twice daily with warm water.

Group B: Ganlu Xiaodu decoction (GLXD) combined with conventional treatment. The composition and daily dosage of GLXD was as follows: 6g Amoni Fructus Rotundus (Doukou), 10g Atractylodis Macrocephalae Rhizoma (Baizhu), 10g Pogostemonis Herba (Guanghuoxiang), 6g Artemisiae Scopariae Herba (Yinchen), 20g Talci Pulvis (Huashifen), 15g Acori Tatarinowii Rhizoma (Shichangpu), 10g Forsythiae Fructus (Lianqiao), 8g Scutellariae Radix (Huangqin), 6g Menthae Haplocalycis Herba (Bohe), 15g Fritillaria thunbergii Miq (Zhebeimu), 10g Arecae Semen (Binlang), 10g Tsaoko Fructus (Caoguo) 6g, Verbenae Herba (Mabiancao), and 10g Shengqu. The prescription comprised herbal granules prepared by Sichuan New Green Pharmaceutical Technology Development Co. Ltd., taken twice daily with warm water.

Group C: Conventional treatment. This treatment included: 1) rest and supportive treatment to maintain the stability of vital signs, oxygen saturation, and adequate calories and electrolyte

balance. 2) timely and effective oxygen therapy, including nasal catheter, mask oxygen, and transnasal high-flow oxygen therapy, and 3) antiviral, antibiotic, and hormone therapy when needed.

The treatment course for all three groups was performed for 14 d, with follow-up at the end of the course until discharge from the hospital.

Outcomes

Primary outcomes

Duration of the SARS-CoV-2 nucleic acid test from positive to negative: Reverse transcription polymerase chain reaction (RT-PCR) was used to detect SARS-CoV-2 nucleic acid levels, and two consecutive negative test results were deemed as the standard for conversion to negative. The duration was the number of days from the positive nucleic acid test to the first negative test.

Hospitalization days: The number of days from admission to discharge of included patients.

Secondary outcomes

The rate of disappearance of symptoms such as fever, fatigue, cough, breathlessness, and decreased appetite was assessed as a secondary outcome.

Compared with the level at admission, each symptom was classified as disappearance, unchanged, or aggravated. Secondary outcomes were recorded and evaluated at admission and 7 and 14 d after treatment. The disappearance rate of each symptom was calculated as follows (disappearance rate of symptoms = the number of symptoms disappear cases / total number of symptoms × 100%).

Safety outcomes

Safety outcomes were treatment-related adverse events, including patient discomfort and abnormal values of liver or kidney function tests. Adverse events were documented as "normal to abnormal" and "abnormal aggravated." Investigators evaluated the relationship between adverse events and XFBD and GLXD.

Criteria for abnormal liver function: alanine aminotransferase (ALT), aspartate transaminase (AST), and total bilirubin (TBIL) values were not within normal values (normal values: ALT < 42 U/L; 8 U/L < AST < 40 U/L; 2 μmol/L < TBIL < 21 μmol/L).

Criteria for abnormal renal function: creatinine (Cr) and blood urea nitrogen (BUN) values were not within the normal range (normal value range: 53 μmol/L < Cr < 33 μmol/L; 1.7 μmol/L < BUN < 8.3 μmol/L).

Incidence of adverse events: Each adverse event was recorded, and the incidence of adverse events was calculated (incidence of adverse events = the number of cases with adverse events / total cases × 100%).

Statistical analysis

Statistical analysis was performed using the R software. The intention-to-treat principle was applied, and mean interpolation was adopted to deal with missing values.

Categorical data (eg, gender and symptoms) are presented as frequencies and percentages. Continuous data (eg, age and temperature) are presented as the mean $\pm$ standard deviation. For continuous data, one-way analysis of variance was used to analyze normally distributed data, while the Kruskal–Wallis test was used for skewed data. For the count data, hypothesis tests were performed using the chi-squared test. $P < 0.05$ was deemed as a statistically significant difference.

Results

General information

In total, 103 patients were randomly allocated to three groups, 34 patients to group A, 35 to group B, and 34

to group C. Five patients withdrew from the study: 2, 2, and 1 from the three groups, respectively. In group A, the reasons for withdrawal were incomplete information and a diagnosis of chronic obstructive pulmonary disease. In group B, two patients withdrew owing to incomplete information and excessive anxiety after enrollment. One patient was withdrawn from group C owing to incomplete information (Figure 1).

Baseline characteristics for included patients included age, gender, days from onset to admission, vital signs (temperature, breath, and pulse), blood cell count (leukocyte, neutrophil, lymphocytes, and platelets), and comorbid chronic disease conditions (hypertension, coronary artery disease, and diabetes mellitus). No statistically significant difference in baseline data was observed among the three groups ($P > 0.05$, Table 1).

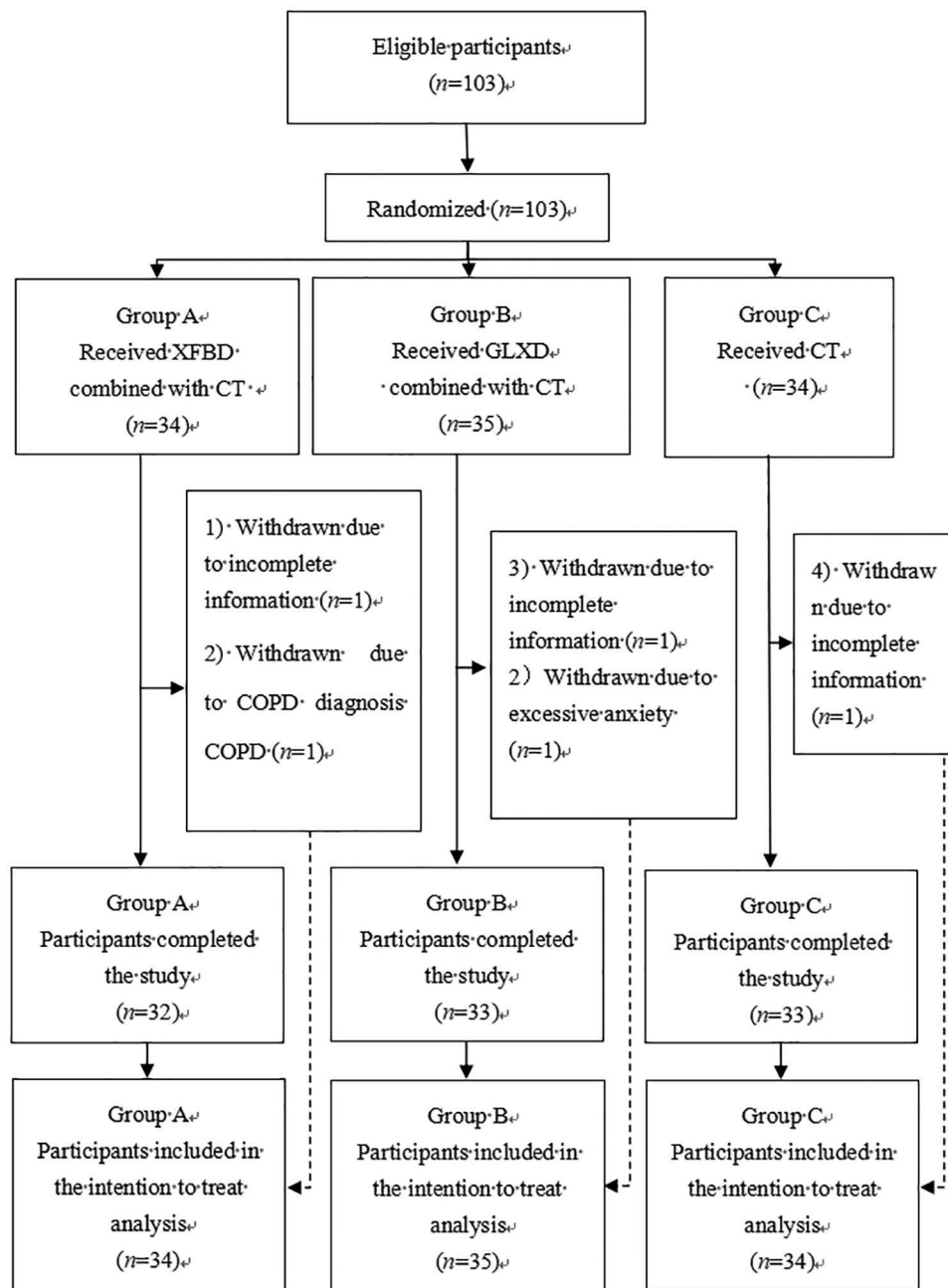


Figure 1. Flowchart of the study. COPD: Chronic obstructive pulmonary disease; CT: Conventional treatment; GLXD: Ganlu Xiaodu decoction; XFBD: Xuanfei Baidu decoction.

Table 1.**Demographic and clinical characteristics**

Baseline	Group A (34 patients)	Group B (35 patients)	Group C (34 patients)	P
Age (y)	41.91 ± 14.39	42.89 ± 15.01	47.44 ± 14.16	0.179
Gender (male/female)	14/20	19/16	20/14	0.318
Days from onset to hospitalize (d)	5.97 ± 6.94	7.03 ± 3.95	6.41 ± 4.05	0.086
Temperature (°C)	37.19 ± 0.86	36.99 ± 0.55	37.12 ± 0.84	0.716
Pulse (times/min)	85.44 ± 10.81	83.00 ± 11.08	84.15 ± 12.13	0.065
Breath (times/min)	20.26 ± 1.91	19.51 ± 2.85	20.12 ± 1.79	0.635
Blood count (10 ⁹ /L)				
Absolute value of leucocyte	5.93 ± 2.05	5.86 ± 3.14	5.13 ± 1.60	0.303
Absolute value of neutrophil	3.81 ± 1.89	4.08 ± 2.84	3.58 ± 1.60	0.948
Absolute value of lymphocytes	1.72 ± 0.72	1.35 ± 0.49	1.19 ± 0.49	0.004
Absolute value of platelet	226.87 ± 61.70	197.69 ± 50.74	204.77 ± 48.36	0.051
Comorbidities (n,%)				
Hypertension	3 (8.82)	1 (2.86)	5 (14.71)	0.219
Diabetes mellitus	0 (0.00)	1 (2.86)	4 (11.76)	0.062
Coronary artery disease	2 (5.88)	1 (2.86)	5 (14.71)	0.163

Data are presented as mean ± standard deviation (SD) unless otherwise specified.

Table 2.**Comparison of primary outcomes**

Primary outcomes	Group A (34 patients)	Group B (35 patients)	Group C (34 patients)	P
Duration for SARS-CoV-2 nucleic acid test from positive to negative (d)	9.88 ± 3.62	12.69 ± 4.11	11.20 ± 2.93	0.010
Duration of hospitalization (d)	14.00 ± 6.55	15.40 ± 4.02	16.38 ± 5.73	0.019

Data are presented as mean ± standard deviation (SD) unless otherwise specified.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Results of primary outcomes

The duration of the SARS-CoV-2 nucleic acid test from positive to negative was (9.88 ± 3.62), (12.69 ± 4.11) and (11.20 ± 2.93) d in groups A, B, and C, respectively. A statistically significant difference was observed among groups ($P = 0.010$), suggesting that XFBD could accelerate virus clearance in patients with ordinary-type COVID-19 (Table 2, Figure 2).

The hospitalization days were (14.00 ± 6.55), (15.40 ± 4.02) and (16.38 ± 5.73) d in groups A, B, and C, respectively, with a statistically significant difference between groups ($P = 0.019$). This result suggested that

XFBD could shorten the hospital stay among patients (Table 2, Figure 3).

Secondary outcomes

After 7 d of treatment, the disappearance rates of fever, fatigue, cough, and decreased appetite in group A (100%, 88.89%, 58.82%, and 100%, respectively) were higher than those in groups B and C. However, there were no statistically significant differences between the groups. After 14 d of treatment, the disappearance rate of fever was 100% in all three groups, and the disappearance rate of fatigue was higher in group A (100%)

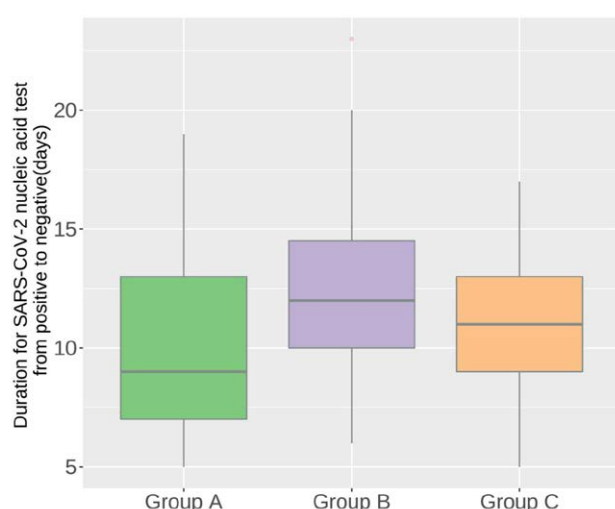


Figure 2. Comparison of the duration for SARS-CoV-2 nucleic acid test from positive to negative among the three groups. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

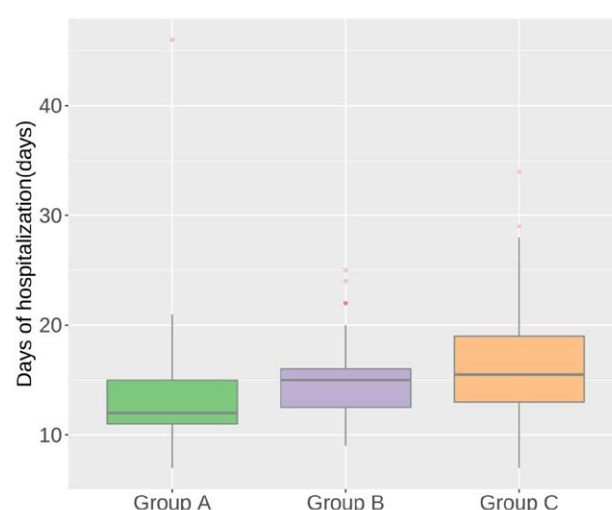


Figure 3. Comparison of the hospitalization days among the three groups.

than that in the other two groups. The disappearance rates of cough and breathlessness were higher in group B than in the other two groups. These results suggested that add-on XFBD and GLXD could improve the disappearance rate of symptoms. However, there were no statistically significant differences among the three groups (Table 3).

Safety outcomes

None of the included patients died or experienced serious adverse events. Forty patients experienced abnormal liver and kidney function: 10 in group A, 15 in group B, and 15 in group C. Details regarding the liver and kidney function abnormalities are shown in Table 4. Potential causes for abnormal liver and kidney functions were as follows: 1) antiviral and antibacterial drug-induced abnormal liver and kidney functions and 2) SARS-CoV-2 infection-induced liver and kidney damage. During follow-up, no patient exhibited deteriorated liver or kidney function after continuing treatment. On comprehensive evaluation, none of the adverse events were considered related to XFBD and GLXD, suggesting that 14 d of XFBD and GLXD therapy were safe.

Discussion

The results of the present study provide evidence that the add-on use of XFBD can benefit patients with ordinary-type COVID-19. XFBD can shorten the duration of the SARS-CoV-2 nucleic acid test from positive to negative, shorten the length of hospitalization, and improve the disappearance rate of symptoms. These findings are similar to that of a previously published clinical trial^[10].

No XFBD and GLXD related adverse events were noted in the present study, indicating that adding XFBD and GLXD to conventional treatments is safe. Furthermore, the XFBD group experienced a lower incidence of abnormal liver and kidney function than the other two groups, suggesting that XFBD may participate in organ protection in patients with ordinary-type COVID-19.

Nevertheless, the present study has several limitations. First, placebo control and double-blinding were not employed because of the special treatment environment for a novel emerging infectious disease. Second, the sample size of the present study was not sufficiently large, which may weaken the strength of the evidence. Third, follow-up was not performed to assess the long-term effects. Fourth, immunological and inflammatory

Table 3.
Comparison of secondary indicators

Symptoms resolution rate	Group A	Group B	Group C	P
Fever				
7 d	10/10 (100.00)	7/9 (77.78)	10/12 (83.33)	0.312
14 d	10/10 (100.00)	9/9 (100.00)	12/12 (100.00)	/
Fatigue				
7 d	8/9 (88.89)	18/21 (85.71)	11/16 (68.75)	0.338
14 d	9/9 (100.00)	20/21 (95.24)	15/16 (93.75)	0.757
Cough				
7 d	10/17 (58.82)	9/22 (40.91)	11/28 (39.29)	0.400
14 d	12/17 (70.59)	19/22 (86.36)	22/28 (78.57)	0.484
Breathlessness				
7 d	1/6 (16.67)	3/7 (42.86)	7/16 (43.75)	0.483
14 d	5/6 (83.33)	7/7 (100.00)	15/16 (93.75)	0.491
Decreased appetite				
7 d	7/7 (100.00)	5/7 (71.43)	6/8 (75.00)	0.315
14 d	7/7 (100.00)	7/7 (100.00)	7/8 (87.50)	0.400

Data are n/t (%) unless otherwise specified. /: not applicable.

Table 4.
Abnormal liver or kidney function

Abnormal liver or kidney function	Group A	Group B	Group C	P
Number of abnormal liver or kidney function	10 (29.41)	15 (42.86)	15 (44.12)	0.385
Normal to abnormal				
Alanine transaminase	1 (2.94)	4 (11.43)	2 (5.88)	0.363
Aspartate aminotransferase	0 (0.00)	2 (5.71)	1 (2.94)	0.369
Total bilirubin	8 (23.53)	6 (17.14)	9 (26.47)	0.635
Creatinine	0 (0.00)	0 (0.00)	0 (0.00)	/
Blood urea nitrogen	0 (0.00)	2 (5.71)	0 (0.00)	0.138
Abnormal aggravated				
Alanine transaminase	0 (0.00)	2 (5.71)	3 (8.82)	0.229
Aspartate aminotransferase	0 (0.00)	0 (0.00)	0 (0.00)	/
Total bilirubin	1 (2.94)	1 (2.86)	2 (5.88)	0.762
Creatinine	0 (0.00)	0 (0.00)	0 (0.00)	/
Blood urea nitrogen	0 (0.00)	0 (0.00)	0 (0.00)	/

Data are n/t (%) unless otherwise specified. /: not applicable.

indicators were not detected owing to the limited research conditions.

In conclusion, XFBD is an effective and safe herbal drug for treating patients with ordinary-type COVID-19. However, the evidence is not robust owing to biases induced by methodological flaws. Additional high-quality studies are warranted to generate in-depth clinical evidence and reveal the effective mechanism of XFBD.

Conflicts of Interest statement

The authors declare no conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China (82004505); the National Key Research and Development Program of the Ministry of Science and Technology of China (2020YFC0841600); and Henan Province Coronavirus Emergency Prevention and Control Special Research (201100310400, 201003050).

Author contributions

Conceptualization was carried out by Min Zhao. Tao Li, Min Zhao, Mingjun Zhu, Shixi Zhang, Jiarong He, He Pan, Mingyi Shao, Zhen Wang, Yu Fu, Ning Li, Long Zhao, Xinyao Jin, Fengwen Yang, and Wentai Pang contributed research methods. Tao Li, Min Zhao, and Wentai Pang wrote the protocol. Participant registration and screening were conducted by Tao Li, Mingjun Zhu, Shixi Zhang, Jiarong He, He Pan and Mingyi Shao. Participant randomization was performed by Zhen Wang, Yu Fu, Ning Li, Long Zhao and Fengwen Yang. Jiarong He, He Pan, Mingyi Shao, Zhen Wang, Yu Fu, Ning Li and Long Zhao carried out the research implementation and data collection. Mingjun Zhu and Shixi Zhang conducted the safety assessment. Data analysis was carried out by Tao Li, Wentai Pang and Xinyao Jin. Tao Li and Wentai Pang wrote the original draft. Min Zhao and Wentai Pang revised the manuscript.

Ethical approval of studies and informed consent

The study protocol was reviewed and approved by the Clinical Trials Ethics Committee of the Hubei Provincial Hospital of Integrative Medicine (2020-003). The study protocol adhered to the Declaration of Helsinki. Informed consent was obtained from all participants.

Acknowledgments

None.

Data availability

The data are not publicly available due to secrecy agreement.

References

- [1] Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324(8):782–793.
- [2] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;5(4):536–544.
- [3] World Health Organization, WHO Coronavirus (COVID-19) Dashboard. Available from: <https://covid19.who.int/>. 2022. Accessed April 14, 2022.
- [4] World Health Organization. 2019-nCoV outbreak is an emergency of international concern. Available from: <https://www.euro.who.int/en/health-topics/health-emergencies/international-health-regulations/news/news/2020/2/2019-ncov-outbreak-is-an-emergency-of-international-concern>. 2020. Accessed January 4, 2021.
- [5] Lyu M, Fan G, Xiao G, et al. Traditional Chinese medicine in COVID-19. *Acta Pharm Sin B* 2021;11(11):3337–3363.
- [6] National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 (Trial Version 8). Available from: <http://www.nhc.gov.cn/yzygj/s7653p/202008/0a7bdf12bd4b46e5bd28ca7f9a7f5e5a/files/a449a3e2e2c94d9a856d5faea2ff0f94>. 2020. Accessed December 21, 2021.
- [7] National Health Commission of the People's Republic of China. Guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection (Revision 8). Available from: <http://www.nhc.gov.cn/xcs/zhengcwj/202104/7de0b3837c8b4606a0594aeb0105232b.shtml>. 2021. Accessed December 21, 2021.
- [8] Wang Y, Sang X, Shao R, et al. Xuanfei Baidu decoction protects against macrophages induced inflammation and pulmonary fibrosis via inhibiting IL-6/STAT3 signaling pathway. *J Ethnopharmacol* 2022;283:114701.
- [9] CONSORT. CONSORT 2010 checklist of information to include when reporting a randomised trial. Available from: <http://www.consort-statement.org/>. 2010. Accessed December 21, 2021.
- [10] Xiong WZ, Wang G, Du J, et al. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: a pilot randomized clinical trial. *Integr Med Res* 2020;9(3):100489.

How to cite this article: Li T, Zhao M, Zhu MJ, Zhang SX, He JR, Pan H, Shao MY, Wang Z, Fu Y, Li N, Zhao L, Jin XY, Yang FW, Pang WT. Xuanfei Baidu decoction, a Chinese herbal medicine for coronavirus disease 2019 (COVID-19): a randomized clinical trial. *Acupunct Herb Med* 2023;3(3):207–212. doi: 10.1097/HM9.0000000000000056