Efficacy Comparison of Azvudine and Qingfei Paidu Decoction as a Monotherapy and a Combination Therapy in the Treatment of Mild and Moderate COVID-19

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Abstract

Background and Objective: The treatment of COVID-19 has presented new challenges to global public health, and a large number of therapeutic drugs are employed for their treatment. However, there is limited data comparing the efficacy of available drugs with Traditional Chinese Medicine (TCM). Aim of this research was to compare the usefulness of monotherapies with Azvudine (FNC) or Qingfei Paidu Decoction (QFPD) or in combination with FNC and QFPD for mild and moderate COVID-19. **Methods:** A retrospective analysis was conducted on data from a public hospital in Zibo City, China, including confirmed mild and moderate COVID-19 cases. Patients were categorized into three treatment groups: (i) FNC monotherapy, (ii) QFPD monotherapy, and (iii) FNC + QFPD combination therapy. **Results:** A total of 300 cases were analyzed, with a mean age of 61.3 ± 7.18 years. Males (n=165, 55.0%) slightly outnumbered females (n=135, 45.0%). The shortest duration of negative nucleic acid conversion (NANC) was observed in the combination therapy group (8.58 ± 2.64 days, $p < 0.001$). Hospital stay was also significantly shorter (12.23 ± 3.52 days, $p < 0.001$). The combination therapy group showed the highest effective rates for pulmonary lesion absorption (97%) and clinical efficacy (95%), with a significant improvement in TCM symptom scores (2.24 ± 0.43, $p < 0.001$). **Conclusion:** FNC combined with QFPD demonstrated significant clinical efficacy in treating mild and moderate COVID-19, warranting further large-scale studies and clinical applications.

Keywords: Azvudine, "Qingfei Paidu Decoction (QFPD)", COVID-19, Clinical Efficacy, Traditional Chinese Medicine.

Introduction

"COVID-19" (caused by the SARS-CoV-2 virus) has had a significant impact on global health and economies since it first emerged.[1] In response to the pandemic's challenges, different regions have implemented various treatment strategies. However, a definitive cure for "COVID-19" is still lacking, and clinical management primarily focuses on alleviating symptoms and controlling the disease.[2]

In response to the COVID-19 epidemic situation, on July 25, 2022, the NMPA provided conditional approval to Azvudine (FNC) from China as the first oral antiviral drug. On August 9, the "Chinese National Health Commission and the National Administration of Traditional Chinese Medicine approved FNC for use in treating adult patients with common "COVID-19" as part of the "Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (Ninth Edition)." Additionally, on January 5, 2023, FNC was incorporated into the "Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (Tenth Edition)" for the treatment of "COVID-19" patients. Following these

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approvals in China, in February 2023, the Ministry of Health of the Russian Federation also approved the usage of FNC for treating COVID-19 patients, further recognizing its potential in managing the disease.

FNC, a thymidine analog reverse transcriptase inhibitor, which is metabolized intracellularly into active 5'-triphosphate was found to have a good efficacy in the treatment of HIV. Its property of viral replication inhibition results in slowing down of the virus spread within the host, provided a theoretical basis for its potential treatment of "COVID-19".[3] Therefore, the thymus was identified as an essential organ for FNC to combat the SARS-CoV-2 virus in rats. Tian *et al*.[4] revealed that FNC and its active phosphorylated triphosphate was enriched in the thymus and peripheral blood mononuclear cells, which implies an immune targeting profile. It also claimed that FNC can decrease viral loads, increase lymphocyte percentage, decrease inflammation and organ injury, restore the thymus, and reduce the ground-glass opacities. It was also discovered to be effective in preventing "COVID-19" virus mutant (Alpha, Beta, Delta, and Omicron). Finally, FNC was safe even at a dosage of 5 mg a day for every human comprising the group with no significant adverse effects observed and so the adverse event rate was not significantly different between the FNC group and the placebo group.

Nevertheless, the antiviral therapy alone may not sufficiently address the immune inflammatory response and severe respiratory damages that COVID-19 virus causes due to the virus' unique nature. Currently, FNC has been included in a few COVID-19 treatment protocols despite the paucity of evidence on its efficacy and safety.[5] FNC demonstrated only antiviral effects, primarily, but may lack other clinical symptoms improvement.[6] Furthermore, mutations in the SARS-CoV-2 virus variants were reported which may make them less susceptible to existing drugs. In summary, treating COVID-19 is complex and challenging, requiring a multifaceted approach to achieve better clinical outcomes.

In China, Qingfei Paidu Decoction (QFPD), a traditional Chinese herbal formula, has a long history of usage in both the prevention and treatment of infectious diseases, especially during pandemics. QFPD demonstrated antiviral, immune-enhancing, and heat-clearing effects via multiple pathways, and has high efficacy in the prevention and treatment of infectious diseases such as SARS and H1N1.[7] QFPD may exert its therapeutic effects against "COVID-19" by inhibiting viral replication, modulating inflammatory responses, and improving immune function.[6] QFPD plays a role in balancing immunity and reducing inflammation by regulating several proteins co-ex pressed with ACE2, in addition to targeting ribosomal proteins, which are essential for viral replication to inhibit viral mRNA translation and protein's interaction with viral proteins to fight against viruses.[8]

Integrating Traditional Chinese Medicine (TCM) and allopathic medicine is a distinctive feature of China's treatment protocols in controlling COVID-19 more effectively. According to the study conducted by Jiang *et al*.[5], the employment of Huoxiang Zhengqi Pill and Lianhua Qingwen Granule alongside the western antiviral medication modestly eased COVID-19 clinical manifestations, decreased the proportion involving antibacterial and antiviral medications, and enhanced the clinical outcome. These clinical outcomes and fast recovery highlight the need to encourage the use of TCM as a healing method to treat patients. Nevertheless, research providing evidence of the effectiveness of FNC in combination with QFPD in the management of "COVID-19" is still scarce. The rationale of this study was to compare the effectiveness of FNC in combination with QFPD with the monotherapy of each drug, which may offer new treatment possibilities for "COVID-19." Another aspect of the study focused on the safety aspect of these medicines.

Methods

Study Design and Patients

The study included 300 "COVID-19" patients admitted between November 2022 and June 2023 at Fourth People's Hospital of Zibo City, China, a designated "COVID-19" treatment facility. The diagnosis and clinical classification followed the "Protocol for Diagnosis and Treatment of 2019 Novel Coronavirus Pneumonia".[9] It should, for simplicity's sake, be referred to as ''the Protocol'' in the rest of the article.

The diagnostic criteria for confirmed "COVID-19" cases required suspected cases to meet both of the following etiological or serological conditions: (1) a positive result from the real-time "fluorescence-based reverse transcriptase-polymerase chain reaction (RT-PCR)" assay for novel coronavirus nucleic acid in respiratory or blood samples; (2) "the viral genome sequence from respiratory or blood specimens being highly similar to that of the known novel coronavirus". The guidelines for Traditional Chinese Medicine (TCM) therapeutic interventions were based on the "*Guidelines for Diagnosis and Treatment of Common Diseases in Internal Medicine of Traditional Chinese Medicine*".[10]

The inclusion criteria for this research: (1) Patients having "COVID-19" diagnosis via RT-PCR; (2) Categorized as mild or moderate COVID-19 as per the Chinese COVID-19 guidelines; (3) Male or female patients aged 18 years and above; (4) Patients treated with either FNC monotherapy or QFPD monotherapy or combination therapy of FNC+QFPD during hospitalization. "The exclusion criteria were: (1) before rash and skin lesions data are missing."

(2) "Patient died in the course of hospitalization or patients who had more than one hospitalization."

(3) Categorized as severe or critical COVID-19 as per the Chinese COVID-19 guidelines.

(4) Severe liver, kidney, or other organ diseases.

(5) Severe respiratory failure requiring mechanical ventilation.

(6) Pregnant or lactating women.
(7) History of allergy or intolerance to the study drugs.

Treatment

The care provided within the Protocol was conducted in accordance to Western medicine treatment as adherent to the principles of the local nursing care. It consisted of bed rest, oxygen treatment, anti-pyretic, antibiotic besides any other additional support if required.
The three groups in our study were treated as described below;

i) FNC monotherapy group: Received oral administration of FNC (Henan Genuine Biotech Co., Ltd., specification: 1 mg*35 tablets), 5 mg once daily, for no more than 14 days.
ii) QFPD monotherapy group: Treated with QFPD Decoction (prescribed by a registered TCM physician) for 14 days. The formula includes: 5g honey-fried Ephedra, 5g honey-fried Licorice, 5g stir-fried bitter Apricot Kernel, 30g Gypsum, 5g Cinnamon Twig, 5g salt-processed Alisma, 5g Polyporus, 10g White Atractylodes Rhizome, 10g Poria, 8g Northern Bupleurum, 3g Scutellaria, 5g prepared Pinellia, 5g fresh Ginger, 9g honey-fried Purple Aster, 5g honey-fried Coltsfoot Flower, 6g Scrophularia, 5g Belamcanda, 5g Atractylodes, 3g Agastache, 5g Turmeric, 5g aged Tangerine Peel, 10g Chinese Yam, 15g Honeysuckle, and 6g Plantain Seed. The decoction was prepared in the hospital's TCM pharmacy and administered warm after meals in the morning and evening.
iii) Combination therapy group: Received both FNC and QFPD Decoction with the same dosages and administration methods as the FNC group and QFPD group described above.

"Clinical Characteristics and Outcome Indicators"

A quantitative cross-sectional data was used in this study since data was collected retrospectively from electronically maintained medical records. Demographic data, disease severity based on ICD-10, TCM symptom scores and temperature on admission, presence of cough. Western medicine treatments such as antibiotic medications during hospital stay.

Adverse Reactions Monitoring

The occurrence of nausea, diarrhea, vomiting, and stomach pain were observed for 28 days or until death.

Statistical Methods

All statistical analyses were made with the Statistical Package for Social Sciences (SPSS) 29.0 software. Normality test was conducted to the defined numerical variables, where numerical variables that adhered to normality were reported as mean ± standard deviation (x ± sd). One-way "ANOVA" was used to compare continuous variables across the three treatment groups, as it is effective in determining whether there are significant differences among multiple groups. Pairwise comparisons were conducted using the Least Significant Difference (LSD-t) method, which is suitable for identifying specific group differences when the overall ANOVA result is significant. For categorical variables, comparisons were made using either the Chi-square test or the Kruskal-Wallis test, depending on data distribution. These methods were chosen because the Chi-square test is ideal for analyzing differences in proportions among categorical variables, while the Kruskal-Wallis test is appropriate for comparing non-normally distributed data across multiple groups. The proportion of cases (%) showing improvement was also determined. A p-value of <0.05 was considered statistically significant, ensuring that the results are unlikely to be due to random chance.

Results

After excluding the incomplete data, number of cases used in the data analysis were 300. It was also noticeable that there were no significant differences among the three groups with respect to demographic features at the beginning of the study (p > 0.05) as presented in Table 1.

Table 1: Socio-Demographic Characteristics of Participants and Comparison among the Treatment Groups.

Characteristics	Overall Participants (N=300)	Treatment Groups			F/χ^2	p-value
		FNC (N=100)	QFPD (N=100)	FNC + QFPD (N=100)		
Age (Mean ± SD, years)[1]	61.3±7.18	60.8±7.36	62.0±7.03	61.2±7.16	0.766	0.466
Gender						
Male[2] (n)	165	58	46	61	5.091	0.078
Female[2] (n)	135	42	54	39		
Clinical Classification of COVID-19						
Mild[2] (n)	64	19	22	23	0.516	0.772
Moderate[2] (n)	236	81	78	77		
TCM symptom scores on admission[1]	14.95±3.22	15.16±3.32	14.97±3.09	14.71±3.25	0.492	0.612
During Hospital Stay						
Fever on admission[2] (n)	241	76	82	83	1.814	0.404
Presence of cough[2] (n)	246	82	81	83	0.136	0.934
Antibiotic course[2] (n)	153	47	48	58	2.961	0.228
Comorbidities						
Diabetes Mellitus[2] (n)	52	20	16	16	0.744	0.711
Chronic Kidney Disease[2] (n)	3	1	1	1	0.431	1.000
Hypertension[2] (n)	111	40	30	41	3.175	0.224
Heart Disease[2] (n)	27	7	10	10	1.348	0.540
Chronic Liver Disease[2] (n)	9	2	3	4	0.744	0.912

Statistical Methods

For ANOVA[1], use F value, and for Chi-square/Fisher's exact test[2] use χ^2

The outcome indicators for the efficacy measures are tabulated in Table 2. Most of the indicators were statistically different except for one that is the improvement in pulmonary lesion absorption, which did not show any significant difference among all the 3 treatment groups. For adverse drug reaction, no significant difference was detected.

Table 2: Comparison of Outcome Indicators for Efficacy and Adverse Reactions among the Treatment Groups.

Outcome Indicators	Treatment Groups			F/χ^2	p-value
	FNC (100)	QFPD (100)	FNC + QFPD (100)		
Nucleic acid negative conversion (NANC, days)[1]	9.89±2.54	13.27±2.88	8.58±2.64	80.901	**<0.001**
Chest CT improvement (days)[1]	10.85±2.60	9.43±3.32	14.51±2.82	74.934	**<0.001**
Length of Hospital stay (days)[1]	14.06±3.58	16.37±2.97	12.23±3.52	37.992	**<0.001**
Effective Rate based on Pulmonary Lesion Absorption[Ψ]	76%	73%	97%	24.977	**<0.001**
Basic Absorption[2] (n)	42	43	62	10.164	**0.006**
Improvement[2] (n)	34	30	35	0.925	0.630
No Change[2] (n)	17	15	2	16.139	**<0.001**
Deterioration[2] (n)	7	12	1	11.060	**0.004**
Effective Rate based on Clinical Efficacy Evaluation[ξ]	90%	83%	95%	7.626	**0.022**
Significantly effective[2] (n)	57	64	83	14.899	**<0.001**
Effective[2] (n)	33	19	12	7.224	**0.031**
Ineffective[2] (n)	10	17	5	7.169	**0.033**
TCM symptom scores after treatment[1]	6.48±1.10	5.99±1.21	2.24±0.43	566.239	**<0.001**
Total no. Adverse Drug Reactions[2] (n)	12	7	4	6.303	0.644
Nausea[2] (n)	6	5	2	2.091	0.453
Diarrhea[2] (n)	2	1	1	0.507	1.000
Vomiting[2] (n)	3	1	1	1.627	0.625
Stomach Pain[2] (n)	1	0	0	2.007	1.000

Statistical Methods

For ANOVA[1], use F value, and for Chi-square/ Fisher's exact test[2] use χ^2

"Bold values refer to the results of $p < 0.05$, which are considered statistical significant in our study."

[Ψ]The effective rate of lesion absorption was calculated as [basic absorption + improvement]/total cases × 100%.

(i) *basic absorption* (lesion area reduced by over 70% inclusive),(ii) *improvement* (lesion area reduced by 30%-70% inclusive),(iii) *no change* (lesion area changed within 30%), and (iv) *deterioration* (lesion area increased by over 30% inclusive).

[ξ]The effective rate of clinical efficacy was calculated as [significantly effective + effective]/total cases × 100%. Clinical efficacy evaluation based on "Criteria for Diagnosis and Efficacy of Internal Medicine Diseases in TCM" were categorized into (i) significantly effective when clinical symptoms and signs were significantly alleviated or disappeared, with a score reduction of over 70%; (ii) effective when clinical symptoms and signs were somewhat improved, with a score reduction of 30 -70% and (iii) ineffective in which no improvement in clinical symptoms and signs were seen, with a score reduction of less than 30%.

TCM Symptom Scores were calculated centered on "Guiding Principles for Clinical Research of New Chinese Medicines." (please refer to Appendix). The comparison of pre- and post-treatment TCM Symptoms Scores are presented in Table 3. All the three groups had demonstrated a huge effect size.

Table 3: Comparison of TCM Symptoms Scores Pre- and Post-Treatment.

Group (n)	Before Treatment	After Treatment	p-value	Cohen's D Effect Size	Effect size
FNC (100)	15.16±3.32	6.48±1.10	**<0.001**	3.510	Huge
QFPD (100)	14.97±3.09	5.99±1.21	**<0.001**	3.827	Huge
FNC + QFPD (100)	14.71±3.25	2.24±0.43	**<0.001**	5.379	Huge

Statistical Methods

Paired t-test to compare pre- and post-treatment TCM symptoms mean scores. Bold values are considered statistical significant in our study.

Comparison within the treatment groups by the severity of COVID-19 i.e. between mild and moderate cases in terms the outcome indicators are tabulated in Table 4. Significant differences were seen in length of hospital stay for mild vs. moderate cases in QFPD monotherapy and combination therapy. In FNC group, improvement in pulmonary lesion absorption was observed for mild vs. moderate cases.

Table 4: Comparison of Outcome Indicators between Mild and Moderate Cases.

Outcome Indicators	Treatment Groups								
	FNC			QFPD			FNC + QFPD		
	Mild (N=19)	Moderate (N=81)	T/χ^2	Mild (N=22)	Moderate (N=78)	T/χ^2	Mild (N=23)	Moderate (N=77)	T/χ^2
Nucleic acid negative conversion (NANC, days)[1]	9.74±2.73	9.93±2.51	0.900	12.86±2.64	13.38±2.95	0.196	8.39±2.61	8.64±2.67	0.329
Chest CT improvement (days)[1]	9.76±2.51	11.09±2.58	0.014	13.14±1.46	14.90±3.00	2.752	9.50±2.65	9.41±3.51	0.200
Length of Hospital stay (days)[1]	14.89±3.33	13.86±3.62	0.085	15.05±1.89	16.74±3.12	**4.416**	12.57±4.34	12.13±3.26	**4.022**
TCM symptom scores after treatment[1]	6.37±1.12	6.51±1.10	0.086	5.77±1.19	6.05±1.22	0.007	2.17±0.39	2.26±0.44	3.400
Improvement in Pulmonary Lesion Absorption[£,2]	11(57.9%)	65 (80.2%)	4.216	14 (63.6%)	59 (75.6%)	1.255	23(100%)	75 (97.4%)	0.610
Effective Clinical Efficacy Evaluation[¥,2]	18 (94.7%)	66 (81.5%)	2.012	18 (81.8%)	69 (88.5%)	0.670	22(95.7%)	75 (97.4%)	0.186

Statistical Methods

[1]For T-test, refer to T value, and [2] for Chi-square test, refer to χ^2

Bold T or "χ^2 values refer to the results of $p < 0.05$"which are considered statistical significant in our study.

[£]Improvement in pulmonary lesion absorption, Chi-square test was performed using the number of cases with ["Basic Absorption" + "improvement"] vs. number of ["Deterioration" + " no change"]

[¥]For effective Clinical Efficacy Evaluation, Chi-square test was performed using the number of cases with ["significantly effective" + "effective"] vs. number of "ineffective cases"

Discussion

COVID-19 pandemic had significant on the morbidity and mortality in addition to socioeconomic impacts despite the many efforts countries all over the world had taken including movement restrictions, developing different treatment protocols to mitigate the severe consequences of the disease and finding an optimal treatment. In China, FNC was the local oral antiviral agent. Fourth People's Hospital of Zibo City, China, is a designated hospital for "COVID-19" and data collected retrospectively from November 2022 to June 2023 to study the efficacy of treatment modalities employed in this hospital, which included FNC and QFPD among mild and moderate cases of COVID-19. In comparing the general characteristics of the patients from all the three treatment groups, no significant differences were founded. However, the outcome indicators for the efficacy measures in the treatment groups were significantly different except for one that is the improvement in pulmonary lesion absorption, which did not show any significant difference.

Interestingly, QFPD monotherapy group had longer NANC and span of hospital while the chest CT improvement days were shorter as compared to FNC monotherapy and FNC+QFPD combination therapy groups. The effective rates based on pulmonary lesion absorption and clinical efficacy evaluation were the highest for FNC+QFPD combination therapy group. The mean TCM symptoms scores after treatment was the lowest for this combination therapy group. Overall, the outcome indicators for efficacy were favoring FNC+QFPD combination therapy group, with one exception i.e. chest CT improvement days that favored QFPD monotherapy. Our findings align with those of Wang *et al.*[11], who reported that the combination of QFPD with Western medicine produced greater anti-inflammatory effects compared to Western medicine alone in patients with mild to moderate "COVID-19." Additionally, our study also observed a significant reduction in hospital stay duration. Notably, QFPD combined with western medicine were reported to decrease NANC, combination of QFPD with Western medicine reduced hospital stay duration, improved overall TCM symptom scores, accelerated recovery, and enhanced laboratory indexes.[12]

On the other hand, in our study, QFPD monotherapy did not significantly demonstrate improvements seen in the combination therapy as compared to FNC monotherapy except for improvements in chest CT days and TCM symptom scores after treatment. Our results support the synergistic effect of FNC and QFPD decoction in treating COVID-19.[13] The likely reasons are: firstly, FNC inhibits the replication of the novel coronavirus, reducing viral proliferation in host cells and lessening viral damage to host cells. Secondly, QFPD decoction contains various natural components with anti-inflammatory, antioxidant, and other bioactive properties, helping to reduce inflammation and boost immunity.[14] The combined use of these two treatments may achieve better therapeutic outcomes through multiple pathways.

Surprisingly, the mean NANC days in our study for FNC group was longer compared to other studies, ranges from 2.60 to 6.24 days.[15,16] Conversely, Gao *et al.*[17] reported longer NANC in FNC group, 10 and 16.5 days, respectively, which were comparable to the NANC means observed in our study. One possible explanation for such variation is that there were different timings when this test is conducted, such as symptom onset to NANC, diagnosis to NANC or drug administration to NANC.[18] Yu *et al.*[19] study found no difference in chest CT improvement between Western medicine alone and its combination with QFPD. However, the combination therapy significantly reduced inflammation, strengthened immunity, shortened hospitalization and nucleic acid negative time, leading to better clinical outcomes. Pan *et al.*[20] found that signs of improvement in chest "CT scans" typically appeared around 14 days after the onset of initial symptoms. This was also observed in our study for the combination therapy of FNC + QFPD, although the other two groups showed improvements in chest CT scans earlier.

The length of hospital stay in our study ranged from 8 to 20

days, the shortest was observed in the combination therapy group while the longest stay in QFPD monotherapy. Zhou *et al*.[21] reported a median of 10.5 (5-23) days for FNC, which are comparable to our results for FNC monotherapy group i.e. 14.06±3.58 days. Yu *et al*.[19] reported shorter length of hospital stay in the combination therapy of Western Medicine + QFPD compared to Western Medicine monotherapy, similar to the observation in our study.

The effective rates based on pulmonary lesion absorption and clinical efficacy evaluation were the highest, 97% and 95%, respectively in the combination therapy group while the lowest rates observed in QFPD monotherapy were 73% and 83%, respectively. In comparing the QFPD monotherapy and combination therapy, χ^2=20.745, $p < 0.001$ for the effective rates of pulmonary lesion absorption while χ^2=6.1798, $p = 0.0129$ for the effective rates of clinical efficacy evaluation, supporting the significantly higher rates for QFPD+FNC combination therapy. Improvements in TCM symptom scores after treatment were seen in all the treatment group with the largest observed in the combination therapy.

Tian *et al*.[4] reported the effectiveness of FNC in reducing in-hospital mortality across the overall population (OR 0.375, 95% CI 0.225-0.623, $P < 0.001$), the severe subgroup (OR 0.239, 95% CI 0.107-0.535, $P < 0.001$), and the critical subgroup (OR 0.091, 95% CI 0.011-0.769, $P < 0.028$). In our study significant improvement was observed for the effective rates of pulmonary lesion absorption (OR 0.339, 95% CI 0.117-0.979, $P = 0.0456$) in FNC monotherapy in comparing mild vs. moderate cases. Furthermore, van Leusden *et al*.[22] reported 87.5% improvement in non-severe patients and 61.1% in severe patients upon completing two courses of QFPD. In contrary, the improvement observed in our study was lower in mild cases as compared to moderate cases in QFPD monotherapy group.

Adverse Reactions

The incidence of adverse reactions was 12% in the FNC group, 7% in the QFPD group, and 4% in the combination therapy group. No statistically significant differences were observed in the incidence of adverse reactions among the three groups ($\chi^2 = 6.303$, $P > 0.05$). Safiabadi Tali *et al*.[23] reported that out of 317 patients who received FNC, 47 individuals (14.83%) experienced a total of 75 adverse reactions, including symptoms such as nausea, diarrhea, and vomiting, which aligns with the findings in our study. Approximately, 13.33% had nervous system related adverse reactions including dizziness, lethargy, and tinnitus.[24]

Overall, this study provides valuable clinical experience for the treatment of "COVID-19" and offers insights for future research. Firstly, it is essential to further refine the optimal combination regimen of FNC and QFPD, including dosage and duration. Secondly, in-depth exploration of the treatment mechanisms through multidisciplinary approaches such as molecular biology and immunology is warranted. Additionally, increasing the sample size and conducting multi-center, large-scale randomized controlled trials are necessary to validate the treatment's efficacy and safety. It will provide a more comprehensive and objective assessment of the feasibility and effectiveness of FNC combined with QFPD treatment.

Conclusion

FNC combined with QFPD therapy has demonstrated significant benefits for "COVID-19" patients, including reduced NANC and hospital stay, enhanced pulmonary lesion absorption, improved clinical efficacy, and better TCM symptom scores. The treatment of mild and moderate "COVID-19" cases with this combination therapy was found effective, emphasizing an integrative approach could be the most effective strategy.

Data Availability Statement

All datasets presented in this study are included in the article/supplementary material.

Ethical Statement

This study was conducted in accordance with the "Declaration of Helsinki, and ethical approval was obtained from the Research Ethics Committee of the Fourth People's Hospital of Zibo in China" and the "AIMST University" Ethics Committee (AUHEC).

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APPENDIX 1: EFFICACY OUTCOME INDICATORS OF THE TREATMENT

1. Nucleic Acid Negative Conversion Time: Defined as the time (days) taken from the first positive nucleic acid test to convert to the first negative nucleic acid test in two consecutive tests.

2. Time to Chest CT Improvement: Defined as the time (days) taken to show improvement in chest CT scans following treatment.

3. Length of Hospital Stay: Discharge criteria included body temperature maintained below 37.3°C for more than 3 days; improvement of respiratory symptoms; significant absorption of acute exudative lesions on chest CT; and two consecutive negative viral nucleic acid tests (sampling interval of more than 24 hours).

4. Pulmonary Lesion Absorption: Lesion absorption of chest CT was evaluated based on the "Guidelines for Radiologic Diagnosis of COVID-19".[21] Lesion absorption was categorized as: (i) basic absorption (lesion area reduced by over 70% inclusive), ii) improvement (lesion area reduced by 30%-70% inclusive), iii) no change (lesion area changed within 30%), and exacerbation (lesion area increased by over 30% inclusive). The effective rate of lesion absorption was calculated as [basic absorption + improvement]/total cases × 100%.

5. Clinical Efficacy Evaluation: TCM symptom scores were determined based on the "Guiding Principles for Clinical Research of New Chinese Medicines" (Zheng et al, 2002), as shown below. Efficacy evaluation according to the "Criteria for Diagnosis and Efficacy of Internal Medicine Diseases in TCM" can be divided into 3 categories as following; (i) significantly effective when clinical symptoms and signs were significantly alleviated or disappeared, with a score reduction of over 70%; (ii) effective when clinical symptoms and signs were somewhat improved, with a score reduction of 30 -70% and (iii) ineffective in which no improvement in clinical symptoms and signs were seen, with a score reduction of less than 30%. The effective rate of clinical efficacy was calculated as [significantly effective + effective]/total cases × 100%.

TCM Sypmtom Score Scale.

Symptom	Normal (0 points)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Fever	<37.3°C	37.3°C-38.0°C	38.1°C-39.0°C	>39.0°C
Cough	None	Occasional	Paroxysmal	Frequent
Fatigue	None	Occasionally tired	Easily fatigued	General weakness and lethargy
Headache	None	Occasionally	Frequent	Persistent
Runny nose	None	Occasionally	Frequent, with little discharge	Frequent, large amount
Sore throat	None	Mild	Painful swallowing	Severe pain and burning sensation
Phlegm	None	Little phlegm	Coughing up phlegm	Rattling in the throat
Nasal congestion	None	Occasional	Frequent	Mouth breathing
Diarrhea	None	Soft stool, not well-formed, <3 times a day	Watery stool 3-5 times a day	Watery stool >5 times a day