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The efficacy of combined therapy of qingfeiPaidu capsule and lianhuaqingwen capsule nursing interventions for hospitalized patients with COVID-19

A retrospective study of medical records

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Abstract

Coronavirus disease-19 (COVID-19) caused a global pandemic burden, affecting hundreds of thousands of individuals, having life-threatening outcomes. Traditional Chinese Medicine plays a crucial role in the treatment of patients with COVID-19. The purpose of this study was to investigate the efficacy of combined therapy of qingfeiPaidu (QFPD) capsule and lianhuaqingwen (LHQW) capsule nursing interventions in the treatment of patients with COVID-19. A total of 318 patients with COVID-19 were enrolled and randomly received QFPD (n = 106), LHQW (n = 106), and QFPD-LHQW (n = 106). The clinical characteristics of COVID-19, the total lung severity scores, and blood laboratory indices were recorded in each patient in each group before treatment and at the end of treatment.

The outcomes demonstrated that QFPD-LHQW group shortened the length of hospitalization, decreased C-reactive protein, creatine kinase, creatine kinase-myocardial band, lactate dehydrogenase, and blood urea nitrogen levels, and improved clinical symptoms, pulmonary inflammation, and prognosis. At the end of treatment, inflammation, immune function, circulating white blood cells, total lymphocyte count, and glutamic-oxaloacetic transaminase levels improved dramatically in 3 groups compared with baseline. All patients met the discharge criteria after 30-day treatment in 3 groups. Combined therapy of QFPD and LHQW demonstrated significant anti-inflammatory effects compared with those of only QFPD or LHQW in patients with mild and moderate COVID-19. The combined therapies may alleviate clinical symptoms of COVID-19 patients by improving inflammation and immune function.

Abbreviations: BUN = blood urea nitrogen, CK = creatine kinase, CK-MB = creatine kinase-myocardial band, COVID-19 = coronavirus disease-19, CRP = C-reactive protein, CT = computed tomography, GOT = glutamic-oxaloacetic transaminase, IL = interleukin, LDH = lactate dehydrogenase, LHQW = lianhuaqingwen, QFPD = qingfeiPaidu, QFPD-LHQW = QFPD combined with LHQW, TCM = Traditional Chinese Medicine, TLC = total lymphocyte count, TNF-α = tumor necrosis factor-alpha, WBCs = white blood cells.

Key words: coronavirus disease-19, lianhuaqingwen capsule, prognosis, pulmonary inflammation, qingfeiPaidu capsule

1. Introduction

The novel coronavirus disease-19 (COVID-19) has become a pandemic with a colossal global impact that is found to be highly aggressive.[1] COVID-19 along with severe acute respiratory distress syndrome and Middle East respiratory syndrome can lead to lung inflammation and severe damage in respiratory system.[2] Importantly, the mutations of COVID-19 may acquire resistance to vaccines and therapeutic antagonists, which further enhances the disease spread and aggravate symptoms.[3] The main symptoms of COVID-19 include myalgia, fever, and fatigue, with occasional hemoptysis, headaches, and septum production.[4] Most of patients (81%) with COVID-19 only show mild symptoms such as mild or no pneumonia, where a small portion of patients (19%) show a critical and severe status.[5]

Critically ill COVID-19 patients have relative high levels of proinflammatory including interleukin (IL)-1, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α).[6,7] Increasing the anti-inflammatory cytokines (IL-2, IL-15, and IL-10) levels could

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The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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indicate dysregulated inflammatory response and better clinical outcomes for patients with COVID-19.[8] In addition, patients with COVID-19 have less CD3 and CD4 interferon-gamma expression, and fewer CD4 and CD8 cells.[9] Furthermore, levels of immune cells CD16+, CD19+, and CD45+T cell-mediated inflammation may contribute to COVID-19-related diarrhea.[10–12] Therefore, analyzing the inflammation and immune function of COVID-19 patients received treatments is the focus of current research.

Traditional Chinese Medicine (TCM) plays a crucial role in the treatment of patients with COVID-19. QingfeiPaidu (QFPD) capsule decoction has various ingredients including *Herba Ephedrae, Radix Glycyrrhizae, Semen Armeniacae Amarum, Gypsum Fibrosum, Ramulus Cinnamomi, Rhizoma Alismatis, Polyporus Umbellatus, Rhizoma Atractylodis Macrocephalae, Poria, Radix Bupleuri, Radix Scutellariae, Rhizome Pinelliae Preparata, Rhizoma Zingiberis Recens, Radix Asteris, Flos Farfarae, Rhizoma Belamcandae, Herba Asari, Rhizoma Dioscoreae, Fructus Aurantii Immaturus, Pericarpium Citri Reticulatae*, and *Herba Pogostemonis*.[13] QFPD exacts antiviral and anti-inflammatory activity in the treatment of patients with COVID-19.[14] A previous study has found that QFPD has a therapeutic effect on patients with COVID-19 by regulating a complex molecular network with safety and efficacy.[15] Interestingly, QFPD may protect COVID-19 via targeting 8 specifically expressed drug-attacked nodes (Cdc20, Ido1, Ifng, Il10, Il6, Ptger4, Spi1, and TNF), which are related to the bacterial and viral responses, cytokine, immune system, signaling transduction, etc.[16] In addition, the combination of QFPD with Western medicine demonstrates significant anti-inflammatory effects compared with those of only Western medicine or QFPD in patients with mild and moderate COVID-19.[17] Furthermore, therapeutic efficacy of QFPD combined with antiviral drugs is identified in the treatment of COVID-19.[18] Therefore, it is worthy of exploring the QFPD-based combination therapy in the treatment of COVID-19.

Lianhuaqingwen (LHQW), a Chinese patent medicine contains 13 medicinal herbs (*Fructus Forsythiae, Flos Lonicerae Japonicae, Herba Ephedrae, Almond, Radix Isatidis, Fortunes Boss fern Rhizome, Herba Houttuyniae, Herba Pogostemonis, Rheum palmatum, Rhodiola rosea, Glycyrrhiza uralensis Fisch, Mentha haplocalyx Briq*, *and Gypsum Fibrosum*).[19] LHQW is clinically used to treat patients with common cold with wind-heat syndrome, symptoms of fever, and stagnation of the lung.[20] Currently, LHQW has been widely used, especially in treating cases of mild symptoms of COVID-19.[21] A study has provided evidence of the efficacy and safety of LHQW for the treatment of COVID-19.[22] In addition, Zhang et al[23] have indicated that some anti-inflammatory ingredients in LHQW probably modulate the inflammatory response in severely ill patients with COVID-19. LHQW can be used to treat COVID-19 by blocking binding of virus with receptor and inhibiting the cytokines storms, which has great potentials to treat COVID-19 in clinical.[24] Furthermore, Kyoto Encyclopedia of Genes and Genomes enrichment analysis indicates that the targets of LHQW are highly enriched to several immune response-related and inflammation-related pathways.[23] Moreover, Fan et al[25] have indicated that LHQW in combination with usual treatment may improve the clinical efficacy in patients with mild or moderate COVID-19 without increasing adverse events.

The purpose of this study was to evaluate the efficacy and safety of QFPD in combination with LHQW for the treatment of patients with COVID-19. This study also analyzed the efficacy of combined therapy of QFPD and LHQW nursing interventions in improving symptoms, biochemical indexes, inflammation, immune function, and prognosis in patients with COVID-19.

2. Materials and Methods

2.1. Study population

A total of 318 patients with COVID-19 were recruited from the department of Central sterile supply in Mudanjiang Medical University, Affiliated Hongqi Hospital from Mudanjiang between January 2019 and April 2019. The information of patients and laboratory indices during hospitalization was collected through hospital information system. The study was approved by the Ethics Committee of Mudanjiang Medical University (MDJHQH2020-C01-04). Written informed consent was obtained from each patient.

2.2. Inclusion and exclusion criteria

The inclusion criteria were performed as following:

(1) Patients diagnosed with COVID-19.
(2) The patients in three groups can be given circulatory support, effective oxygen therapy, and other support therapies.
(3) The measurement indicators should include the following indicators: clinical efficacy, relief time of main symptoms, hematology index, and adverse reactions.

The exclusion criteria were performed as follows:

(1) The patients were diagnosed with cancer.
(2) The patients were pregnant woman.
(3) COVID-19 patients involved other TCM prescriptions, TCM patent prescriptions, or acupuncture and moxibustion.

2.3. QFPD capsule and LHQW nursing interventions

QFPDs were provided by Jointown Pharmaceutical Group Co., Ltd (Shanghai, China). LHQW was purchased from Beijing Yiling Pharmaceutical Co., Ltd., specification: 6 g/bag) and received nursing intervention of QFPD (n = 106), LHQW (n = 106), and QFPD-LHQW (n = 106).

2.4. Patient evaluation

Clinical characteristics, blood laboratory tests, inflammatory factors, immune function, and chest computed tomography (CT) images were performed in each patient in Mudanjiang Medical University. Blood laboratory tests included white blood cells (WBCs), total lymphocyte count (TLC), glutamic-oxaloacetic transaminase, blood urea nitrogen (BUN), creatine kinase (CK), CK myocardial band, lactate dehydrogenase, C-reactive protein (CRP), IL-1, IL-6, IL-8, IL-17, TNF-α, IL-2, IL-15, IL-10, CD3+, CD4+, CD8+, CD16+, CD19+, and CD45+ T cells.

2.5. Measurement

Respiratory specimens were collected, and the severe acute respiratory distress syndrome CoV-2 virus nucleic acid test was detected by using real-time RT-PCR (Liferiver Bio-Tech, Shanghai, China). CT was performed using a 64-slice scanner (Aquilion CXL, Toshiba Medical, Japan). The CT score was accessed by using the total lung severity score with a 5-point scale, as described by previously.[26] Symptom score was calculated as described previously.[27]

2.6. Statistical analysis

The data are expressed as the mean ± SD or median and interquartile range or number and proportion. All statistical analyses were analyzed using SAS 9.4 software (SAS Institute, Cary,

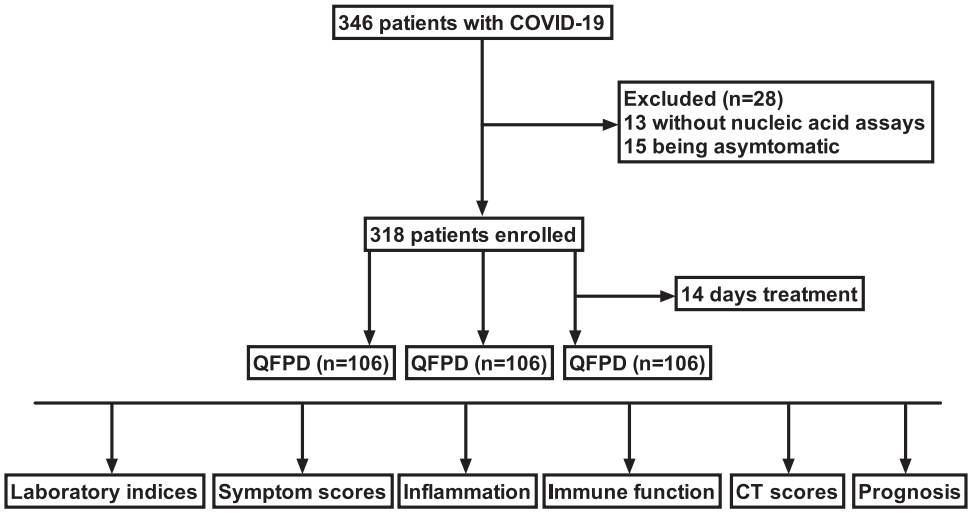

Figure 1. Study flowchart. COVID-19 = coronavirus disease-19, CT = chest computed tomography, QFPD = qingfeiPaidu.

NC). Data among three groups are analyzed by using Wilcoxon test, the independent sample *t* test, or the chi-square test. *P* value <.05 was considered statistically significant for all analyses.

3. Results

3.1. Study selection and characteristics of patients with COVID-19

A total of 318 patients were enrolled in Mudanjiang Medical University, Affiliated Hongqi Hospital, between May 2019 and December 2020. Flowchart for patient with COVID-19 is shown in Figure 1. A total of 13 patients without 24-hour nucleic acid assays by checking the nucleic acid detection system were excluded. Asymptomatic patients (n = 15) were also excluded from the study. Patients with COVID-19 were received treatment with QFPD (n = 106), LHQW (n = 106), and QFPD-LHQW (n = 106). Characteristics of patients with COVID-19 are summarized in Table 1. The most common symptoms were fever, fatigue, cough, and diarrhea in patients with COVID-19. All participants' past medical history was recorded in 3 groups. There was no significant difference in the baseline data of characteristics of patients among 3 groups ($P > .05$).

Table 1

Baseline clinical characteristics of patients with COVID-19.

Variables	QFPD	LHQW	QFPD-LHQW
Age (yr, $x \pm s$)	48.2 ± 10.5	50.2 ± 11.7	49.5 ± 10.8
Males (n [%])	52 (16.3)	51 (16.0)	53 (16.7)
Female (n [%])	54 (17.0)	55 (17.3)	53 (16.7)
Temperature (°C, $x \pm s$)	37.5 ± 0.9	37.2 ± 0.7	37.6 ± 0.8
Systolic blood pressure (mm Hg, $x \pm s$)	125.4 ± 13.7	122.8 ± 12.4	128.2 ± 15.5
Diastolic blood pressure (mm Hg, $x \pm s$)	82.0 ± 8.6	81.5 ± 9.4	82.6 ± 10.3
Heart rate (bpm, $x \pm s$)	88.8 ± 11.6	87.9 ± 12.4	88.3 ± 12.0
Respiratory rate (bpm, $x \pm s$)	20.7 ± 2.0	21.4 ± 2.6	21.5 ± 2.5
Symptoms, n (%)			
Fever	54 (50.9)	52 (49.1)	50 (47.2)
Fatigue	56 (52.8)	54 (50.9)	60 (56.6)
Coughing	58 (54.7)	56 (52.8)	53 (50.0)
Concomitant medications, n (%)			
Antiviral	93 (87.7)	89 (83.4)	91 (85.8)
Antibiotics	82 (77.4)	80 (75.5)	84 (79.2)
Immune modulators	54 (50.9)	58 (54.7)	55 (51.9)
Systemic corticosteroids	22 (20.1)	20 (18.9)	21 (19.8)

Data are shown as the median (interquartile range) or number (proportion).
COVID-19 = coronavirus disease-19, LHQW = lianhuaqingwen, QFPD = qingfeiPaidu.

3.2. The efficacy of the combined therapy of QFPD and LHQW in improving recovery rate in patients with COVID-19

The recovery rate of patients with COVID-19 was analyzed among 3 groups. As shown in Figure 2A, the mean recovery rate at day 14 was approximately equal among three groups. A significantly shorter median time to symptom recovery was observed in QFPD-LHQW group Figure 2B. QFPD-LHQW group showed a shorter time to the recovery of fever, coughing, fatigue, and pneumonia (Figure 2C-F).

3.3. The efficacy of combined therapy of QFPD and LHQW in improving biochemical indexes in patients with COVID-19

The combined treatment (QFPD-LHQW) group significantly decreased CRP, CK, lactate dehydrogenase, CK myocardial band, and BUN levels compared with QFPD and LHQW (Figure 3). As shown in Figure 4, a significant improvement of WBC, TLC, and glutamic-oxaloacetic transaminase was observed in QFPD-LHQW group compared with QFPD and LHQW group. At the end of treatment, we observed that CRP, CK, BUN, WBC, and TLC were in the proportion of normal values in QFPD-LHQW group. Only CRP, BUN, and WBC showed a significant improvement in QFPD group, and CRP, CK, BUN, WBC, and TLC showed a significant improvement in LHQW group.

3.4. The efficacy of combined therapy of QFPD and LHQW in improving clinical symptoms in patients with COVID-19

Improvements of clinical symptoms of patients diagnosed with COVID-19 were compared among 3 groups. There was no significant difference in the improvement rate of clinical symptoms among the 3 groups before treatment. The combined treatment (QFPD-LHQW) group had an advantage in the treatment of nausea, vomiting, fatigue, chest tightness, limb soreness, and shortness of breath over QFPD or LHQW alone. Fever, tired, anorexia, and diarrhea were found to be improved in 3 groups (Table 2). Symptom scores were also analyzed among 3 groups.

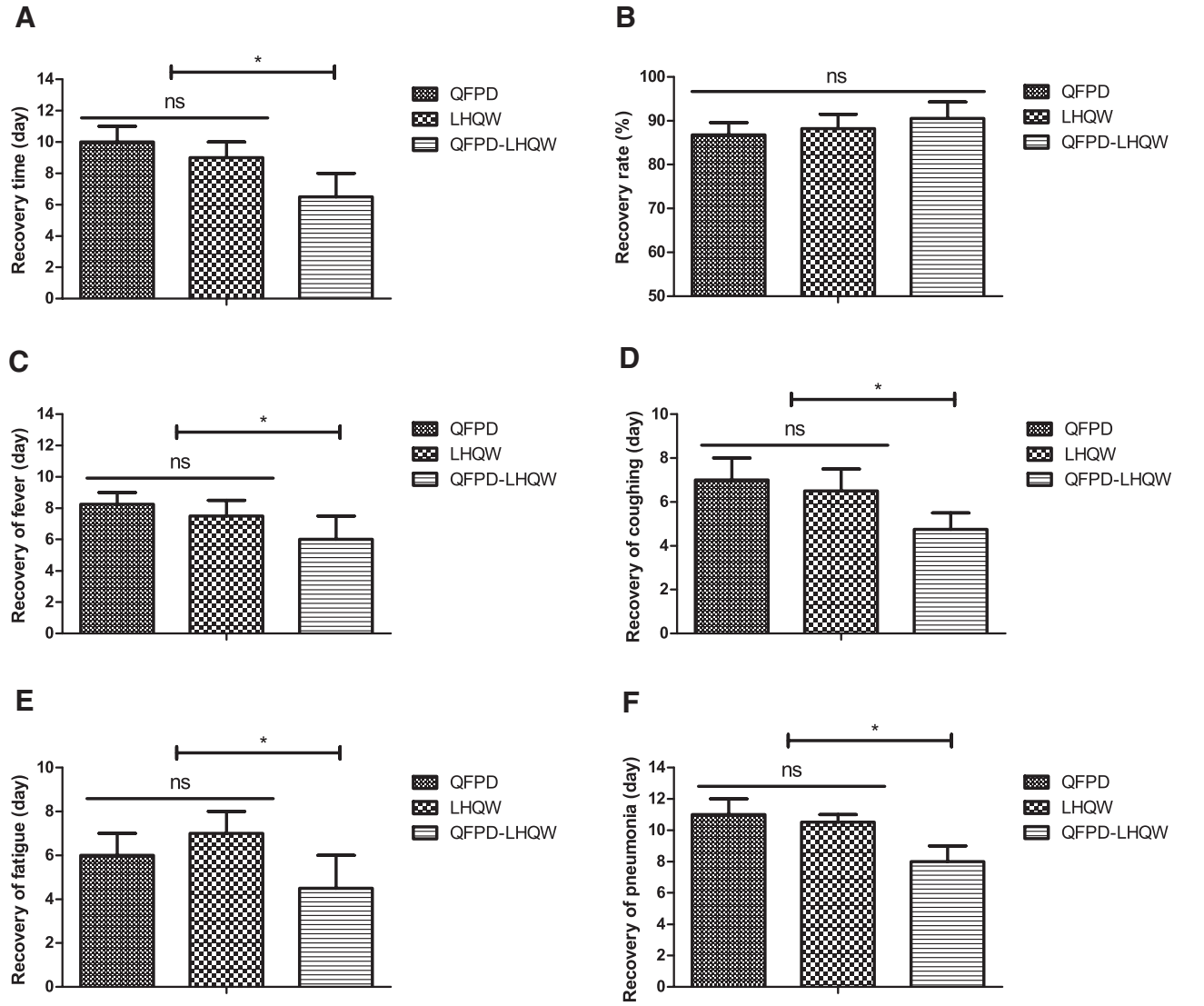

Figure 2. Combined therapy of QFPD and LHQW improves the rate of and the time to symptom recovery of patients with COVID-19. (A) Comparison of the rate of symptom recovery in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. Comparison of the recovery rate of fever (B), coughing (C), fatigue (D), and pneumonia (E) in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. *$P < .05$. COVID-19 = coronavirus disease-19, LHQW = lianhuaqingwen, ns = XXX, QFPD = qingfeiPaidu.

There was no significant difference among 3 groups at baseline. The combined treatment (QFPD-LHQW) dramatically decreased symptom scores compared with QFPD or LHQW alone. No differences were observed between QFPD and LHQW groups (Figure 5).

3.5. The efficacy of combined therapy of QFPD and LHQW in improving inflammation and immune function in patients with COVID-19

It is now known that an underlying inflammatory cytokine and alteration of expression of immune cells may be responsible for the COVID-19 progression.[28] Thus, inflammation and immune function in patients diagnosed with COVID-19 were compared among 3 groups. As shown in Table 3, combined therapy of QFPD and LHQW (QFPD-LHQW) inhibited IL-1, IL-6, IL-8, IL-17, and TNF-α, increased IL-2, IL-15, and IL-10 serum level compared with QFPD or LHQW alone. A significant increasing of CD3+, CD4+, CD8+, CD16+, CD19+, and CD45+T was observed in patients in QFPD-LHQW group.

3.6. The efficacy of combined therapy of QFPD and LHQW in improving clinical observational indices and CT scores in patients with COVID-19

At the end point of clinical trial, clinical observational indices and CT scores were compared among 3 groups. The length of hospitalization was also decreased in QFPD-LHQW group. There was no significant difference in the death rate among 3 groups (Table 4). Among groups, CT scores were significantly decreased in the QFPD-LHQW group compared with control groups (Figure 6).

3.7. Safety of combined therapy of QFPD and LHQW in patients with COVID-19

Adverse events of patients diagnosed with COVID-19 were observed among 3 groups. As shown in Table 5, the most common adverse events were rash, diarrhea, the elevated alanine aminotransferase levels, and aspartate aminotransferase levels. There were 25 patients who progressed to adverse events, including 8 cases in the QFPD group (7.5%), 6 cases in LHQW

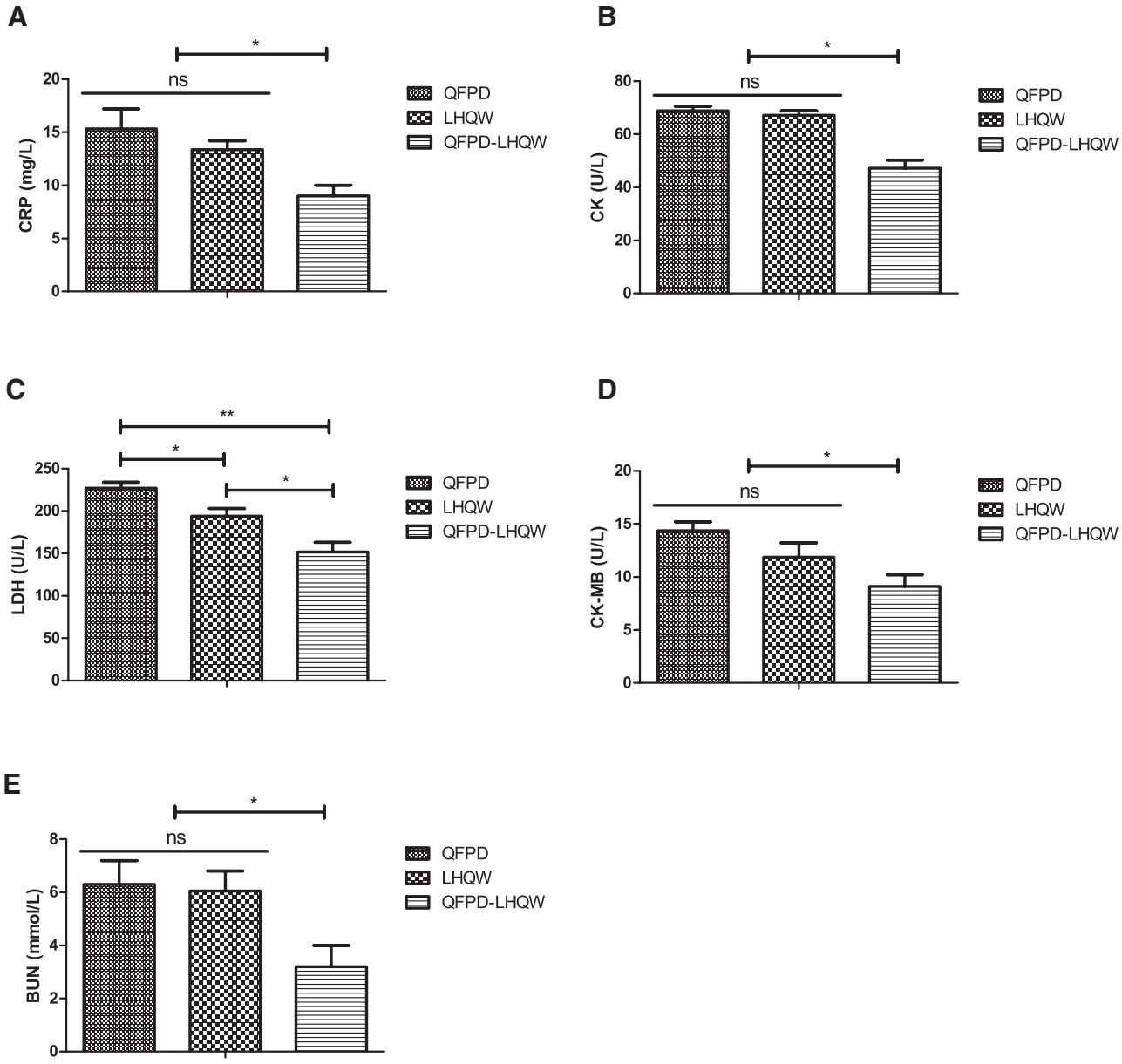

Figure 3. Combined therapy of QFPD and LHQW improves laboratory indices in patients with COVID-19. Comparison of the laboratory indices of CRP (A), CK (B), LDH (C), CK-MB (D), and BUN (E) in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. *$P < .05$. BUN = blood urea nitrogen, CK = creatine kinase, CK-MB = creatine kinase-myocardial band, COVID-19 = coronavirus disease-19, CRP = C-reactive protein, LDH = lactate dehydrogenase, LHQW = lianhuaqingwen, ns = XXX, QFPD = qingfeiPaidu.

group (5.7%), and 11 cases in QFPD-LHQW group (10.4%). No overall significant difference in the rate of adverse events was found among 3 groups ($P > .05$).

3.8. The efficacy of combined therapy of QFPD and LHQW in improving prognosis of COVID-19 patients

The prognosis of patients with COVID-19 who completed the trial was recorded among 3 groups. As shown in Table 6, there were 15 patients who progressed to a severe status, including 7 cases in the QFPD group (6.6%), 6 cases in LHQW group (5.7%), and 2 cases in QFPD-LHQW group (1.9%). There was significant statistical difference in the proportion of severe disease status among the 3 groups ($P < .05$). These data suggest that the combination of QFPD-LHQW has a potential advantage in improving prognosis of patients with COVID-19.

4. Discussion

TCM has been approved by the National Health Commission for the treatment of patients diagnosed with COVID-19.[29] The combination of TCM and Western medicine is seemed to more effective than either TCM or Western medicine alone for the treatment of COVID-19.[30,31] Studies have also showed that QFPD and LHQW present antiviral effect by inhibiting viral propagation and regulating immune function.[16,32] In this study, the combined therapy of QFPD and LHQW was investigated in patients with COVID-19. We have showed that QFPD in combination with LHQW had an advantage in improving the length of hospitalization, clinical symptoms, inflammation, and immune function over either QFPD or LHQW in patients with COVID-19, which provided a combination strategy to explore the effective treatment for COVID-19 patients.

QFPD is effective drug for patients with 92.09% effective rate through regulating immune status and preventing cytokine

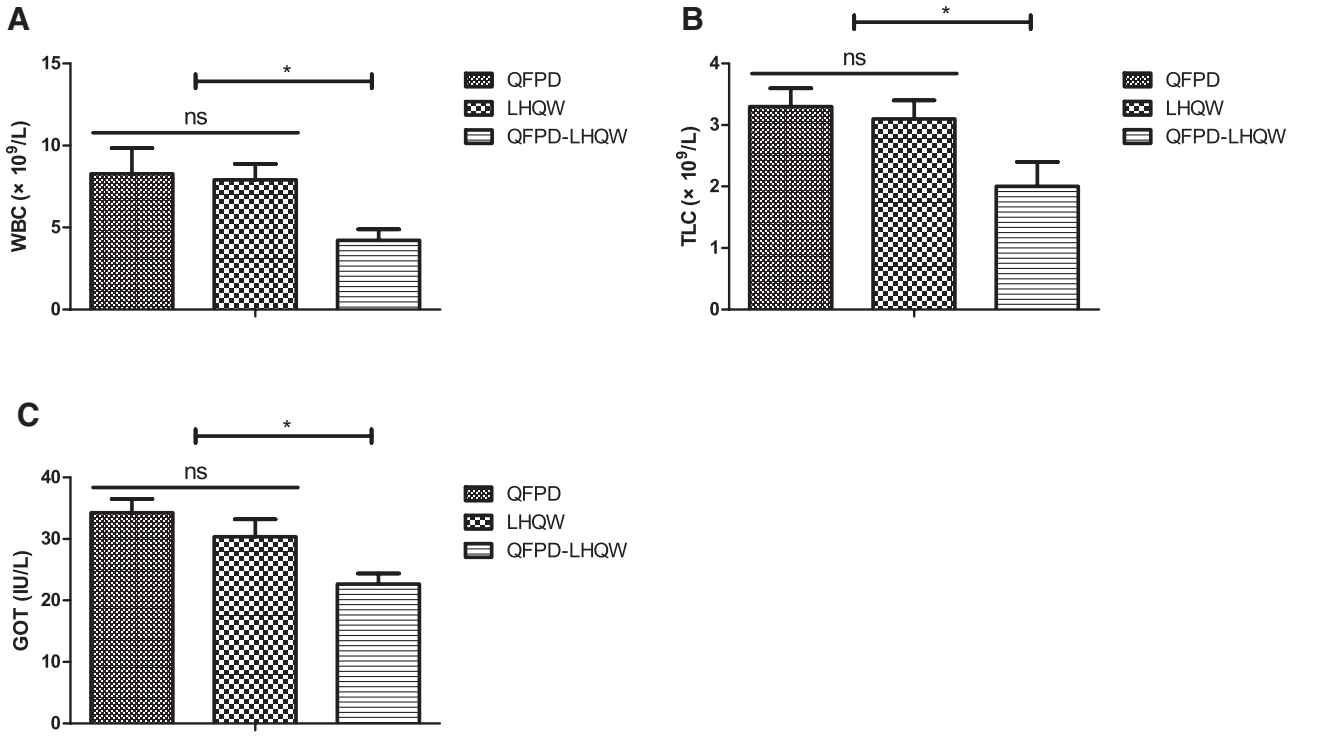

Figure 4. Combined therapy of QFPD and LHQW improves biochemical indexes in patients with COVID-19. Comparison of the changes of WBC (A), TLC (B), and GOT (C) in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. *$P < .05$. COVID-19 = coronavirus disease-19, GOT = glutamic-oxaloacetic transaminase, LHQW = lianhuaqingwen, ns = XXX, QFPD = qingfeiPaidu, TLC = total lymphocyte count, WBC = white blood cell.

Table 2

Improvements of clinical symptoms of patients diagnosed with COVID-19.

Term	QFPD	LHQW	QFPD-LHQW
Fever	96 (90.6%)	95 (89.6%)	100 (94.3%)
Diarrhoea	102 (96.2%)	103 (97.2%)	106 (100.0%)
Anorexia	86 (81.1%)	88 (83.0%)	96 (90.6%)
Nausea	95 (89.6%)	98 (92.5%)	106 (100.0%)*,#
Vomiting	97 (91.5%)	96 (90.6%)	104 (98.1%)*,#
Cough	94 (88.7%)	96 (90.6%)	104 (98.1%)*,#
Sore limbs	92 (86.7%)	92 (86.7%)	103 (97.2%)*,#
Tired	104 (98.1%)	105 (98.1%)	106 (100.0%)
Chest tightness	96 (90.6%)	97 (91.5%)	106 (100.0%)*,#
shortness of breath	96 (90.6%)	95 (89.6%)	103 (97.2%)*,#

Data are shown as number (%). *P* values are for chi-square test.

COVID-19 = coronavirus disease-19, LHQW = lianhuaqingwen, QFPD = qingfeiPaidu.

*$P < .05$ versus QFPD.

#$P < .05$ versus LHQW.

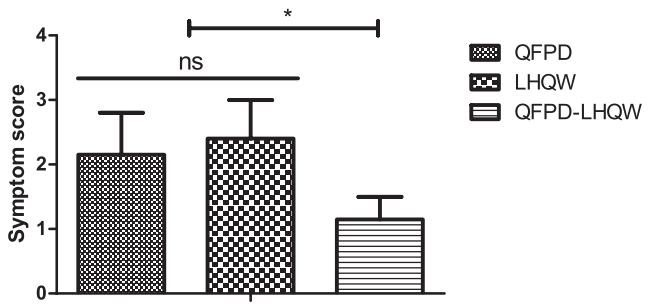

Figure 5. Combined therapy of QFPD and LHQW improves clinical symptoms in patients with COVID-19. Comparison of symptom scores in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. *$P < .05$. COVID-19 = coronavirus disease-19, LHQW = lianhuaqingwen, ns = XXX, QFPD = qingfeiPaidu.

storms.[33] A previous study demonstrated that the effect of QFPD is mainly to interfere with viral infection-related pathways and cancer-related pathways.[34] Here, we explored the clinical efficacy of QFPD and identified its anti-inflammatory and immunoregulatory function role in patients with COVID-19. Outcomes in the current study showed that QFPD markedly improved clinical symptoms including fever, coughing, fatigue, and pneumonia, decreased clinical observational indices and CT scores, reduced inflammation, and enhanced immune function in patients with COVID-19. Interestingly, based on the results of clinical patients, QFPD presented the therapeutic effects of QFPD against COVID-19, which may be attributed to the decreasing of inflammation and the increasing of immune function. Early treatment with QFPDD may serve as an effective strategy in controlling the epidemic, as early treatment with QFPDD is associated with favorable outcomes, including faster recovery, shorter time to viral shedding, and a shorter duration of hospital stay for patients with COVID-19.[15] Consistently, results in this study confirmed previous data and found that QFPD was safe and contributed to the prognosis of patients with COVID-19. The integration of clinical symptoms and laboratory indices indicated that QFPD may interfere with COVID-19 through multiple signaling pathways by multiple constituents.

LHQW has been proven effective for patients with COVID-19 and decreases the incidence of diarrhea.[35] Chen et al[21] have provided chemical and biochemical evidences for exploring molecular mechanisms of therapeutic effects of LHQW capsule for the treatment of COVID-19 patients. In our study, we observed that LHQW treatment significantly improved clinical symptoms, decreased inflammation, and enhanced immune function in patients with COVID-19, which was approximately equal to that in the QFPD group.

Table 3

Comparison of inflammation and immune function.

	QFPD	LHQW	QFPD-LHQW
IL-1 (pg/mL)	442.7 ± 145.6	411.0 ± 132.2	343.6 ± 97.4*,#
IL-6 (pg/mL)	78.2 ± 43.8	66.3 ± 32.5	34.5 ± 21.2*,#
IL-8 (pg/mL)	18.3 ± 9.1	16.5 ± 10.7	10.2 ± 6.8*,#
IL-17 (pg/mL)	214.5 ± 101.8	205.2 ± 112.3	170.5 ± 94.3*,#
TNF-α (pg/mL)	184.6 ± 86.4	172.5 ± 80.0	132.2 ± 73.5*,#
IL-2 (pg/mL)	8.2 ± 4.0	9.6 ± 5.0	12.6 ± 5.4*,#
IL-15 (pg/mL)	6.6 ± 2.8	7.3 ± 3.2	10.3 ± 3.8*,#
IL-10 (pg/mL)	7.2 ± 3.0	7.7 ± 3.6	11.6 ± 4.4*,#
CD3+ (%)	43.63 ± 9.97	41.50 ± 10.66	65.54 ± 15.84*,#
CD4+ (%)	32.56 ± 12.10	30.78 ± 11.05	40.24 ± 14.46*,#
CD8+ (%)	25.44 ± 9.26	23.52 ± 8.86	30.54 ± 10.42*,#
CD16+ (%)	20.50 ± 9.20	22.28 ± 8.48	28.93 ± 10.56*,#
CD19+ (%)	23.50 ± 7.85	21.28 ± 8.54	32.11 ± 11.25*,#
CD45+ (%)	27.46 ± 8.66	25.40 ± 9.58	34.67 ± 12.69*,#

P values were calculated using the Mann-Whitney *U* test or χ^2 test.
CD = XXX, IL = interleukin, LHQW = lianhuaqingwen, QFPD = qingfeiPaidu, TNF-α = tumor necrosis factor-alpha.
*$P < .05$ versus QFPD.
#$P < .05$ versus LHQW.

Table 4

Clinical observational indices.

Adverse events	QFPD	LHQW	QFPD-LHQW
The length of hospitalization	18.0 (14.0–23.0)	17.0 (13.0–22.0)	14.0 (10.0–19.0)*,#
Death (n [%])	1 (0.9)	1 (0.9)	1 (0.9)

Data are shown as the median (interquartile range) or number (proportion); *P* values are for Mann-Whitney test and chi-square test.
LHQW = lianhuaqingwen, QFPD = qingfeiPaidu.
*$P < .05$ versus QFPD.
#$P < .05$ versus LHQW.

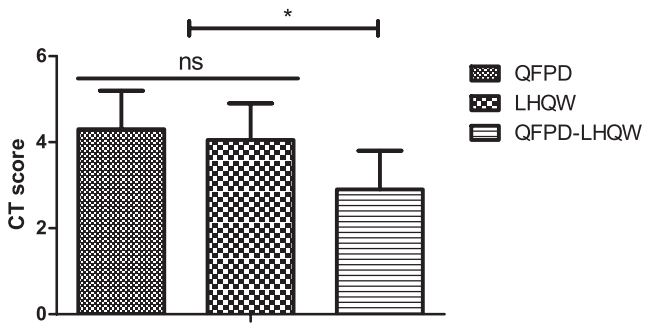

Figure 6. Combined therapy of QFPD and LHQW improves CT scores in patients with COVID-19. Comparison of CT scores in patients with COVID-19 among QFPD, LHQW, and QFPD-LHQW groups. *$P < .05$. COVID-19 = coronavirus disease-19, CT = chest computed tomography, LHQW = lianhuaqingwen, ns = XXX, QFPD = qingfeiPaidu.

Shen et al[36] have showed that LHQW significantly improved clinical symptoms of patients with COVID-19 and could be effectively applied alongside standard treatment of patients with moderate type COVID-19, which also increased lymphocyte counts, albumin and hemoglobin levels. However, single treatment with LHQW may be insufficient for patients with COVID-19. In addition, LHQW combined with conventional treatment seems to be more effective for patients with mild or ordinary COVID-19.[37] We observed the curative symptoms in patients in the QFPD-LHQW group, verifying

Table 5

Comparison of the adverse events in the full analysis set.

Adverse events	QFPD	LHQW	QFPD-LHQW
Total	45 (42.5%)	47 (44.3%)	66 (62.3%)
Abnormal liver function	10 (9.4%)	12 (11.3%)	15 (14.2%)
Renal dysfunction	6 (5.7%)	6 (5.7%)	9 (8.5%)
Headache	1 (0.9%)	1 (0.9%)	2 (1.9%)
Nausea	2 (1.9%)	3 (2.8%)	3 (2.8%)
Vomiting	2 (1.9%)	2 (1.9%)	4 (3.8%)
Diarrhea	10 (9.4%)	11 (10.4%)	14 (13.2%)
Loss of appetite	5 (4.7%)	4 (3.8%)	7 (6.6%)
Rash	9 (8.5%)	8 (7.5%)	12 (11.3%)

Data are shown as number (proportion).
LHQW = lianhuaqingwen, QFPD = qingfeiPaidu.

Table 6

Prognosis of diagnosed patients who completed the trial.

Adverse events	QFPD	LHQW	QFPD-LHQW
Medication time (d, [$x \pm s$]) (n [%])	45 (42.5)	47 (44.3)	66 (62.3)
Aggravation of disease (n [%])	10 (9.4)	12 (11.3)	15 (14.2)
Rate difference and bilateral 95% CI (LHQW-LHQW + HXZQ) (n [%])	6 (5.7)	6 (5.7)	9 (8.5)
Rate difference and bilateral 95% CI (LHQW-WM) (n [%])	1 (0.9)	1 (0.9)	2 (1.9)
Rate difference and bilateral 95% CI (LHQW + HXZQ-WM) (n [%])	2 (1.9)	3 (2.8)	3 (2.8)

Data are shown as the median (interquartile range) or number (proportion).
CI = XXX, HXZQ = XXX, LHQW = lianhuaqingwen, QFPD = qingfeiPaidu, WM = XXX.

the prediction of inflammation levels, CT scores and progression. Furthermore, Fang et al[32] have showed that the early combined usage of LHQW and Arbidol may accelerate recovery and improve the prognosis of patients with moderate COVID-19. Our data also showed the improved blood laboratory indices in the QFPD-LHQW group, which, to an extent, reflected the improvement of inflammation and immune function. Accordingly, in patients with COVID-19, QFPD combined with LHQW had similar side effects and showed better therapeutic effects and progression for patients with COVID-19. However, further multicenter, prospective studies with a larger sample size should be conducted to confirm the benefits of QFPD-LHQW.

5. Conclusions

Data in this study indicate that LHQW combined with LHQW can relieve the symptoms, decrease inflammation, and improve immune function. The combined therapy of QFPD and LHQW decreases median time to symptom recovery, shortens length of hospitalization, and had less impact on side effects in patients with COVID-19. The combined treatment QFPD-LHQW tends to mitigate the extent of clinical symptoms, clinical observational indices, CT scores, and progression for patients with COVID-19. Owing to the limited sample size, long-term randomized controlled trials with follow-up evaluations in a larger number of populations are required to confirm the present outcomes.

Author contribution

YL summarized experimental data, conducted data analysis, and wrote the article. ZD designed this study and revised the article. All authors read and approved the final article.

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