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Original article

Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19)[2] has emerged as a global pandemic. However, as effective treatments for this disease are still unclear, safe and efficient therapies are urgently needed. Qingfei Paidu decoction (QPD)[3] is strongly recommended in the Chinese Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 6th Edition). However, clinical research data on the effects of QPD on COVID-19 are scarce. Our study aimed to explore the effects of combined treatment with QPD and Western medicine on COVID-19.

Methods: In this study, 63 patients with confirmed COVID-19 were analyzed. During the first 14 days of hospitalization, patients with deteriorating symptoms were administered QPD along with Western medicine therapy (the antiviral medicine selected from interferon, lopinavir, or arbidol). The clinical characteristics and blood laboratory indices (blood routine, inflammatory factors, and multi-organ biochemical indices) were examined, and the total lung severity scores were evaluated in each patient by reviewing chest computed tomography before treatment and at the end of treatment.

Results: Before QPD treatment, the combined treatment group showed higher blood C-reactive protein levels and more severe pulmonary inflammation and clinical symptoms than the Western medicine treatment group. Both groups met the discharge criteria after a similar length of hospitalization. At the end of treatment, circulating white blood cells, total lymphocyte count, and glutamic-oxaloacetic transaminase levels improved dramatically in both groups ($P < 0.05$). In contrast, C-reactive protein, creatine kinase, creatine kinase-myocardial band, lactate dehydrogenase, and blood urea nitrogen levels were improved only in the combined treatment group ($P < 0.05$), and C-reactive protein and creatine kinase were the most pronounced ($P < 0.01$). Compared with baseline, at the end of treatment, the proportion of patients with normal values of C-reactive protein, total lymphocyte count, and lactate dehydrogenase were increased in the combined treatment group ($P < 0.05$),

Abbreviations: BUN, blood urea nitrogen; CAD, coronary artery disease; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; COVID-19, coronavirus disease 2019; CRE, creatinine; CRP, C-reactive protein; CT, computed tomography; cTnI, cardiac Troponin I; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; GPT, glutamic-pyruvic transaminase; GOT, glutamic-oxaloacetic transaminase; HBP, high blood pressure; LDH, lactate dehydrogenase; MYO, myoglobin; PCT, procalcitonin; QPD, Qingfei Paidu decoction; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TCM, Traditional Chinese medicine; TLC, total lymphocyte count; WBC, white blood cell; WM, Western medicine

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[2] COVID-19, Coronavirus Disease 2019.
[3] QPD, Qingfei Paidu decoction.

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whereas no significant difference was observed in the Western medicine treatment group ($P > 0.05$).
Conclusion: The combination of QPD with Western medicine demonstrated significant anti-inflammatory effects compared with those of only Western medicine in patients with mild and moderate COVID-19; however, neither mortality nor length of hospitalization was affected. Moreover, the combined treatment tended to mitigate the extent of multi-organ impairment. Long-term randomized controlled trials with follow-up evaluations are required to confirm the results presented here.

1. Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously named provisionally as 2019 novel coronavirus or 2019-nCoV), was identified in December 2019 in China and is the cause of the coronavirus disease 2019 (COVID-19) [1]. The disease has spread rapidly to many other countries; since early March 2020, there have been far more active new cases from Europe and the Americas than from China [2]. Thus, COVID-19 has already become a global health threat [3].

Although China was the first country in which SARS-CoV-2 was identified [4], no effective medicines have been developed for the treatment of SARS-CoV-2 infection; thus, safe and efficient treatments are still required urgently. Based on the practical clinical experience in the treatment of this novel coronavirus disease, the official guidelines, Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 6th Edition) (hereinafter referred to as Treatment Plan 6th) [5,6] were published in China; these were the newest version available when this study was designed. The guidelines recommend several Western antiviral medicines (e.g., interferon, lopinavir, and arbidol). In addition, the usage of traditional Chinese medicine (TCM) was proposed in SARS-CoV-2 infection [6]. Notably, the TCM Qingfei Paidu decoction (QPD) is strongly recommended for confirmed cases of different clinical categories [6].

SARS-CoV-2 is 82 %–89 % genetically similar to severe acute respiratory syndrome coronavirus (SARS-CoV), which was endemic in China in 2003 [7]. Given the high homology between the viruses, the experience of treating SARS-CoV may be instructive for SARS-CoV-2. In 2003, TCM was shown to exert therapeutic effects on SARS-CoV in China [8–12]. QPD, as an optimized combination of classic TCM recipes, has been used widely since 200 CE for the treatment of exogenous fever in China. The effects of QPD on SARS-CoV-2 are expected to be promising [13]. QPD comprises 21 TCMs (Table 2) [6], which may reflect the multi-functional protective effects, not only on the lung, but also on the spleen, stomach, heart, liver, and kidney [13]. Moreover, five of the components (*Gan Cao, Chai Hu, Zi Wan, Kuan Dong Hua,* and *Huang Qin*) are supposed to have potential anti-SARS-CoV-2 effects, as some studies identified they were beneficial for severe SARS-CoV infection [14–16]. Consistent with this, another study found that QPD contains 948 different chemical compounds, which affect 790 potential target proteins; the interaction between these targets was identified to form a molecular network that plays a crucial role in effects on the lung and in the protection of multiple organs [17]. Therefore, QPD combined with Western medicine (WM) is expected to exert synergistic effects and improve the treatment of COVID-19.

However, to date, the clinical research data on the effects of QPD on COVID-19 are limited; most QPD therapy cases are based on local clinical experience. During our retrospective study, we considered discharge or death as the endpoint. The purpose of this study was to provide clear evidence of the combination treatment of COVID-19 with QPD and WM.

2. Materials and methods

2.1. Study population

Confirmed patients with COVID-19 who were admitted between January 24 and February 15, 2020 at the Xiangyang No. 1 People's Hospital, affiliated hospital of Hubei University of Medicine, were included in this study. In accordance with Treatment Plan 6th, the patients with COVID-19 were grouped into four categories based on the extent of infection: mild, moderate, severe, and critical. This hospital mainly admitted mild and moderate cases. The study protocol was approved by the local ethics committee (Ethics Committee of Xiangyang No.1 People's Hospital, Affiliated Hospital of Hubei University of Medicine, 2020GCP016), and written informed consent was obtained from all patients.

2.2. Inclusion criteria

Patients having any one of the clinical manifestations (respiratory symptoms with or without fever, significant radiological imaging features of COVID-19) would receive the novel coronavirus nucleic acid test (real-time fluorescence reverse transcription polymerase chain reaction (RT-PCR) detection). A patient that tested positive was considered a confirmed case [6]. These confirmed cases were included in our study.

2.3. Exclusion criteria

Patients with the following conditions were excluded: a) pregnant or lactating women; b) patients with other severe primary diseases; c) history of a psychiatric or neurological disorder; d) history of abuse (alcohol or drug); and e) other factors affecting the observation of curative effects, such as irregular medication and taking other TCM preparations within 2 weeks before or during treatment.

Table 1
Symptoms rating scale.

Primary symptoms	**0 points**	**2 points**	**4 points**	**6 points**
Fever	no	37.3℃–38.0℃	38.1℃–38.9℃	≥ 39.0℃
Cough	no	Occasionally	Often, but does not affect life and sleep	Frequently, affects life and sleep
Fatigue	no	Mild, does not affect life and sleep	Moderate, affects life and sleep but tolerable	Severe, affects life and sleep, unbearable
Secondary syndromes	**0 point**	**1 point**	–	–
Sore throat	no	yes	-	-
Nasal congestion	no	yes	-	-
Diarrhea	no	yes	-	-
Dyspnea	no	yes	-	-

2.4. Criteria for hospital discharge

All the following criteria were required to be satisfied: a) normal body temperature for at least three consecutive days; b) improved respiratory symptoms; c) respiratory acute exudative lesions showing substantial improvement by chest radiology, and d) two consecutive negative nucleic acid tests using respiratory tract samples (taken at least 24 h apart).

2.5. Study design

Based on the aforementioned diagnostic standards, 63 patients with confirmed cases of COVID-19 were included in this retrospective analysis. All the confirmed patients were receiving general WM therapy throughout the hospitalization period, including effective oxygen therapy measures, antipyretic measures, rehydration, nutritional support, antiviral treatment, combined with antibiotic treatment in case of bacterial infection, and corticosteroids used only in case of inflammation caused by a cytokine storm.

We assessed the patient's state based on the symptom-rating scale (Table 1) [18]. When the symptoms of the patients worsened (score increased) during the first 2 weeks of hospitalization (as the incubation period of clinical presentation is 1–14 days [6]), they were administered 6 days of QPD treatment (comprising two consecutive courses, each course lasting 3 days, without a pause between the courses) in addition to WM treatment.

After evaluation of the treatment protocols of each patient, the included patients were divided into either the WM-only group or the QPD combined with WM group (QPD + WM). The treatment ended when each subject matched the discharge criteria or died (the endpoint of this study). The components and doses of QPD are shown in Table 2. The QPD dose was fixed for the administration period. To ensure quality control, all procedures from the purchase of raw materials (batch numbers are shown in Table 2) for mixture and boiling were performed by our hospital pharmacy. After boiling the herbs, the herbal liquid was filled into sterilized airtight bags; each bag contained one dose of QPD (200 mL). Trained nurses delivered and guided the patients at each administration of the drug.

This study complied with the regulations in China for studies involving the use of human subjects: registration number of clinical trials: ChiCTR2000029778 and registration number of TCM clinical trial registry: ChiMCTR2000003003.

2.6. Patient evaluation

General information, clinical characteristics, blood laboratory tests, and chest computed tomography (CT) images were collected for review. Blood laboratory tests included routine blood (white blood cells (WBC), total lymphocyte count (TLC)), hepatic function (glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT)), renal function (creatinine (CRE), blood urea nitrogen (BUN)), cardiac function (creatine kinase (CK), creatine kinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), cardiac troponin I (cTnI), myoglobin (MYO)), inflammatory factors (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT)), and D-dimer. Respiratory specimens (including nasopharyngeal swabs, bronchoalveolar lavage, sputum, or bronchial aspiration) were collected and examined using the CoV-SARS-2 virus nucleic acid test with real-time RT-PCR (Liferiver Bio-Tech, Shanghai, China). CT was performed using a 64-slice scanner (Aquilion CXL, Toshiba Medical, Japan). The severity of chest CT was judged through assessment of the total lung severity score (hereinafter referred to as the CT score), as described by Bernheim et al. [19]. Briefly, each of the lobes was scored on a scale of 0–4 by evaluating 11 representative CT images; and the final score was determined by summing five lobe scores (to give a score from 0 to 20) [19]. A higher score indicated more severe pulmonary impairment.

2.7. Statistical analysis

The results are reported as the mean ± SD (for parametric distributed variables) or median and interquartile range (for non-parametric distributed variables) or number and proportion (for counts). Data comparisons between groups were based on the independent sample Wilcoxon test, the independent sample *t*-test, or the Chi-square test. For pairwise comparisons, the paired samples Wilcoxon test, paired-samples *t*-test, or McNemar's test was used. Owing to incomplete datasets at the endpoint, there was too few data for paired analysis of MYO, cTnI, ESR, and D-dimer levels. P-value < 0.05 was considered statistically significant for all analyses. Analyses were performed using SPSS v.23.0 (IBM, USA).

3. Results

3.1. Data at baseline

From January 24 to February 15, 2020, 63 of the 99 confirmed patients were eligible. Thirty-six patients were excluded for the following reasons: a) 1 - pregnant, 2 - lactating; b) 16 - other severe primary diseases (e.g., cancer, severe heart diseases, hepatopathy, nephropathy); c) 2 - history of neurological disorder; d) 4 - history of abuse (alcohol or drugs); and e) 11 - taking other TCM preparations in the 2 weeks before or during treatment.

When admitted to hospital (baseline), with the exception of two mild cases in the WM group, most patients with COVID-19 were categorized into moderate form. Only CRP levels differed significantly between groups ($P < 0.05$), as shown in Table 3. The proportion of patients who were normal/abnormal for each laboratory index was not different between groups (including CRP, $P = 0.103$, in Appendix A, Table A1).

In the QPD + WM group, CRP levels were significantly higher than those in the WM group ($P = 0.018$, Fig. 1A). The same was observed for CT scores ($P = 0.035$, Fig. 1B), which suggested that patients in the QPD + WM group had more robust responses to inflammation and more severe pulmonary impairment than those in the WM group.

Table 2
Components of Qingfei Paidu decoction.

Chinese name	Latin name	Dose (grams)	Batch number
Ma Huang	*Ephedra*	9	20170402
Zhi Gan Cao	*Glycyrrhiza uralensis Fisch*	6	20191101
Xing Ren	*Amygdalus communis*	9	20190301
Bai Zhu	*Atractylodes macrocephala Koidz*	9	20200101
Chai Hu	*Radix bupleuri*	16	20200101A
Huang Qin	*Scutellaria baicalensis*	6	2019061E
Jiang Ban Xia	*Pinellia ternata*	9	D9060101
Zi Wan	*Asteris radix et rhizoma*	9	20190401
Kuan Dong Hua	*Farfarae flos*	9	20190501
She Gan	*Belamcanda chinensis*	9	20161201
Xi Xin	*Asarum*	6	20190301
Shan Yao	*Dioscorea polystachya*	12	20191001A
Zhi Shi	*Citrus aurantium*	6	20190501
Huo Xiang	*Agastache rugosus*	9	20191001
Sheng Jiang	*Zingiber officinale Rosc.*	15	20190601A
Fu Ling	*Wolfiporia cocos*	15	20190501E
Chen Pi	*Pericarpium citri Reticulatae*	6	20190401A
Sheng Shi Gao	*Raw Gypsum*	10/30[a]	20190801
Gui Zhi	*Cinnamomum cassia Presl*	9	20190301B
Ze Xie	*Alismatis*	9	20190601B
Zhu Ling	*Polyporus umbellatus*	9	20191001

Instruction: Herbs were soaked in 1000 mL of pure water for 30 min, and then boiled until 400 mL of water remained; 200 mL was administered each morning and evening (40 min after a meal).

[a] 30 g is for patients with fever.

Table 3
General information and laboratory indices at baseline.

	Normal range	Treatments		*P*-value
		QPD + WM (n = 37)	WM (n = 26)	
Gender, male (%)	–	17 (46.0)	12 (46.2)	.987
Age (Median, years)	–	46.1 (23.5–89.9)	50.7 (15.3–81.9)	.356
Regular: Mild form		37: 0	24: 2	.166
Symptoms scores		6.8 ± 2.5	7.8 ± 3.0	.168
with DM	–	4 (10.8)	3 (11.5)	.928
with HBP	–	7 (18.9)	9 (34.6)	.159
with CAD	–	4 (10.8)	1 (2.7)	.314
Historical Epidemiology[a]	–	24 (64.9)	13 (50.0)	.411
Blood routine				
WBC ($\times 10^9$/L)	3.5–9.5	4.82 (3.67–5.52)	4.29 (3.39–5.08)	.328
TLC ($\times 10^9$/L)	1.1–3.2	1.04 (0.78–1.44)	1.23 (0.92–1.52)	.206
Hepatic function				
GPT (IU/L)	7–40	23.1 (16.0–37.8)	22.1 (15.0–40.1)	.933
GOT (IU/L)	13–35	25.1 (19.5–38.1)	24.9 (19.7–38.3)	.911
Renal function				
CRE (μmol/L)	41–81	64.3 (52.8–79.6)	68.0 (57.0–80.8)	.759
BUN (mmol/L)	3.1–8.8	4.19 (3.06–5.20)	4.42 (3.24–6.48)	.589
Cardiac function				
CK (U/L)	50–310	72.8 (48.1–214.1)	72.8 (46.5–123.9)	.648
CK-MB (U/L)	0–24	11.4 (8.2–14.3)	10.0 (7.4–15.0)	.847
cTnI (ng/mL)	0–0.04	0.020 (0.010–0.030)	0.010 (0.010–0.020)	.066
MYO (μg/L)	12–75	22.2 (8.4–55.0)	13.0 (8.6–16.9)	.066
LDH (U/L)	120–250	236.2 (183.7–262.8)	203.0 (177.0–276.6)	.679
Inflammation factors				
CRP (mg/L)	0–8	23.9 (6.5–57.3)	9.1 (2.4–21.6)	**.018**
ESR (mm/h)	0–15	28.5 (17.0–47.0)	19.5 (13.0–36.5)	.169
PCT (μg/L)	0–0.1	0.06 (0–0.12)	0.05 (0.01–0.07)	.501
D-Dimer (mg/L)	0–0.5	0.03 (0.03–0.11)	0.03 (0.03–0.18)	.916

Bold values depict significant differences in the comparison of the baseline values between the two groups.

[a] History of contact with persons in Wuhan area in the last 15 days; QPD, Qingfei Paidu decoction; WM, Western medicine; DM, Diabetes mellitus; HBP, High blood pressure; CAD, Coronary artery disease; WBC, White blood cell; TLC, Total lymphocyte count; GPT, Glutamic-pyruvic transaminase; GOT, Glutamic-oxaloacetic transaminase; CRE, Creatinine; BUN, Blood urea nitrogen; CK, Creatine kinase; CK-MB, Creatine kinase-myocardial band; cTnI, cardiac Troponin I; MYO, Myoglobin; LDH, Lactate dehydrogenase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PCT, Procalcitonin; Data are shown as the median (interquartile range) or mean ± SD or number (proportion); *P*-values are for the Mann-Whitney test, independent-samples t-test and Chi-square test.

3.2. Western medicine treatment status

With a maximum of two antibiotics allowed simultaneously during hospitalization, the number of antibiotics was not significantly different between groups ($P = 0.269$). Three antiviral drugs were available in our hospital; the usage of lopinavir only was lower in the QPD + WM group ($P = 0.049$). The usage of corticosteroids was not significantly different between groups ($P = 0.390$), as shown in Table 4.

3.3. Comparison of laboratory indices at baseline and endpoint

At the endpoint, the WBC, TLC, and GOT showed significantly improved levels in both groups ($P < 0.05$), whereas BUN, CK, CK-MB, LDH, and CRP levels declined only in the QPD + WM group ($P < 0.05$), as shown in Table 5. We assessed the improvement in the proportion of normal values at the endpoint; only CRP, TLC, and LDH showed a significant improvement in the QPD + WM group ($P < 0.05$), and no significant difference was found in the WM group ($P > 0.05$, in

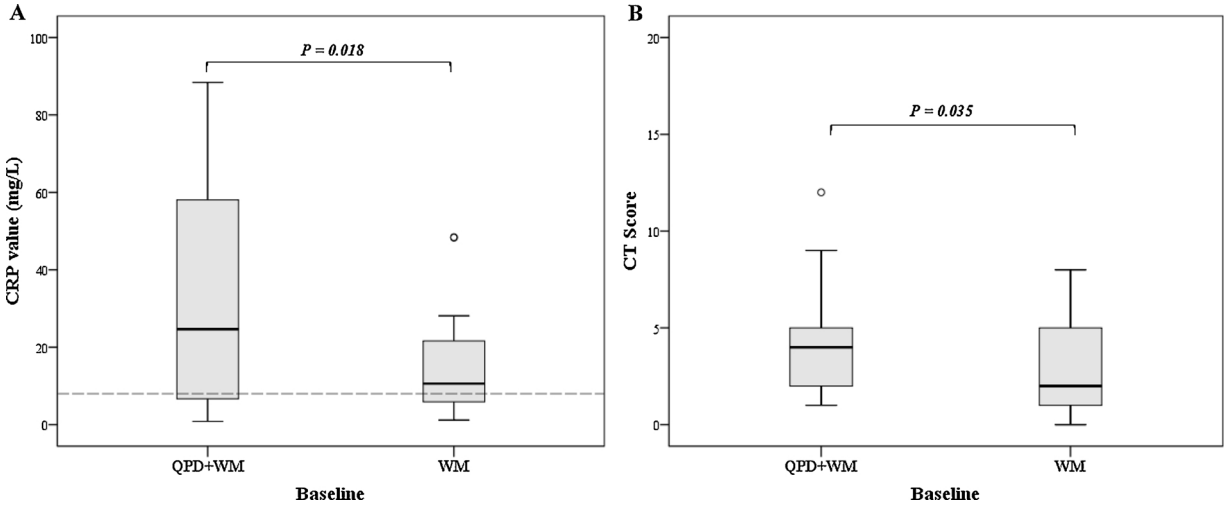

Fig. 1. Comparison of CRP levels (A) and CT scores (B) at the baseline between groups.

Table 4
Western medicine treatment status.

	QPD + WM (N = 37)	WM (N = 26)	*P*-value
Number of Antibiotics			.269
0 (n, %)	6 (16.2)	1 (3.8)	
1 (n, %)	17 (45.9)	9 (34.6)	
2 (n, %)	8 (21.6)	11 (42.3)	
3 (n, %)	2 (5.4)	3 (11.5)	
4 (n, %)	2 (5.4)	1 (3.8)	
5 (n, %)	2 (5.4)	1 (3.8)	
Antiviral drugs			
Interferon (n, %)	34 (91.9)	26 (100.0)	.140
Arbidol (n, %)	24 (64.9)	16 (61.5)	.997
Lopinavir (n, %)	29 (78.4)	25 (96.2)	**.049**
Corticosteroids	7 (18.9)	5 (19.2)	.390

Bold values depict significant differences for comparison baseline between two groups. QPD, Qingfei Paidu decoction; WM, Western medicine; Data are shown as number (proportion). *P* values are for Chi-Square Test.

Appendix A, Table A2).

To determine the degree of variation in the indices varying significantly, we calculated the rate of variation (revised value/baseline × 100 %) as shown in Fig. 2. The levels of WBC and TLC were upregulated in both groups, and the remaining indices declined; however, there were no differences between groups ($P > 0.05$). Within groups, for the upregulated indices, the rates of variation of TLC were higher than those of WBC only in the QPD + WM group ($P < 0.05$); for the downregulated indices of the QPD + WM group, the rates of variation of CRP and CK were significantly higher than those of GOT, LDH, and BUN, as shown in Fig. 2.

3.4. Symptom scores

Symptom scores were not different between the groups at baseline (Table 3). At the point at which QPD was added, the symptom scores were significantly higher than those at baseline in the QPD + WM group (8.9 ± 2.7 vs. 6.8 ± 2.5, $P < 0.001$, Fig. 3A). At the endpoint, symptom scores dramatically decreased in both groups, and no differences were observed (0.0 (0.0–1.0) vs. 0.0 (0.0–2.0), $P = 0.615$, Fig. 3B).

3.5. Clinical observational indices and CT scores

At the endpoint, with the exception of the deaths in the WM group, all subjects were discharged. However, mortality was not significantly different between groups ($P = 0.065$). Between groups, CT scores and the length of hospitalization were not different at the endpoint (Table 6).

4. Discussion

In this study, we have provided evidence of the efficacy of QPD when used in combination with WM for the treatment of COVID-19, highlighting the roles of anti-inflammatory agents, and identified a trend of mitigating the extent of multi-organ impairment.

TCM exerted anti-inflammatory effects when used for the treatment of SARS-CoV in 2003. TCM enabled a decrease in the dosage of glucocorticoids during initial treatment in 461 cases of SARS [10]. A meta-analysis of 1678 patients with SARS also indicated that, compared with WM treatment alone, TCM plus WM played a greater role in pulmonary infiltrate absorption, reduced corticosteroid usage, and shortened the duration of fever; however, mortality rates or cure rates were equal between treatments [9]. *Houttuynia cordata* ameliorated symptoms in patients infected with SARS-CoV; in addition, it inhibited edema and attenuated the inflammatory response in rodents [11]. *Yu Ping Feng San* and *Sang Ju Yin* were shown to have beneficial immune modulatory effects on healthy people by increasing blood T-lymphocyte CD4/CD8 ratio [12]. Notably, *Huangqi* and *Baizhu*—two principal components of *Yu Ping Feng San*—are also two of the 21 herbs in QPD.

A strong immune response is possible in patients with COVID-19, and may cause an inflammatory storm [20]. Treatment Plan 6th also mentions that inflammatory cytokine levels are often higher in severe and critical patients [6]. Furthermore, clinical research has identified that CRP levels [21] and CT image scores are among several factors contributing to the progression of COVID-19 [19,22]. In our study, at baseline, although the proportion of patients with normal CRP in the QPD + WM group was equal to that in the WM group, significantly higher CRP levels and CT scores were observed, suggesting that patients in the QPD + WM group would be more severe than those in the WM group. Subsequently, we observed exacerbated symptoms in patients in the QPD + WM group, verifying the prediction of CRP levels and CT scores on COVID-19 progress.

Nevertheless, at the endpoint in our study, there was an impressive reduction in CRP levels (70 %) and an increased proportion of normal values in the QPD + WM group. Improved outcomes in WBC and TLC were also found, which may have beneficial immune modulatory effects in humans. In addition, the patients experienced a similar curative effect (CT and symptoms scores, mortality rates) in both groups over the same length of hospitalization. As described above, the combination of QPD and WM appears to have a greater anti-inflammatory effect than WM alone, with significant signs of pulmonary inflammation

Table 5
Blood laboratory indices in the two groups at baseline and endpoint.

Index	QPD + WM				WM			
	Paired Number	Baseline	Endpoint	*P*-value	Paired Number	Baseline	Endpoint	*P*-value
WBC	37	4.82 (3.67–5.52)	5.51 (4.48–6.61)	**.001**	26	4.29 (3.39–5.08)	4.96 (4.37–6.61)	**.006**
TLC	37	1.04 (0.78–1.44)	1.47 (1.27–1.81)	**< .001**	26	1.23 (0.92–1.52)	1.47 (1.22–1.91)	**.037**
GPT	36	22.6 (15.8–34.9)	25.6 (14.7–42.8)	.185	22	24.9 (16.3–44.4)	23.1 (14.2–36.6)	.189
GOT	36	25.1 (19.1–37.7)	20.4 (16.9–28.1)	**.011**	22	26.1 (20.0–38.8)	20.8 (16.5–31.6)	**.019**
CRE	35	64.3 (54.4–79.1)	60.8 (51.0–76.4)	.062	18	71.1 (57.6–83.3)	76.2 (54.3–90.9)	.845
BUN	35	4.19 (3.00–5.19)	3.28 (2.67–4.12)	**.026**	10	4.59 (3.15–6.55)	4.70 (3.47–11.69)	.508
CK	24	67.3 (46.4–220.9)	37.3 (29.3–51.0)	**< .001**	16	75.9 (45.5–133.8)	48.2 (33.7–135.1)	.234
CK-MB	24	11.4 (8.3–14.5)	6.3 (5.8–8.2)	**.001**	16	9.6 (7.7–15.9)	6.7 (4.3–25.3)	.196
LDH	33	232.9 (181.7–262.7)	174.4 (151.1–198.7)	**.001**	18	212.8 (182.7–265.4)	178 (151.9–269.6)	.586
CRP	29	24.7 (6.5–59.0)	5.7 (2.0–14.3)	**< .001**	21	10.6 (4.1–21.6)	2.9 (1.2–17.2)	.455
PCT	17	0.08 (0.05–0.17)	0.08 (0.06–0.11)	.426	9	0.05 (0.05–0.07)	0.11 (0.03–0.74)	.065

Bold values depict significant differences in the comparison between the baseline and endpoint within each group. WM, Western medicine; QPD, Qingfei Paidu decoction; WBC, White blood cell; TLC, Total lymphocyte count; GPT, Glutamic-pyruvic transaminase; GOT, Glutamic-oxaloacetic transaminase; CRE, Creatinine; BUN, Blood urea nitrogen; CK, Creatine kinase; CK-MB, Creatine kinase-myocardial band; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin. Data are shown as the median (interquartile range); *P*-values are for the Wilcoxon Signed Ranks test.

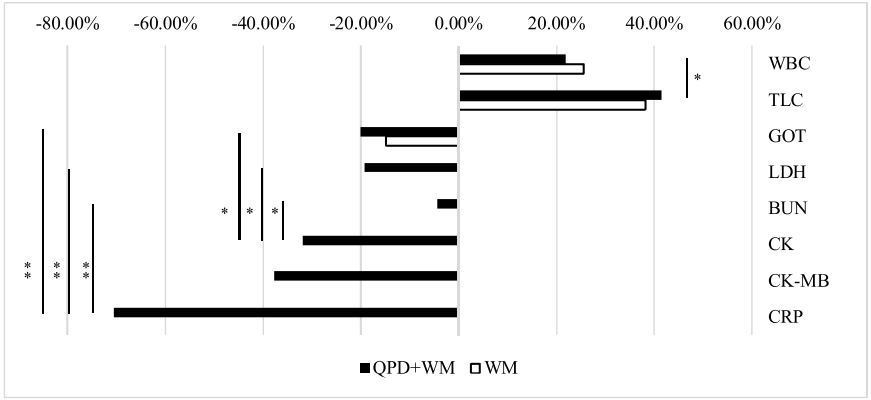

Fig. 2. Comparison of rates of variation 15.

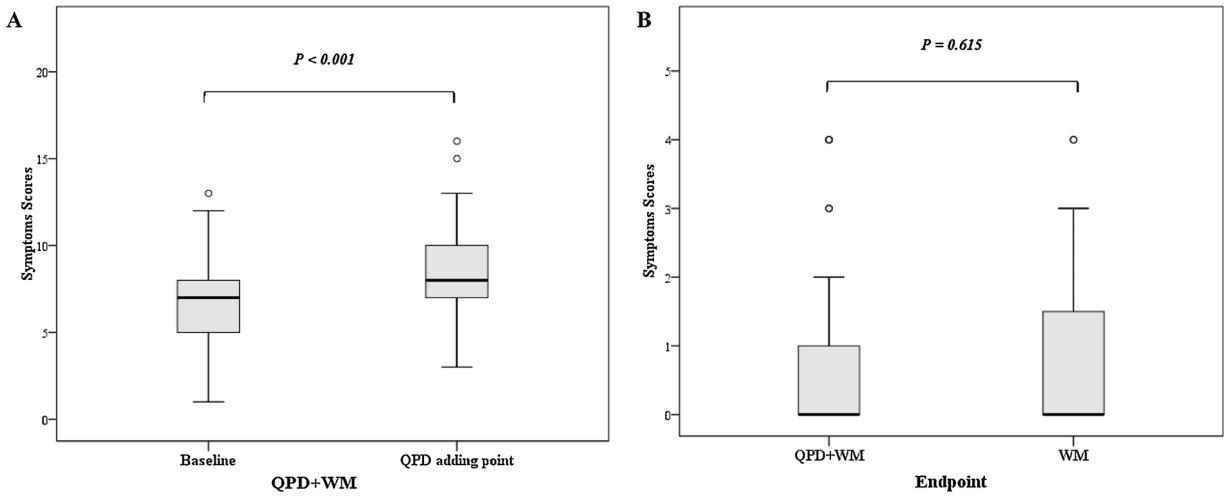

Fig. 3. Symptom scores within QPD + WM group (A) and between groups (B). 16.

Table 6
Clinical observational indices and CT scores.

	QPD + WM	WM	*P*-value
Death (n, %)	0 (0.0)	3 (11.5)	.065
Length of hospitalization (days)	19.0 (15.3–22.0)	17.0 (15.0–19.3)	.165
CT scores at endpoint	1.0 (1.0–2.0)	1.0 (0.0–2.0)	.482

QPD, Qingfei Paidu decoction; WM, Western medicine; CT, computed tomography; Data are shown as the median (interquartile range) or number (proportion); *P*-values are for Mann-Whitney Test and Chi-Square test.

absorption compared to those in the WM group.

In addition, a recent study demonstrated that the receptor of SARS-CoV-2 in human cells is angiotensin-converting enzyme 2 (ACE2), which is abundant in the lung and other organs [23]. Unfortunately, the extrapulmonary spread of SARS-CoV in $ACE2^{+}$ organs has been observed [24,25]. As a virus with affinity to SARS-CoV, SARS-CoV-2 can be expected to do the same. Meanwhile, extrapulmonary syndromes were observed in patients with COVID-19, such as symptoms of diarrhea in the early stages, or of the cardiac, hepatic, and renal systems, which may be an indication of poor prognosis [20]. Therefore, protection of the related organs is essential as part of antiviral therapy.

Our study also demonstrated the deteriorated blood laboratory indices, which to an extent, reflected multi-organ impairment. Gray et al. [26] have pointed out that the usage of TCM in the treatment of COVID-19 may be “potentially deleterious”. In our study, at least during hospitalization, we did not observe any deleterious effects on patients who had taken QPD.

Conversely, in the QPD + WM group, CK, CK-MB, LDH, BUN, and GOT levels decreased significantly; however, only LDH had a significant proportion of patients who improved to within the normal range. This difference may result from the disease form in our study subjects, who were patients categorized with moderate and mild symptoms, with no serious multi-organ damage. Thus, the degree of improvement was limited. Accordingly, in patients with mild and moderate disease, QPD combined with WM had a smaller impact on improving the proportion of normal patients with multi-organ indices, but tended to mitigate the extent of multi-organ impairment.

The limitations of this study should be noted. First, owing to the limited number of cases, our results may have been obtained by chance. The results must be confirmed in a more extensive study, including patients with different categories of disease. Second, our study design was limited by the situation, and the choice of antiviral medicine was limited; thus, a randomized well-controlled trial could not be achieved. Randomized studies with multiple antiviral medicine treatments are needed to further verify these results. Finally, in our research, QPD was administered for only 6 days (two courses of treatment) in the QPD + WM group. Whether patients achieve greater benefit from combination therapy for prolonged periods of QPD treatment remains to be seen.

5. Conclusion

The purpose of our study was to explore the effects of the combination treatment of QPD with Western therapy in patients with COVID-19. Our results indicate that QPD, when used as an adjunctive therapy

to Western medication, could relieve the symptoms and improve inflammation resolution in the lung. Furthermore, the combined therapy had less impact on the improvement in the proportion of normal multi-organ indices, but showed a tendency to mitigate the extent of multi-organ impairment in patients with COVID-19, however, without any difference in their mortality and length of hospitalization. Owing to the limited sample size, restricted Western antiviral drug selection, and single-center study design, the conclusions that can be drawn are limited in the studied patients. Long-term randomized controlled trials with follow-up evaluations are still required to confirm the present results.

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Author contributions

Rui Yu, Bo Zhu, Siyi Xin, and Xueqi Cheng designed the study. Xueqi Cheng and Siyi Xin analyzed the data and wrote the manuscript. Bo Zhu, Xiaolong Liao, Jian Wang, Limin Xing, Xiping Xu, Renyi Su, Lin Jin, Yanping Liu, Wei Zhou, Dongwei Zhang, Liang Liang, and You Yu collected and sorted the data. Feng Yang and Lina Song reviewed all CT images. Rui Yu, Yan Shi, and Xuefeng Guan proofread the manuscript. All authors read and approved the final manuscript. Rui Yu has primary responsibility for the final content.

Declaration of Competing Interest

No financial or commercial conflict of interest exists.

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Appendix A

Table A1
Proportion of patients with normal/abnormal laboratory indices at baseline.

		QPD + WM	WM	*P–value*
WBC	3.5–9.5 × 10^9/L	29 (78.4)	19 (73.1)	.627
	< 3.5 or > 9.5 × 10^9/L	8 (21.6)	7 (26.9)	
TLC	1.1–3.2 × 10^9/L	14 (37.8)	16 (61.5)	.064
	< 1.1 or > 3.2 × 10^9/L	23 (62.2)	10 (38.5)	
GPT	7–40 IU/L	28 (75.7)	20 (76.9)	.909
	> 40 IU/L	9 (24.3)	6 (23.1)	
GOT	13–35 IU/L	24 (64.9)	19 (73.1)	.491
	> 35 IU/L	13 (35.1)	7 (26.9)	
CRE	41–81 μmol/L	30 (81.1)	20 (76.9)	.688
	> 81 μmol/L	7 (18.9)	6 (23.1)	
BUN	3.1–8.8 mmol/L	35 (94.6)	10 (90.9)	.551
	> 8.8 mmol/L	2 (5.4)	1 (9.1)	
CK	50–310 U/L	31 (86.1)	25 (96.2)	.191
	> 310 U/L	5 (13.9)	1 (3.8)	
CK-MB	0–24 U/L	33 (91.7)	23 (88.5)	.497
	> 24 U/L	3 (8.3)	3 (11.5)	
cTnI	0–0.04 ng/mL	23 (88.5)	22 (100.0)	.150
	> 0.04 ng/mL	3 (11.5)	0 (0.0)	
MYO	12–75 μg/mL	25 (92.6)	21 (100.0)	.311
	> 75 μg/mL	2 (7.4)	0 (0.0)	
LDH	120–250 U/L	24 (66.7)	18 (69.2)	.831
	> 250 U/L	12 (33.3)	8 (30.8)	
CRP	0–8 mg/L	11 (29.7)	13 (50.0)	.103
	> 8 mg/L	26 (70.3)	13 (50.0)	
ESR	0–15 mm/h	6 (17.6)	8 (33.3)	.169
	> 15 mm/h	28 (82.4)	16 (66.7)	
PCT	0–0.1 μg/L	25 (71.4)	21 (84.0)	.256
	> 0.1 μg/L	10 (28.6)	4 (16.0)	
D–dimer	0–0.5 mg/L	34 (94.4)	24 (96.0)	.636
	> 0.5 mg/L	2 (5.6)	1 (4.0)	

QPD, Qingfei Paidu decoction; WM, Western medicine; WBC, White blood cell; TLC, Total lymphocyte count; GPT, Glutamic-pyruvic transaminase; GOT, Glutamic-oxaloacetic transaminase; CRE, Creatinine; BUN, Blood urea nitrogen; CK, Creatine kinase; CK-MB, Creatine kinase- myocardial band; cTnI, cardiac Troponin I; MYO, Myoglobin; LDH, Lactate dehydrogenase; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; PCT, Procalcitonin. Data are shown as number (proportion). *P*-values are for the Chi-Square test.

Table A2
Proportion of patients with normal laboratory indices at baseline and endpoint.

Index	QPD + WM				WM			
	Paired Number	Baseline (normal, %)	Endpoint (normal, %)	*P*-value	Paired Number	Baseline	Endpoint	*P*-value
WBC	37	29 (78.4)	35 (94.6))	.070	26	19 (73.1)	22 (84.6)	.375
TLC	37	14 (37.8)	33 (89.2)	**< .001**	26	16 (61.5)	21 (80.8)	.125
GOT	36	24 (66.7)	31 (86.1)	.065	22	15 (68.2)	17 (77.3)	.687
GPT	36	28 (77.8)	27 (75.0)	1.000	22	16 (72.7)	18 (81.8)	.687
CRE	35	29 (82.9)	30 (85.7)	1.000	18	13 (72.2)	12 (66.7)	1.000
BUN	35	34 (97.1)	34 (97.1)	1.000	10	9 (90.0)	7 (70.0)	.500
CK	24	21 (87.5)	24 (100.0)	.250	16	15 (93.8)	16 (100.0)	1.000
CK-MB	24	22 (91.7)	24 (100.0)	.500	16	13 (81.3)	12 (75.0)	1.000
LDH	33	22 (66.7)	30 (90.9)	**.039**	18	13 (72.2)	12 (66.7)	1.000
CRP	29	8 (27.6)	17 (58.6)	**.022**	21	10 (47.6)	14 (66.7)	.388
PCT	17	9 (52.9)	12 (70.6)	.375	9	8 (88.9)	4 (44.4)	.125

Bold values depict significant differences for comparison between the baseline and endpoint within each group. QPD, Qingfei Paidu decoction; WM, Western medicine; WBC, White blood cell; TLC, Total lymphocyte count; GOT, Glutamic-oxaloacetic transaminase; GPT, Glutamic-pyruvic transaminase; CRE, Creatinine; BUN, Blood urea nitrogen; CK, Creatine kinase; CK-MB, Creatine kinase- myocardial band; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PCT, Procalcitonin. Data are shown as number (proportion). *P*-values are for the McNemar test.

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