Original Article

Effectiveness and Safety of Baidu Jieduan Granules for COVID-19: A Retrospective Observational Multicenter Study*

XU Xiang-ru[1], ZHANG Wen[1], WU Xin-xin[1], HUANG Ting-rong[2], ZUO Jian-guo[3], SHAO Zhong[4], ZHOU Shuang[5], and FANG Bang-jiang[1,6]

ABSTRACT **Objective:** To evaluate the effectiveness and safety of Baidu Jieduan Granules (BDJDG) to treat common type coronavirus disease 2019 (COVID-19). **Methods:** This multicenter, retrospective, and observational clinical trial included 230 common COVID-19 patients in Leishenshan, Huangshi, and Laohekou Hospitals in Wuhan from January 21 to March 26, 2020. The included patients were further divided into two subgroups according to the use of supplemental oxygen, mild and moderate groups. During the first 14 d of hospitalization, all patients were administered BDJDG combined with conventional Western medicine, and observed for continuous 28 d. Primary outcomes were disease progression rate and discharge rate. Secondary outcomes included negative conversion time of nucleic acid, hospitalization duration, clinical symptom subsidence time, and symptom regression rate. **Results:** A total of 230 common COVID-19 patients were analyzed (138 in moderate group and 92 in mild group). By day 28, the disease progression rate was 4.3% and the discharge rate was 95.7%. All mild cases recovered and were discharged from hospital. The median negative conversion time of nucleic acid of all 230 COVID-19 patients was 12 d [inter-quartile range (IQR) 3.5–17], the median hospitalization duration was 15 d (IQR 12–20). The median time to fever, cough, and fatigue recovery was 4 d (IQR 2–6), 8 d (IQR 5–12), and 8 d (IQR 5–11), respectively. The recovery rate of fever, cough, and fatigue was 94.6%, 90.5%, and 93.5%. The median time to clinical improvement was 12 d (IQR 10–17). Compared with the baseline, total leukocyte, neutrophil, lymphocyte, and platelet counts were all increased significantly on days 7 and 14 ($P<0.01$). C-reactive protein markedly increased on day 3 and significantly decreased on days 7 and 14 ($P<0.01$). No serious adverse events occurred during treatment. **Conclusion:** BDJDG may be effective and safe for treatment of common type COVID-19. (Registration No. ChiCTR2000030836)

KEYWORDS COVID-19, common type, Baidu Jieduan Granule, integrated Chinese and Western medicine

The pandemic as a public health problem of coronavirus disease 2019 (COVID-19) has caused worldwide attention. The clinical manifestation of COVID-19 can be characterized by urgent onset, rapid progress, and severe condition. As of November 2021, there have been more than 250 million confirmed cases and over 5 million deaths worldwide.[1] COVID-19 can be divided into 4 types as mild, moderate, severe, and critical types according to the "Guidelines on diagnosis and treatment of novel coronavirus pneumonia (trial 8th edition)".[2] The epidemiologic characteristics of the COVID-19 have been revealed in the early study. There are almost 81% mild cases, 14% severe cases, and 5% critical cases in the early outbreak of COVID-19.[3] Although significant knowledge has accumulated in the process of clinical diagnosis and treatment, there is still few evidence-based treatment for COVID-19. Current

treatments include antiviral therapy, neutralization antibody, plasma therapy, immunomodulatory therapy, and symptomatic supportive therapy, but there is no evidence of long-term clinical benefit and safety in these treatments.[4] The vaccines are expected to reduce the infection rate of COVID-19, but they are not recommended in all patient groups, e.g., children, the elderly, or those with hyperimmune disorders. Besides, it is unclear whether the current vaccines will offer long-term protection and whether the vaccines are effective against viral variants.[5] Therefore, corresponding treatments for different stages of COVID-19 are needed.

Integrated Chinese and Western medicine are important experiences in epidemic prevention in China. Chinese medicine (CM) can effectively relieve symptoms, increase cure rate, decrease mortality rate, and prevent disease progression. In addition, new drugs developed based on CM also show good efficacy and safety.[6] By clinical observation, integrative medicine promotes clinical recovery faster than Western medicine alone.[7] Our group developed Baidu Jieduan Granule (败毒截断颗粒, BDJDG) for common COVID-19 based on the "internal and external relieving-truncated torsion" strategy. It means that using relieving superficies method (diaphoresis) and interior-dredging method (catharsis and diuresis) simultaneously in the early stage of COVID-19, so as to remove pathogenic factors in time and prevent the further deterioration of the disease. BDJDG was found to be effective in reducing the mortality and disease progression rate and improving the cure rate of common COVID-19 cases in preliminary observation. BDJDG is developed on the combination of Maxing Shigan Decoction (麻杏石甘汤) and Jinhong Decoction (锦红汤) with modification. Our previous study has shown that Jinhong Decoction can inhibit inflammation and regulate immunity, which has a significant effect on the treatment of infectious diseases.[8] Recent research has shown that, as the core component of Qingfei Paidu Decoction (清肺排毒汤), Maxing Shigan Decoction enhances the anti-inflammatory and antiviral effects of Qingfei Paidu Decoction by regulating thrombin and Toll-like receptor signaling pathways.[9] Therefore, BDJDG has a theoretical and clinical basis for the treatment of COVID-19. This study reviewed all common cases of COVID-19 that were administrated the BDJDG in the designated hospitals and evaluated the effectiveness and safety of BDJDG. We hope this study will provide a new idea for the treatment and prevention of COVID-19.

METHOD

Study Design and Participants

This multicenter, retrospective, and observational clinical study was conducted in Leishenshan Hospital, Huangshi Hospital, and Laohekou Hospital in Wuhan, China from January 21 to March 26, 2020. There were 304 patients diagnosed as COVID-19 were screened and 230 patients corresponding to common type COVID-19 were included. Of these, 138 patients required supplemental oxygen (moderate group) and 92 patients did not (mild group). The study was approved by the Ethics Committee of Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine (approval No. 2020LCSY007). The protocol has been registered at the Chinese Clinical Trial Registry (ChiCTR2000030836). All patients provided informed consents.

Diagnostic Criteria

The diagnostic criteria of COVID-19 was based on the "Guidelines on diagnosis and treatment of novel coronavirus pneumonia (Trial 8th edition)".[2] Suspected cases were those with one of the following etiological evidence: (1) positive result of novel coronavirus nucleic acid detected by RT-PCR; (2) viral gene sequence is highly homologous to SARS-CoV-2; (3) positive result of novel coronavirus-specific IgM and IgG antibody; (4) novel coronavirus-specific IgG antibodies change from negative to positive or IgG antibody titer in the recovery period is ⩾4 times than that in the acute period.

The disease severity classifications were as follows: (1) mild type: mild symptoms with no evidence of pneumonia on imaging; (2) moderate type: fever and respiratory symptoms with radiological manifestations of pneumonia; (3) severe type: any of the following: a) breathlessness with a respiratory rate (RR) of ⩾30 times/min; b) oxygen saturation (SpO_2) of ⩽93% at resting state; c) a partial arterial oxygen pressure to the fraction of inspiration O_2 ratio (PaO_2/FiO_2) of ⩽300 mm Hg; and d) progressively aggravated clinical symptoms with lesion progression >50% within 24–48 h on imaging; (4) critical type: any of the following: a) respiratory failure with mechanical

ventilation; b) shock; and c) ICU monitoring for other organ failures. The mild and the moderate type were considered as common type COVID-19.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) age over 14 years old and (2) confirmed SARS-CoV-2 infection meeting the diagnostic criteria for common type COVID-19 mentioned above.

Exclusion criteria were as follows: (1) patients not meet the diagnostic criteria of common type COVID-19; (2) aggravated disease progression or death within 48 h after admission; (3) patients with severe primary diseases, e.g., malignant tumor, hematological disease, severe hepatorenal insufficiency, etc.; (4) severe psychiatric disorder; (5) pregnant or lactating women; (6) other conditions, e.g., taking other herbs or participating in other clinical trials, drug withdrawal during treatment, surgery required during the trial, etc.

Intervention

All included patients were treated with BDJDG combined with conventional Western medicine in our study. The effectiveness and safety of BDJDG were observed for continuous 28 days. The BDJDG was administered orally from the first day of hospitalization, twice a day for 14 days. After 14-day treatment, basic Western medical therapy and routine care were maintained for the remaining days until discharge from hospital. Western medical therapy involves antiviral drugs, antibiotics, corticosteroids, and α-interferon inhalation. Routine care includes oxygen therapy, human immunoglobulin, symptomatic treatment, and treatment of underlying diseases. BDJDG was manufactured by Beijing Tcmages Pharmaceutical Co., Ltd. (lot No. Jing 20180032). The granule is composed of *Radix Scutellariae* 30 g, *Radix et Rhizoma Rhei* 15 g, *Gypsum Fibrosum* 45 g, *Herba Ephedrae* 9 g, *Talcum* 45 g, *Herba Taraxaci* 30 g, *Caulis Sargentodoxae* 30 g, *Semen Armeniacae Amarum* 12 g, *Rhizoma Polygoni Cuspidati* 30 g, *Herba Verbenae* 30 g, *Bombyx Batryticatus* 12 g, *Radix Glycyrrhizae* 9 g, packaged into 2 sachets for 1 day.

Data Collection

The data were extracted independently by two researchers using standard forms. The data obtained demographic characteristics (age and sex), chronic disease history (diabetes, hypertension, cardiovascular disease, cerebrovascular disease), clinical status, course of disease, clinical symptoms (fever, cough, expectoration, fatigue, diarrhea), treatment, efficacy, and laboratory examination results.

Outcome Evaluation
Primary Outcome

The primary outcomes were disease progression rate and discharge rate on day 28. The disease progression was defined as clinical worsening from mild/moderate to severe/critical. The discharge criteria were as follows: (1) body temperature returned to normal for more than 3 days; (2) respiratory symptoms were significantly improved; (3) pulmonary imaging showed that the acute exudative lesions were significantly improved; (4) nucleic acid tests negative twice consecutively (the sampling interval was at least 1 day.

Secondary Outcome

The secondary outcomes were negative conversion time of nucleic acid accessed as the time from the first detection; hospitalization duration; clinical symptom (fever, cough, fatigue) reduction time, and symptom regression rate; time to clinical improvement within 28 days; the proportions of patients in each category of the Six-Point Ordinal Scale at days 7, 14, and 28. The clinical improvement was defined as 1-point reduction in the Six-Point Ordinal Scale or discharge from the hospital. The Six-Point Ordinal Scale was defined as:[10] 6=death; 5=hospital admission for extracorporeal membrane oxygenation or mechanical ventilation (critical); 4=hospital admission for noninvasive ventilation or high-flow oxygen therapy (severe); 3=hospital admission requiring supplemental oxygen (moderate); 2=hospital admission but not requiring supplemental oxygen (mild); 1=alive (discharge).

Infection Indicator

The infection indicators included white blood cell counts, neutrophil counts, lymphocyte counts, C-reactive protein (CRP), procalcitonin, and erythrocyte sedimentation rate. The infection indicators were collected on baseline and days 3, 7, 14. The safety indices were collected on baseline and day 14. If there was an omission, it will be supplemented with data from 1 day before or after the specified date of collection.

Adverse Events

The adverse events include lymphopenia, leukopenia, thrombocytopenia, increased D-dimer, alanine amiotransferase (ALT), aspartate aminotransferase (AST), creatine (CR), blood urea nitrogen (BUN), lactic dehydrogenase (LDH), creatine kinase (CK) and creatine kinase-myocardial band (CK-MB), which were all collected.

Statistical Analysis

For the continuous variables, the normality test was carried out at first. Normal distribution data was expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and analyzed by independent-sample t-test. Non-normal distribution data was expressed as median with inter quartile range (IQR) and Wilcoxon rank-sum test was used. A linear mixed model was used to analyze repeated measurement data. The categorical variables were summarized by presenting the frequency and proportion (%), and a chi-square test was used for comparison. All statistical analyses were performed with SPSS 26.0 (IBM Corp, USA). Statistical significance was defined as $P \leqslant 0.05$ (two-sided test).

RESULTS

Baseline Characteristics

There were 304 patients diagnosed as COVID-19 for screening. Seventy-four patients that did not meet the criteria were excluded and a total of 230 patients were enrolled finally (Appendix 1). All included patients were divided into two subgroups, 138 patients required supplemental oxygen (moderate group) and 92 patients did not (mild group). The baseline characteristics of the population and each subgroup are shown in Table 1.

Clinical Outcomes
Primary Outcomes

As shown in Table 2, the disease progression rate was 4.3% after combined treatment of CM and Western medicine on the 28th day. The discharge rate of all patients was 95.7%. All mild cases recovered and were discharged from the hospital.

Secondary Outcomes

The median negative conversion time of nucleic acid was 12 days (IQR: 3.5, 17) and the median hospitalization duration was 15 days (IQR: 12, 20). The length of time may be related to the severity of the disease. The median time to fever, cough, and fatigue

recovery was 4 days (IQR: 2, 6), 8 days (IQR: 5, 12), and 8 days (IQR: 5, 11), respectively. The recovery rate of fever, cough, and fatigue was 94.6%, 90.5%, and 93.5%, respectively.

The primary and secondary clinical outcomes in the population stratified by age was shown in Appendix 2. Besides the negative conversion time of nucleic acid, the clinical outcomes between patients <60 years and ≥60 years in both mild and moderate groups showed no significant difference ($P>0.05$). However, the negative conversion time of nucleic acid was shorter in patients over 60 years than in those under 60 years ($P<0.01$). In the mild group, the median course of disease in patients under 60 years was 7 days (IQR: 3, 20) and 20 days (IQR: 6, 40) in patients over 60 years, while in the moderate group, the median course in patients under 60 years was 5 days (IQR: 3, 8) and 7 days (IQR: 4, 20) in patients over 60 years.

The proportions of patients in each category of the Six-Point Ordinal Scale on days 7, 14, and 28 were shown in Figure 1. The median time to clinical improvement was 12 days (IQR: 10, 17). The clinical improvement rates on days 7, 14, and 28 were 9.6%, 67.4%, and 95.7%. In addition, 12 were converted to severe and 2 to critical on day 7, 3 were converted to severe and 1 to critical on day 14, and 1 was converted to critical on day 28. All mild COVID-19 patients were improved without aggravation (Appendix 3).
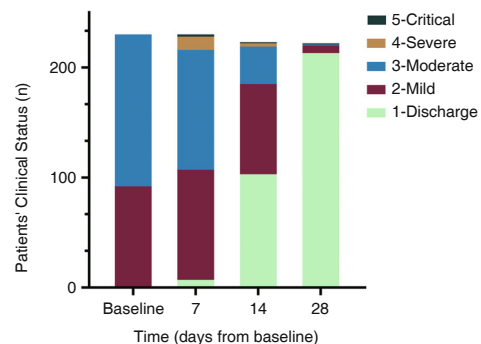
Figure 1. Distribution of Patients' Clinical Status at Different Times by Six-Point Ordinal Scale

Infection Indicators

Infection indicators were shown in Appendix 4 and the dynamic changes were shown in Figure 2. Compared with the baseline, total leukocyte count, neutrophil count, lymphocyte count, and

Table 1. Baseline Demographic and Clinical Characteristics of Patients with COVID-19

Index	Total (230 cases)	Mild group (92 cases)	Moderate group (138 cases)
Age ($\bar{x} \pm s$, year)	52.5 ± 16.0	47.8 ± 14.3	55.6 ± 16.4
Gender [Case (%)]			
Male	105 (45.7)	43 (46.7)	62 (44.9)
Female	125 (54.3)	49 (53.3)	76 (55.1)
Time from symptom onset to baseline			
Median (d, IQR)	7.0 (3.0, 15.0)	7.0 (3.0, 29.5)	6.0 (3.0, 10.0)
≤14 d [Case (%)]	165 (71.7)	57 (62)	108 (78.3)
>14 d [Case (%)]	65 (28.3)	35 (38)	30 (21.7)
Symptoms [Case (%)]			
Fever	149 (64.8)	50 (54.3)	99 (71.7)
Cough	168 (73.0)	65 (70.7)	103 (74.6)
Expectoration	45 (19.6)	12 (13.0)	33 (23.9)
Fatigue	123 (53.3)	33 (35.9)	90 (65.2)
Diarrhea	26 (11.3)	7 (7.6)	19 (13.8)
Comorbidities [Case (%)]			
Diabetes	32 (13.9)	12 (13.0)	20 (14.5)
Hypertension	50 (21.7)	11 (12.0)	39 (28.3)
Cardiovascular diseases	21 (9.1)	4 (4.3)	17 (12.3)
Cerebrovascular diseases	8 (3.5)	2 (2.2)	6 (4.3)
Concomitant medication [Case (%)]			
Oxygen therapy	138 (60.0)	0	138 (100.0)
Antiviral drugs	207 (90.0)	77 (83.7)	130 (94.2)
Antibacterial	131 (57.0)	40 (43.5)	91 (65.9)
Corticosteroids	59 (25.7)	9 (9.8)	50 (36.2)
Human immunoglobulin	53 (23.0)	3 (7.6)	46 (33.3)
Biochemical parameters [Median (IQR)]			
ALT (U/L)	20.0 (14.0, 34.0)	19.0 (14.0, 34.0)	21.0 (14.0, 34.0)
AST (U/L)	24.0 (19.0, 32.0)	22.0 (16.0, 27.0)	27.0 (21.0, 35.0)
CR (μmol/L)	62.7 (52.7, 76.0)	62.3 (51.6, 76.7)	63.0 (53.5, 75.5)
BUN (mmol/L)	3.9 (3.1, 5.2)	3.7 (2.9, 4.8)	4.3 (3.6, 5.4)
CK (ng/mL)	66.0 (43.3, 104.8)	62.5 (40.0, 87.3)	67.5 (45.0, 121.3)
CK-MB (ng/mL)	1.2 (0.8, 2.2)	1.2 (0.8, 2.2)	1.3 (0.8, 2.3)
LDH (U/L)	246.0 (205.5, 308.9)	184.5 (161.0, 220.3)	216.0 (187.0, 261.5)
Coagulation function [Median (IQR)]			
PT (s)	11.4 (11.0, 12.0)	11.3 (10.8, 11.8)	11.6 (11.2, 12.2)
APPT (s)	31.7 (27.7, 37.0)	29.6 (26.0, 34.6)	34.4 (29.1, 39.6)
D-dimer (mg/L)	0.3 (0.1, 0.5)	0.3 (0.2, 0.5)	0.2 (0.1, 0.5)

Notes: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, creatinine; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time

platelet count were increased significantly on days 7 and 14 (P=0.000). The inflammatory biomarker CRP markedly increased on day 3 and significantly decreased after treatment on day 14 (P=0.000). The levels of procalcitonin and erythrocyte sedimentation rate showed a downward trend but demonstrated no significant change (P>0.05).

Adverse Events

No serious adverse events occurred during 14 days treatment duration. The most frequent adverse events that occurred in common type COVID-19 were increased

Table 2.   Primary and Secondary Clinical Outcomes in Patients with COVID-19

Index	Total (230 cases)	Mild (92 cases)	Moderate (138 cases)
Primary outcome on day 28 [Case (%)]			
Disease progression rate	10 (4.3)	0	10 (7.2)
Discharge rate	220 (95.7)	92 (100.0)	128 (92.8)
Secondary outcome [Median (IQR) / Case (%)]			
Negative conversion time of nucleic acid (d)	12.0 (3.5, 17.0)	9.0 (3.0, 14.8)	13.0 (7.5, 19.0)
Hospitalization duration (d)	15.0 (12.0, 20.0)	12.0 (10.0, 16.0)	18.0 (14.0, 23.0)
Fever relief case	141 (94.6)	50 (100.0)	91 (91.9)
Fever relief time (d)	4.0 (2.0, 6.0)	4.0 (2.0, 5.5)	4.0 (3.0, 6.0)
Cough relief case	152 (90.5)	60 (92.3)	92 (89.3)
Cough relief time (d)	8.0 (5.0, 12.0)	7.0 (5.0, 10.0)	9.0 (5.3, 13.0)
Fatigue relief case	115 (93.5)	33 (100.0)	82 (91.1)
Fatigue relief time (d)	8.0 (5.0, 11.0)	5.0 (3.0, 8.0)	9.5 (6.0, 12.0)

Note: IQR, inter quartile range

D-dimer, ALT, AST LDH, and lymphopenia (Table 3).

DISCUSSION

Since the outbreak of COVID-19, it has been characterized as an acute infectious disease with rapid progress and a high fatality rate. Emergency treatment is required for the COVID-19. Under this circumstance, there are a series of difficulties such as difficulty in setting up a control group and difficulty in randomization when conducting a randomized controlled study. So observational research has become a more feasible type of research. In addiction, under the requirements of the National Health Commission and the State Administration of CM, CMs were commonly used in clinical treatment. Therefore, we conducted a retrospective observational multicenter study in which all included patients were

Table 3.   Summary of Adverse Events [Case (%)]

Adverse event	Total (230 cases)	Mild group (92 cases)	Moderate group (138 cases)
Increased D-dimer	55 (23.9)	18 (19.6)	37 (26.8)
Increased ALT	51 (22.2)	14 (15.2)	37 (26.8)
Lymphopenia	29 (12.6)	6 (6.5)	23 (16.7)
Increased AST	25 (10.9)	6 (6.5)	19 (13.8)
Increased LDH	24 (10.4)	3 (3.3)	21 (15.2)
Increased CR	13 (5.7)	6 (6.5)	7 (5.1)
Leukopenia	11 (4.8)	4 (4.3)	7 (5.1)
Increased BUN	9 (3.9)	3 (3.3)	6 (4.3)
Thrombocytopenia	7 (3.0)	2 (2.2)	5 (3.6)
Increased CK	5 (2.2)	0	5 (3.6)
Increased CK-MB	3 (1.3)	2 (2.2)	1 (0.7)

Notes: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, creatinine; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; LDH, lactate dehydrogenase
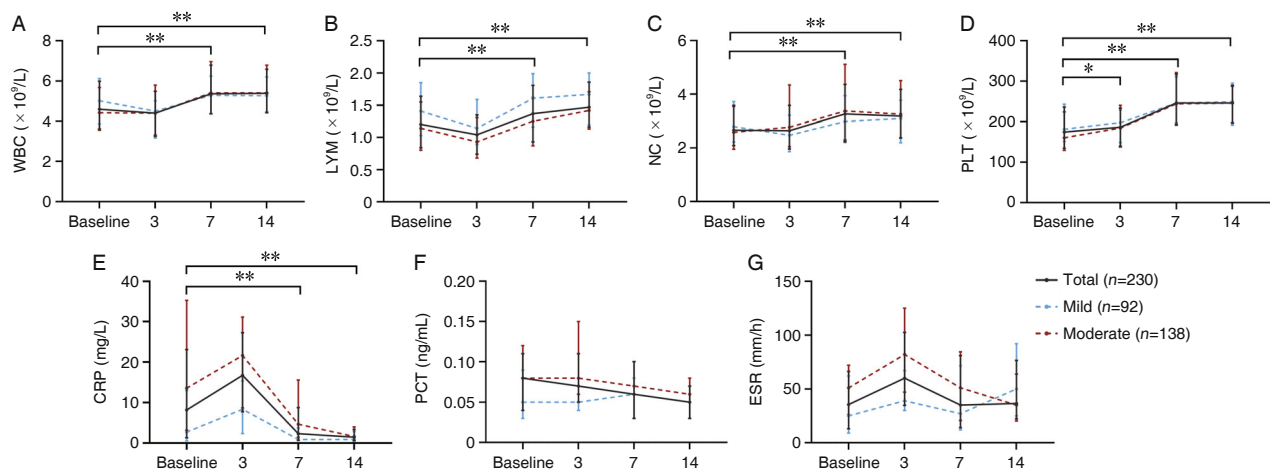
Figure 2.   Dynamic Changes of Infection Indicators [Medium (IQR)]

Notes: WBC: white blood cell; LYM: lymphocyte; NC: neutrophil count; PLT: platelet; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; $^*P<0.05$, $^{**}P<0.01$

treated with BDJDG combined with conventional Western medicine. In this study, 230 common type COVID-19 patients were enrolled in the analysis. Our findings indicated that BDJDG combined with routine Western medicine achieved zero mortality. A previous systematic review enrolled 7 randomized controlled trials and 1,079 non-severe COVID-19 patients showed that Chinese patent medicine (CPM) combined with conventional Western therapy (CWT) was superior to CWT alone in increasing the cure rate (71.5% vs. 59.0%) and decreasing the aggravation rate (5.2% vs. 9.4%). Besides, the add-on CPM was probably superior to the CWT alone in improving the recovery rate of fever (81.4% vs. 59.5%), cough (74.5% vs. 52.8%), and fatigue (81.8% vs. 61.1%).[11] However, our results found that the disease progression rate of all patients was 4.3% and the discharge rate was 95.7% on the 28th day. The recovery rate of fever, cough, and fatigue was 94.6%, 90.5%, and 93.5%, which was significantly higher than those in the previous review.

The results also showed that in non-critical type patients, the median negative conversion time of nucleic acid was 12 days and the median hospitalization duration was 15 days, which was close to the results of a previous study.[12] The results of Qingfei Paidu Decoction indicated that the median time for virus clearance was 13 days and the hospital stay was 15 days.[12] The results showed that the efficacy of BDJD in elderly patients is comparable to that in young and middle-aged patients. But an abnormal result in this study was the reduced negative conversion time of nucleic acid. We speculate that it may be because the research was conducted in the early outbreak of COVID-19, some elderly patients had symptoms but did not receive medical treatment in time. They took drugs at home and did not detect nucleic acid until receiving medical treatment, so the negative conversion time of nucleic acid seemed to be shortened.

Previous study has demonstrated that COVID-19 patients have varying degrees of blood biochemical abnormalities.[13] Most COVID-19 patients showed decreased lymphocyte count and elevated CRP level and a few patients showed a decrease in white blood cell count and platelet count.[13] However, after treatment with BDJDG, CRP level significantly decreased and the white blood cell count, lymphocyte count, and neutrophil count gradually increased. AST,

CR, CK, CK-MB, and APTT decreased significantly compared with those before treatment. Our study showed that BDJDG could alleviate the inflammatory state of the body and improve tissue damage.

Novel coronavirus has been officially declared a global pandemic by the World Health Organization since March 11, 2020.[15] It is highly contagious and seriously endangers human health. However, there are no specific drugs through the clinical verification. Current treatments include antiviral therapy, neutralization antibody, plasma therapy, immunomodulatory therapy, and symptomatic supportive therapy.[4] The present study has indicated that antiviral drugs do not show clear clinical benefits, and sometimes there are significant side effects.[16] Treatment with convalescent plasma was not significantly associated with all-cause mortality reduction or with any benefit for other clinical outcomes.[17] Early injection of high doses of immunoglobulin was associated with a reduction in 28-day mortality only in patients with severe COVID-19.[18] Presently, the Chinese guidelines do not recommend drugs such as remdesivir, lopinavir/ritonavir, hydroxychloroquine, monoclonal neutralization antibody, convalescent plasma, human immunoglobulin, and interferon for routine treatment of COVID-19 patients. Glucocorticoid and tocilizumab are only recommended for patients requiring oxygen therapy or mechanical ventilation.[4] The efficacy and safety of these drugs in the treatment of COVID-19 need further clinical trials to confirm. Although more than 7 billion people worldwide have been vaccinated,[1] the protective effect of the vaccine has declined because of the novel coronavirus variant and immune escape.[19] Due to the lack of effective measures, the treatment of COVID-19 is mainly focused on symptomatic treatment and supportive treatment.

CM has accumulated thousands of years of experience in the fight against infectious diseases. The State Administration of CM has recommended Qingfei Paidu Decoction throughout the country in the early outbreaks. In real-world research, Qingfei Paidu Decoction showed a reduction of 50% in-hospital COVID-19 related mortality without extra risk of acute liver or kidney injury.[20] Besides, early treatment within 1 week with Qingfei Paidu Decoction was associated with faster recovery and shorter time to viral shedding.[11] BDJDG can be used in the treatment of common COVID-19. It is developed on the prevention and

treatment strategy of "truncation and reversion". That means removing the pathogenic factors in the early stages to prevent the development of disease through relieving superficies method or interior-dredging method. Cytokine storm is an important cause of the disease from mild to severe.[21] Our results suggest that BDJDG has an obvious anti-inflammatory effect, and has a good effect in reducing disease mortality and preventing disease progression. The composition of BDJDG includes Maxing Shigan Decoction, a classic prescription, and Jinhong Decoction, which was studied in our laboratory at an early stage. It has been found that Maxing Shigan Decoction can exert its anti-inflammatory effect by inhibiting the production of cytokines by macrophages.[9] Jinhong Decoction can significantly inhibit inflammatory factors such as CRP, interleukin (IL)-6, IL-8, and tumor necrosis factor-α.[23] Our results show that the treatment of BDJDG may improve the symptoms and prognosis of the disease by inhibiting the systemic inflammatory response.

Our findings provide new evidence and insights for the treatment of COVID-19. However, there are still some limitations in this research. First of all, this study is a retrospective and observational study. The study population only includes patients in Hubei Province of China, resulting in a low level of evidence and poor representation of the population. Secondly, COVID-19 is a serious threat to human health and there are no specific drugs. Considering the early experience that BDJDG could achieve the effect of antipyretic and symptom improvement in COVID-19 patients, there is a lack of data on patients who did not receive BDJDG treatment, resulting in poor comparability and argumentation intensity of the study. At the same time, a variety of supportive Western medicine may have an impact on the results and cause bias. Finally, BDJDG is a compound preparation of CM. The effective components and the interaction process among them need to be verified by further experiments.

In summary, our study preliminarily demonstrated that BDJDG may be effective and safe in the treatment of common type COVID-19. However, strictly designed randomized controlled clinical trials should be carried out in the future to further confirm the benefits of CM in the treatment of COVID-19.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Funding acquisition and supervision: Fang BJ; investigation: Xu XR, Zhang W, Wu XX; methodology: Huang TR, Zuo JG, Shao Z; software: Xu XR; writing–original draft: Xu XR; writing–review & editing: Fang BJ, Shuang Z.

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