Chinese Journal of Integrative Medicine
Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Original Article

Efficacy and Safety of Huashi Baidu Granules in Treating Patients with SARS-CoV-2 Omicron Variant: A Single-Center Retrospective Cohort Study*

CHEN Cai-yu[1], ZHANG Wen[1], XU Xiang-ru[1], PU Yu-ting[1], TU Ya-dan[2], PENG Wei[1], YAO Xuan[1], ZHOU Shuang[3], and FANG Bang-jiang[1,4]

ABSTRACT **Objective**: To evaluate the efficacy and safety of Huashi Baidu Granules (HSBD) in treating patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant. **Methods**: A single-center retrospective cohort study was conducted during COVID-19 Omicron epidemic in the Mobile Cabin Hospital of Shanghai New International Expo Center from April 1st to May 23rd, 2022. All COVID-19 patients with asymptomatic or mild infection were assigned to the treatment group (HSBD users) and the control group (non-HSBD users). After propensity score matching in a 1:1 ratio, 496 HSBD users of treatment group were matched by propensity score to 496 non-HSBD users. Patients in the treatment group were administrated HSBD (5 g/bag) orally for 1 bag twice a day for 7 consecutive days. Patients in the control group received standard care and routine treatment. The primary outcomes were the negative conversion time of nucleic acid and negative conversion rate at day 7. Secondary outcomes included the hospitalized days, the time of the first nucleic acid negative conversion, and new-onset symptoms in asymptomatic patients. Adverse events (AEs) that occurred during the study were recorded. Further subgroup analysis was conducted in vaccinated (378 HSBD users and 390 non-HSBD users) and unvaccinated patients (118 HSBD users and 106 non-HSBD users). **Results**: The median negative conversion time of nucleic acid in the treatment group was significantly shortened than the control group [3 days (IQR: 2–5 days) *vs*. 5 days (IQR: 4–6 days); $P<0.01$]. The negative conversion rate of nucleic acid in the treatment group were significantly higher than those in the control group at day 7 (91.73% *vs*. 86.90%, $P=0.014$). Compared with the control group, the hospitalized days in the treatment group were significantly reduced [10 days (IQR: 8–11 days) *vs*. 11 days (IQR: 10.25–12 days); $P<0.01$]. The time of the first nucleic acid negative conversion had significant differences between the treatment and control groups [3 days (IQR: 2–4 days) *vs*. 5 days (IQR: 4–6 days); $P<0.01$]. The incidence of new-onset symptoms including cough, pharyngalgia, expectoration and fever in the treatment group were lower than the control group ($P<0.05$ or $P<0.01$). In the vaccinated patients, the median negative conversion time and hospitalized days were significantly shorter than the control group after HSDB treatment [3 days (IQR: 2–5 days) *vs*. 5 days (IQR: 4–6 days), $P<0.01$; 10 days (IQR: 8–11 days) *vs*. 11 days (IQR: 10–12 days), $P<0.01$]. In the unvaccinated patients, HSBD treatment efficiently shorten the median negative conversion time and hospitalized days [4 days (IQR: 2–6 days) *vs*. 5 days (IQR: 4–7 days), $P<0.01$; 10.5 days (IQR: 8.75–11 days) *vs*. 11.0 days (IQR: 10.75–13 days); $P<0.01$]. No serious AEs were reported during the study. **Conclusion**: HSBD treatment significantly shortened the negative conversion time of nuclear acid, the length of hospitalization, and the time of the first nucleic acid negative conversion in patients infected with SARS-COV-2 Omicron variant (Trial

*Supported by Traditional Chinese Medicine Emergency Project on Novel Coronavirus-Infected Pneumonia of State Administration of Traditional Chinese Medicine (No. 2022ZYLCYJ05-4), Shanghai Key Clinical Specialty Project (No. shslczdzk04401), National Traditional Chinese Medicine Emergency Medical Rescue Base Construction Project [No. ZY(2021-2023)-0101-01], National Traditional Chinese Medicine Multidisciplinary Cross Innovation Team Project (No. ZYYCXTD-D-202203)

1. Department of Emergency, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai (200032), China; 2. Department of Classical Traditional Chinese Medicine, Chongqing Hospital of Traditional Chinese Medicine, Chongqing (400021), China; 3. Acupuncture and Massage College, Shanghai University of Traditional Chinese Medicine, Shanghai (201203), China; 4. Institute of Emergency and Critical Care Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai (200032), China
Correspondence to: Prof. FANG Bang-jiang, E-mail: fangbji@163.com

DOI: https://doi.org/10.1007/s11655-023-3549-8

Chin J Integr Med 2024 Feb;30(2):107-114

registry No. ChiCTR2200060472).

KEYWORDS Huashi Baidu Granule, severe acute respiratory syndrome coronavirus 2, Omicron variant, retrospective cohort trial, Chinese medicine

The coronavirus disease (COVID-19) is a new pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has been spreading relentlessly worldwide since December 2019.[1] Despite the reduction of SARS-CoV-2 infection due to vaccination and antiviral treatments, it has posed a significant risk to global public health and had a detrimental impact on economic progress across the world. Scientists have discovered several variants of SARS-CoV-2, including alpha, beta, gamma, delta, and Omicron, with the latter exhibiting enhanced infectiousness and ability to evade the body's immune defense mechanisms. As a result, Omicron has quickly become the most prevalent novel coronavirus strain and continues to spread even in regions where most of the population have been immunized.[2-4] Scientists around the globe are actively exploring potential drugs and vaccines that may be utilized in the treatment of COVID-19. At present, although several antiviral drugs such as paxlovid and VV116 are being employed to treat COVID-19 patients in clinical settings,[5,6] the number of infections globally is still increasing due to the virus's ongoing mutability and limited vaccination availability. Further clinical validation is necessary to verify the efficacy and safety of these drugs.

Chinese medicine (CM) has exhibited efficacy in controlling infectious diseases for millennia, underscoring the paramount importance of synthesizing CM and Western medicine for preventing and treating COVID-19 in China.[7,8] The CM diagnosis and treatment program has been included in COVID-19 diagnosis and treatment guidelines (trial version 9) issued by the National Health Commission of the People's Republic of China.[9] High-quality multicenter randomized controlled trials (RCTs) have shown that CM therapy effectively shortens the time of viral clearance, improves clinical symptoms of patients, and decreases mortality.[10,11]

Huashi Baidu Granules (化湿败毒颗粒, HSBD) have been approved by the State Food and Drug Administration, which could enhance efficacy in treatment of COVID-19.[12] A RCT conducted during the Wuhan outbreak confirmed the potency of HSBD in improving clinical symptoms of the novel coronavirus.[13] Through network pharmacology and molecular docking, research suggested that the active elements of HSBD, baicalein and quercetin, potentially interact with the angiotensin-converting enzyme 2 (ACE_2) receptor to mediate multiple signaling pathways that could potentially be of aid in the treatment of patients with severe COVID-19.[14] In addition, HSBD has been further indicated to aid in anti-inflammatory and immunological regulation by targeting up to 45 related proteins of severe COVID-19.[15]

Although numerous previous results have demonstrated the efficacy of HSBD treatment for COVID-19, no existing studies have been conducted to evaluate the efficacy and safety of HSBD for treatment of SARS-CoV-2 Omicron. Here, we conducted a retrospective cohort study to evaluate the efficacy and safety of HSBD in treating patients with SARS-CoV-2 Omicron in Shanghai, China.

METHODS

A single-center retrospective cohort study was conducted during the COVID-19 Omicron epidemic in the Mobile Cabin Hospital of Shanghai New International Expo Center from April 1st to May 23rd, 2022. The cabin hospital, comprising of over 15,000 beds and medical facilities, had experienced medical professionals offering symptomatic treatment and emergency rescue. The study was performed in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee of Longhua Hospital of Shanghai Traditional Chinese Medicine (No. 2022LCSY026) and registered in the Chinese Clinical Trial Registry (No. ChiCTR2200060472).

Diagnosis, Inclusion and Exclusion Criteria

Patients who were diagnosed as COVID-19 with asymptomatic or mild infection in the Mobile Cabin Hospital of Shanghai New International Expo Center were retrospectively analyzed.

The inclusion criteria included: (1) participants were diagnosed with asymptomatic or mild SARS-CoV-2 infection according to the diagnostic criteria for COVID-19 issued by the National Health Commission of the People's Republic of China.[9] The asymptomatic cases

were defined as SARS-CoV-2 positive patients [open reading frame (ORF) gene and nucleocapsid (N) gene cycle threshold (Ct) values less than 35] without clinical symptoms.[16] The mild cases were defined as slight clinical symptoms with no imaging sign of pneumonia.[9] (2) patients aged 18–80 years, regardless of gender; and (3) patients voluntarily signed informed consent.

The exclusion criteria included: (1) patients with severe primary cardiovascular, pulmonary, renal, and hematopoietic diseases; (2) women with pregnant or parturient; (3) patients who were allergic or sensitive to CM components; and (4) patients who took the Chinese patent medicines recommended by the guidelines for the treatment of COVID-19.

Study Medications

The HSBD in the study were provided by Guangdong Yifang Pharmaceutical Co., Ltd., China. Patients in the control group received standard care and routine treatment according to the Guideline for Diagnosis and Treatment of COVID-19 (On Trials, the Ninth Edition).[9] Patients in the treatment group were administrated HSBD (5 g/bag) orally for 1 bag twice a day for 7 consecutive days. The throat swabs of patients were collected for reverse transcription-polymerase chain reaction (RT-PCR) analysis of SARS-CoV-2 every day until discharge. The Ct value from RT-PCR test for SARS-CoV-2 ORF 1ab or N genes was analyzed.

Outcomes and Measurements

The primary outcomes were the negative conversion time of nucleic acid and negative conversion rate at day 7. Secondary outcomes included the hospitalized days, the time of the first nucleic acid negative conversion, and new-onset symptoms in asymptomatic patients.

The definition of negative conversion of nucleic acid was 2 consecutive nucleic acid tests with ORF and N gene Ct values over 35 with an interval of at least ⩾24 h. The definition of the time of the first nucleic acid negative conversion was the days between the positive RT-PCR test and the first negative nucleic acid conversion. The discharge criteria were as follows: (1) body temperature of patients returns to normal for more than 3 days; (2) respiratory symptoms improve significantly; (3) patients who had 2 consecutive negative conversion results of nucleic acid with an interval of at least ⩾24 h.

Safety Evaluation

Adverse events (AEs) that occurred during the study were recorded.

Data Collection

The database was established with Excel 2021 software (Microsoft Corp, USA). Two hospital researchers collected and examined the data from electronic medical records that included demographics, clinical symptoms, treatment methods, and results, while a third researcher resolved a disagreement between the first two researchers.

Statistical Analysis

All statistical analyses were performed with SPSS version 26.0 (IBM Corp, USA). Continuous variables with normal variables were analyzed by the independent-sample *t*-test and expressed as mean ± standard deviation ($\bar{x} \pm s$). Continuous variables with non-normal variables were analyzed by the *Mann-Whitney* test and reported as medians and interquartile ranges (IQR). The categorical variables were summarized by presenting the frequency and proportion (%), and a Chi-square test or Fisher's exact test was used for comparison. The Kaplan-Meier method was used to analyze the time to the primary endpoint and draw the survival curve. The negative conversion rate was compared by using the log-rank test, and the median time and 95% confidence interval (CI) were calculated. The hazard ratios were estimated using the Cox regression model. Propensity score matching (PSM) was performed to adjust for confounding factors; the two variables (age and sex) as confounding factors to calculate the propensity scores were chosen based on clinical significance. Propensity scores underwent 1:1 nearest neighbor matching of the logit of the propensity score with a caliper width of 0.02. Matching was performed without replacement and unpaired subjects, those not meeting matching criteria were excluded, and conditional logistic regression models were conducted to analyze the data. All tests were two-tailed, and $P<0.05$ was considered statistically significant.

RESULTS

Demographic and Patient Characteristics

Totally 22,260 cases of COVID-19 patients were hospitalized in the Mobile Cabin Hospital of Shanghai New International Expo Center from April 1st to May

23rd, 2022. Totally 16,542 patients were excluded who did not meet eligibility criteria or declined to participate. Finally, a total of 992 patients were included by PSM (1:1 ratio), of these, 496 cases in the treatment group and 496 cases in the control group. The study flow diagram is shown in Figure 1.

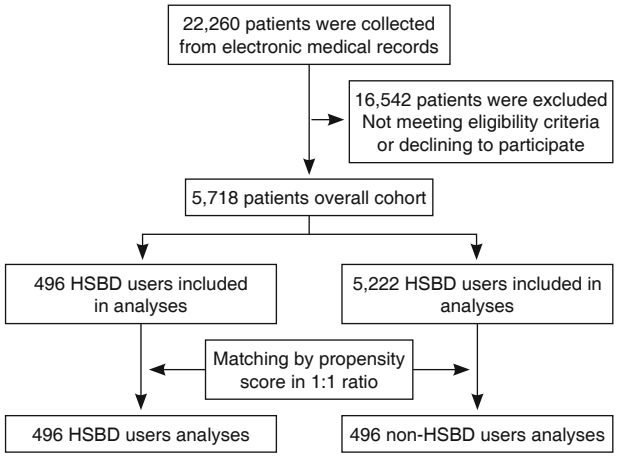

Figure 1. Study Flowchart of Huashi Baidu Granules Treating Patients Infected with SARS-CoV-2 Omicron Variant

At baseline, the median age of 992 patients was 43-year old (IQR: 33–54), with a higher proportion of males. Hypertension (10.89%) was the most common comorbidity, and cough (19.86%) was the most common symptom. There were asymptomatic (76.61%) and mild infections (23.39%) at baseline. The number of patients who received the vaccine was 768 (77.42%). All above baseline characteristics of patients in the two groups had no statistical differences (P>0.05). Demographic and patient characteristics are summarized in Table 1.

Table 1. Baseline Characteristics of Infected Patients

Variables	Control group (496 cases)	Treatment group (496 cases)	*P* value
Sex, case (%)			0.761
Male	382 (77.02)	386 (77.82)	
Female	114 (22.98)	110 (22.18)	
Age, median (IQR), year	43 (33, 54.75)	44 (31.25, 54)	0.343
<20	10 (2.02)	14 (2.82)	
20–29	78 (15.73)	94 (18.95)	
30–39	112 (22.58)	100 (20.16)	
40–49	106 (21.37)	107 (21.57)	
50–59	119 (23.99)	114 (22.98)	
60–69	65 (13.10)	55 (11.09)	
⩾70	6 (1.21)	12 (2.42)	
Comorbidity, case (%)			
Hypertension	54 (10.89)	54 (10.89)	1.000
Diabetes	26 (5.24)	18 (3.63)	0.217
Coronary heart disease	10 (2.02)	12 (2.42)	0.666
Arrhythmia	5 (1.01)	6 (1.21)	0.762
Stroke	6 (1.21)	6 (1.21)	1.000
Asthma	3 (0.60)	2 (0.40)	1.000
Symptoms, case (%)			
Cough	106 (21.37)	91 (18.35)	0.233
Expectoration	61 (12.30)	51 (10.28)	0.316
Fever	37 (7.46)	30 (6.05)	0.376
Pharyngalgia	63 (12.70)	52 (10.48)	0.275
Stuffy nose	14 (2.82)	15 (3.02)	0.851
Runny nose	9 (1.81)	16 (3.23)	0.156
Hypodynamia	30 (6.05)	33 (6.65)	0.696
Muscular soreness	33 (6.65)	21 (4.23)	0.093
Initial symptoms, case (%)			0.099
Asymptomatic infection	369 (74.40)	391 (78.83)	
Mild infection	127 (25.60)	105 (21.17)	
Vaccination history, case (%)			
0 dose	106 (21.37)	118 (23.79)	0.362
1 dose	20 (4.03)	18 (3.63)	0.741
2 doses	155 (31.25)	152 (30.65)	0.837
3 doses	211 (42.54)	202 (40.73)	0.562
⩾4 doses	4 (0.81)	6 (1.21)	0.751
Vaccine manufacturer, case (%)			
Sinovac Biotech Co., Ltd.	243 (48.99)	257 (51.81)	0.374
China Pharmaceutical Group Co., Ltd.	132 (26.61)	106 (21.37)	0.053
CanSino Biologics Inc.	13 (2.62)	10 (2.02)	0.527
Anhui Zhifei Longcom Biopharmaceutical Co., Ltd.	2 (0.40)	6 (1.21)	0.287

Primary Outcomes

The median negative conversion time in the treatment group was 3 days (IQR: 2–5 days) and 5 days (IQR: 4–6 days) in the control group (HR: 1.523, 95% CI: 1.344–1.726, P<0.001). In the log-rank analysis, patients of COVID-19 who received HSBD showed a higher negative conversion rate of nucleic acid than the control group (P<0.001, Figure 2A). The negative conversion rate in the treatment group was significantly higher than those in the control group at day 7 (91.73% *vs*. 86.90%, P=0.014, Appendix 1).

Secondary Outcomes

The median hospitalized days in the treatment group were 10 days (IQR: 8–11 days), while those in the control group were 11 days (IQR: 10.25–12 days, P<0.001). We observed that patients receiving HSBD whose discharge rates were higher than that in the control group (HR: 1.634, 95% CI: 1.441–1.852,

P<0.001; Figure 2B).

The median time of the first nucleic acid negative conversion in the treatment group was 3 days (IQR: 2–4 days) and 5 days (IQR: 4–6 days) in the control group (HR: 1.820, 95% CI: 1.604–2.065, *P*<0.001). Patients who received HSBD had shown a higher the first negative conversion rate of nucleic acid than the control group by the log-rank analysis (Figure 2C, *P*<0.001).

Table 2. New-Onset Symptoms of Asymptomatic Infected Patients (Cases, %)

Symptoms	Control group (496 cases)	Treatment group (496 cases)	*P* value
Cough	78 (15.73)	52 (10.48)*	0.014
Pharyngalgia	55 (11.09)	25 (5.04)**	<0.001
Expectoration	46 (9.27)	29 (5.85)*	0.041
Fever	27 (5.44)	10 (2.02)**	0.004
Hypodynamia	11 (2.22)	6 (1.21)	

Note: *P<0.05, **P<0.01 *vs*. control group

The new-onset symptoms of asymptomatic patients are shown in Table 2. Cough, pharyngalgia, expectoration and fever had statistically significant differences between the treatment and control groups (*P*<0.05 or *P*<0.01).

Table 3. Subgroups Analysis of Negative Conversion Time and Hospital Duration in Vaccinated and Unvaccinated Patients [Day, Median (IQR)]

Vaccination status	Group	Cases	Negative conversion time	Hospital duration
Unvaccinated	Control	106	5 (4, 7)	11 (10.75, 13)
	Treatment	118	4 (2, 6)*	10.5 (8.75, 11)*
Vaccinated	Control	390	5 (4, 6)	11 (10, 12)
	Treatment	378	3 (2, 5)*	10 (8, 11)*

Note: *P<0.01 *vs*. control group

Subgroup Analysis

Patients were dichotomized into two groups based on whether they had received a vaccination or not. In the vaccinated group, the median negative conversion time in the treatment group was 3 days (IQR: 2–5 days), which was shorter than the control group [5 days (IQR: 4–6 days), *P*<0.001]. For patients who had not been vaccinated, we observed that the median negative conversion time in the treatment group was 4 days (IQR: 2–6 days) and 5 days in the control group (IQR: 4–7 days, *P*<0.001; Table 3).

As shown in Figure 3 and Appendix 2, we found that for both patients who were vaccinated or unvaccinated, the cumulative negative conversion rates in the treatment group were significantly higher than those in the control group at day 2–7. Though there were no significant differences at day 7 (*P*>0.05), the cumulative negative conversion rate of the treatment group was still higher than the control group, both in the vaccinated or unvaccinated groups.

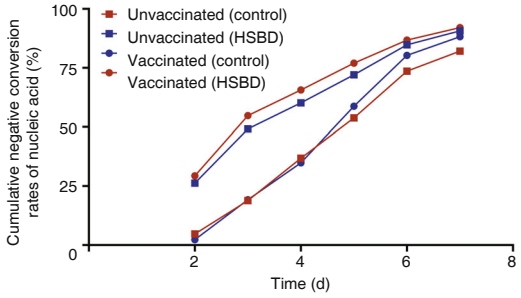

Figure 3. Negative Conversion Rates of Nucleic Acid in Vaccinated and Unvaccinated Patients at Day 2–7

For patients who were vaccinated, the median hospitalized days in the treatment group were 10 days (IQR: 8–11 days), which was shorter than patients in the control group [11 days (IQR: 10–12 days), *P*<0.001]. In the unvaccinated subgroup, we found that the median hospitalized days in the treatment group were 10.5 days (IQR: 8.75–11 days), while those in the control group were 11 days (IQR: 10.75–13 days; *P*<0.001), as shown in Table 3.

Safety Observation

As shown in Table 4, among 992 patients, a total

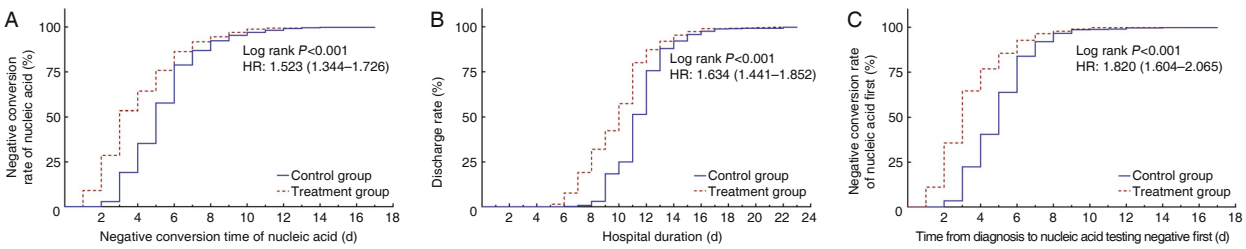

Figure 2. Kaplan-Meier Curves for Negative Conversion Rate of Nucleic Acid (A), Discharge Rate (B) and Negative Converstion Rate of Nucleic Acid Testing Negative First (C) of Infected Patients

of 124 AEs occurred, of them 61 cases in the control group and 63 cases in the treatment group. No serious AEs were reported during the study. We assessed that diarrhea (3.02%) was likely associated with HSBD treatment. AEs were treated with symptomatic therapy, till the symptoms improved.

Table 4. Summary of AEs in Safety Population (Case, %)

AEs	Control group (496 cases)	Treatment group (496 cases)	*P* value
Diarrhea	16 (3.23)	14 (2.82)	0.711
Anxiety	6 (1.21)	6 (1.21)	1.000
Constipation	9 (1.81)	4 (0.81)	0.264
Chest tightness	8 (1.61)	10 (2.02)	0.634
Vomiting	1 (0.20)	3 (0.60)	0.616
Gastralgia	7 (1.41)	9 (1.81)	0.614
Dry eye	2 (0.40)	6 (1.21)	0.287
Rash	9 (1.81)	8 (1.61)	0.807
Allergy	3 (0.60)	3 (0.60)	1.000

Note: AEs: adverse events

DISCUSSION

COVID-19 is an acute respiratory infectious disease caused by SARS-COV-2, with the Omicron strain becoming the main variant since November 2021.[17] Despite significant therapeutic outcomes provided by conventional Western medicine for COVID-19, its overall clinical efficacy remains suboptimal with potentially severe consequences. According to previous research, the majority of patients suffering from Omicron were male and middle-aged, which is in agreement with the results gleaned from this study.[18] In addition, hypertension (10.89%) and cough (19.86%) were the most prevalent comorbidities and symptoms among the sample population, respectively. In this study, about 76.61% patients were asymptomatic infection, and 23.39% were mild infection. The vaccine coverage rate neared 77.42%.

CM has demonstrated considerable benefits in the prevention and treatment of COVID-19, during the outbreak of COVID-19, CM had made significant contributions to alleviating symptoms, delaying disease progression, improving the negative conversion rate, and decreasing the mortality rate of patients.[19-26] In this study, after the HSBD treatment, there was an effective reduction in the median negative conversion time of nucleic acid between the treatment and control groups, which was significantly shorter than many previous reports.[20,22,27] The median hospitalized days in the treatment group were 10 days (IQR: 8–11 days), while those in the previous studies was 12 days.[28] In the vaccinated subgroup, a significant improvement was found in the negative conversion time of nucleic acid and hospitalized days after the HSBD treatment which was also shortened than the unvaccinated patients. In addition, we explored the proportion of new-onset symptoms in asymptomatic patients in this study. The results showed that the incidence of new-onset symptoms in the treatment group was lower than in the control group. The results of above studies might be attributable to the pharmaceutical ingredients of HSBD, while oral administration was also observed to enhance drug absorption.

HSBD is capable of reducing inflammation, enhancing immunity, and increasing protection against viral infections, which has been approved officially to treat COVID-19 by China's National Health Commission,[29] and also included in the Guideline for the Diagnosis and Treatment of COVID-19 (On Trials, the 9th Edition).[9] According to the 9th version of the diagnosis and treatment plan, HSBD should be considered for patients with severe infections. For this study, factors such as relevant conditions, clinical signs, and a high proportion of patients with underlying diseases were considered, and the patients were assessed based on syndrome differentiation and treatment according to CM. During the COVID-19 outbreak in Wuhan, China, HSBD combined with lopinavir-ritonavir were demonstrated to have great efficacy in the treatment of COVID-19.[12] HSBD has been proven to improve infected symptoms of COVID-19 patients, reduce disease severity, and decrease the mortality rate.[30] Studies have shown that HSBD can reduce the viral load in the lung tissue of mouse models by up to 30%.[31] For severe COVID-19 patients, the HSBD tends to shorten the time for relieving blood oxygen saturation.[32] Additionally, the clinical results proved that HSBD combined with CM injections such as Xiyanping Injection (喜炎平注射液), Xuebijing Injection (血必净注射液), and Shenmai Injection (参麦注射液) reduce inflammation in severe COVID-19 patients, compared with antiviral therapy of Western medicine.[33] Our findings showed that the median negative conversion time of nucleic acid in this study was 3 days (IQR: 2–5 days), compared with the previous study in Wuhan, which was shorter than the 10 or 12 days in previous reports.[13,33] These

discrepancies might be attributable to the fact that most patients in Shanghai had been vaccinated, with the Omicron strain being weakly pathogenic and highly transmissible, resulting in infected individuals often having only mild or asymptomatic infections.[34]

Previous studies by network pharmacologic analysis showed that the therapeutic mechanism of HSBD for severe COVID-19 might attribute to its pharmacological effects of anti-inflammation and immune regulation through acting on 45 potential target genes of severe COVID-19.[15] In addition, the chemical components of HSBD have been characterized by using ultra-performance liquid chromatography-quadrupole time-of-flight/mass spectrometry. The results demonstrated that HSBD could reduce the levels of interleukin-6 and tumor necrosis factor-alpha in cell models. It is suggested that the antiviral effects of HSBD might be achieved due to regulating the production of inflammatory cytokines.[35]

This study was limited by its single-center retrospective cohort design, which may introduce potential bias in the assessment. Furthermore, due to the limited sample size, further multicenter randomized placebo-controlled trials with larger sample sizes are necessary to confirm the efficacy and underlying mechanisms of HSBD. Additionally, moderate, severe, and critical COVID-19 cases were not included, thus additional high-level clinical trials are needed to enhance the reliability of the results.

In conclusion, our finding showed that patients who received HSBD had significantly reduced nuclear acid negative conversion time, increased negative conversion rate, shortened hospitalized days, as well as the time of first nucleic acid negative conversion, and reduced new-onset symptoms among asymptomatic patients. The vaccinated patients received HSBD, resulting in a significantly shorter negative conversion time and reduced hospitalization days compared to the control group and unvaccinated subgroup patients. Furthermore, we did not observe serious AEs in the study. All the above results provide evidence of HSBD treatment as an effective approach against SARS-COV-2 Omicron variant.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Chen C and Zhang W: manuscript preparation and editing, data and statistical analysis; Xu X and Pu Y: data curation and investigation; Tu Y, Peng W and Yao X: data curation and supervision. Fang B and Zhou S: study conception and design. All authors read and approved the final version for publication.

Acknowledgements

We acknowledge the medical team for their contributions to fight against the epidemic in Shanghai and collect data for this study in the Shanghai New International Expo Center.

Electronic Supplementary Material: Supplementary material (Appendixes 1 and 2) are available in the online version of this article at http://dx.doi.org/10.1007/s11655-023-3549-8.

REFERENCES

1. World Health Organization. Weekly epidemiological update on COVID-19. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19–26-october-2022.
2. Nealon J, Cowling BJ. Omicron severity: milder but not mild. Lancet 2022;399:412-413.
3. World Health Organization. Enhancing response to Omicron SARS-CoV-2 variant. Available at: https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states.
4. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nature 2022;603:679-686.
5. Wang Z, Yang L. In the age of Omicron variant: Paxlovid raises new hopes of COVID-19 recovery. J Med Virol 2022;94:1766-1767.
6. Shen Y, Ai J, Lin N, Zhang H, Li Y, Wang H, et al. An open, prospective cohort study of VV116 in Chinese participants infected with SARS-CoV-2 omicron variants. Emerg Microbes Infect 2022;11:1518-1523.
7. Li JG, Xu H. Chinese medicine in fighting against COVID-19: role and inspiration. Chin J Integr Med 2021;27:3-6.
8. Qing GC, Zhang H, Bai Y, Luo Y. Traditional Chinese and Western medicines jointly beat COVID-19 pandemic. Chin J Integr Med 2020;26:403-404.
9. National Health Commission of the People's Republic of China. Guideline on diagnosis and treatment of COVID-19 (Trial 9th edition). Available at: http://www.nhc.gov.cn/yzygj/s7653p/202203/b74ade1ba4494583805a3d2e40093d88/files/ef09aa4070244620b010951b088b8a27.
10. Zhou S, Feng J, Xie Q, Huang T, Xu X, Zhou D, et al.

Traditional Chinese medicine shenhuang granule in patients with severe/critical COVID-19: a randomized controlled multicenter trial. Phytomedicine 2021;89:153612.
11. Zhuang J, Dai X, Zhang W, Fu X, Zhang G, Zeng J, et al. Efficacy and safety of integrated traditional Chinese and Western medicine against COVID-19: a systematic review and meta-analysis. Phytother Res 2022;36:4371-4397.
12. Shi N, Guo L, Liu B, Bian Y, Chen R, Chen S, et al. Efficacy and safety of Chinese herbal medicine *versus* Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: a non-randomized controlled trial. Phytomedicine 2021;81:153367.
13. Liu J, Yang W, Liu Y, Lu C, Ruan L, Zhao C, et al. Combination of Hua Shi Bai Du granule (Q-14) and standard care in the treatment of patients with coronavirus disease 2019 (COVID-19): a single-center, open-label, randomized controlled trial. Phytomedicine 2021;91:153671.
14. Tao Q, Du J, Li X, Zeng J, Tan B, Xu J, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. Drug Dev Ind Pharm 2020;46:1345-1353.
15. Zhu YW, Yan XF, Ye TJ, Hu J, Wang XL, Qiu FJ, et al. Analyzing the potential therapeutic mechanism of Huashi Baidu Decoction on severe COVID-19 through integrating network pharmacological methods. J Tradit Complement Med 2021;11:180-187.
16. The National Health Commission. New Coronavirus Pneumonia Prevention and Control Program, 8th edition. Available at: http://www.nhc.gov.cn/xcs/zhengcwj/202105/6f1e8ec6c4a540d99fafef52fc86d0f8/files/4a860a7e85d14d55a22fbab0bbe77cd9.
17. Brussow H. COVID-19: Omicron—the latest, the least virulent, but probably not the last variant of concern of SARS-CoV-2. Microb Biotechnol 2022;15:1927-1939.
18. Zhang W, Zhou S, Wang G, Cao M, Sun D, Lu W, et al. Clinical predictors and RT-PCR profile of prolonged viral shedding in patients with SARS-CoV-2 Omicron variant in Shanghai: a retrospective observational study. Front Public Health 2022;10:1015811.
19. Ren W, Liang P, Ma Y, Sun Q, Pu Q, Dong L, et al. Research progress of traditional Chinese medicine against COVID-19. Biomed Pharmacother 2021;137:111310.
20. Chen B, Geng P, Shen J, Liangpunsakul S, Lyu H, Zhang J, et al. Traditional Chinese medicine JingYinGuBiao Formula therapy improves the negative conversion rate of SARS-CoV2 in patients with mild COVID-19. Int J Biol Sci 2022;18:5641-5652.
21. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, et al. Efficacy and safety of Lianhuaqingwen Capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine 2021;93:153775.
22. Zhang J, Liu L, Zhang G, Li M, Ma B, Yang W. Treating patients infected with the SARS-CoV-2 omicron variant with a traditional Chinese medicine, Shufeng Jiedu Capsule. Biosci Trends 2022;16:238-241.
23. Zhang L, Zheng X, Bai X, Wang Q, Chen B, Wang H, et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: a national retrospective registry study. Phytomedicine 2021;85:153531.
24. Xu XR, Zhang W, Wu XX, Huang TR, Zuo JG, Shao Z, et al. Effectiveness and safety of Baidu Jieduan Granules for COVID-19: a retrospective observational multicenter study. Chin J Integr Med 2022;28:885-893.
25. Sun XH, Zhang S, Yang Z, Chen ZL, Yue SJ, Zhang S, et al. Efficacy and safety of Lianhua Qingwen for patients with COVID-19: a systematic review and meta-analysis. Chin J Integr Med 2022;28:650-660.
26. Ma J, Wu HY, Chen YZ, Huang M, Zhang LS. Thoughts on traditional Chinese medicine treatment of novel coronavirus pneumonia based on two cases. Chin J Integr Med 2021;27:375-378.
27. Chen B, Yu X, Zhang L, Huang W, Lyu H, Xu Y, et al. Clinical efficacy of Jingyin Ganules, a Chinese patent medicine, in treating patients infected with coronavirus disease 2019. Phytomedicine 2022;108:154496.
28. Fang J, Li H, Du W, Yu P, Guan YY, Ma SY, et al. Efficacy of early combination therapy with Lianhuaqingwen and arbidol in moderate and severe COVID-19 patients: a retrospective cohort study. Front Pharmacol 2020;11:560209.
29. Xia KY, Zhao Z, Shah T, Wang JY, Baloch Z. Composition, clinical efficiency, and mechanism of NHC-approved "Three Chinese Medicines and Three Chinese Recipes" for COVID-19 treatment. Front Pharmacol 2021;12:781090.
30. Pan X, Dong L, Yang L, Chen D, Peng C. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. Virus Res 2020;286:198057.
31. Li Q, Wang H, Li X, Zheng Y, Wei Y, Zhang P, et al. The role played by traditional Chinese medicine in preventing and treating COVID-19 in China. Front Med 2020;14:681-688.
32. Xiong Y, Tian Y, Ma Y, Liu B, Ruan L, Lu C, et al. The effect of Huashibaidu Formula on the blood oxygen saturation status of severe COVID-19: a retrospective cohort study. Phytomedicine 2022;95:153868.
33. Wang Y, Lu C, Li H, Qi W, Ruan L, Bian Y, et al. Efficacy and safety assessment of severe COVID-19 patients with Chinese medicine: a retrospective case series study at early stage of the COVID-19 epidemic in Wuhan, China. J Ethnopharmacol 2021;277:113888.
34. Bhattacharyya RP, Hanage WP. Challenges in inferring intrinsic severity of the SARS-CoV-2 omicron variant. New Engl J Med 2022;386:e14.
35. Wei WL, Wu SF, Li HJ, Li ZW, Qu H, Yao CL, et al. Chemical profiling of Huashi Baidu prescription, an effective anti-COVID-19 TCM formula, by UPLC-Q-TOF/MS. Chin J Nat Med 2021;19:473-480.

(Accepted February 4, 2023; First Online May 24, 2023)
Edited by TIAN Lin