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A COMPARATIVE RETROSPECTIVE STUDY ON THE EFFICACY OF AZVUDINE AND LIANHUA QINGWEN CAPSULES COMBINATION IN THE TREATMENT OF COVID-19 PATIENTS IN CHINA

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The purpose of this retrospective study is to compare and analyse the efficacy of Azvudine (FNC) and Lianhua Qingwen (LHQW) capsules in the treatment of mild and moderate cases of coronavirus infection in China. The combined approach is used to evaluate treatment effectiveness in COVID-19 patients by analysing clinical data and comparing treatment outcomes. The methodology includes an analysis of clinical data and a comparison of treatment outcomes using FNC, LHQW, and their combination (FNC + LHQW) for the treatment of COVID-19 in 307 patients undergoing inpatient care at a hospital in Zibo, China. According to the findings, combination therapy proved effective in treating COVID-19 by integrating antiviral and supportive treatment, compared to monotherapy. The complementary action of these agents facilitates a more rapid reduction in overall inflammation, alleviates symptoms, and shortens recovery time. The combination treatment group demonstrated superior laboratory outcomes, including reduced C-reactive protein (CRP) levels as a primary inflammation marker and a decrease in the duration of negative nucleic acid conversion to 7 days. Moreover, the improvement time of chest computed tomography (CT) was significantly shortened in the combined treatment group ($p < 0.001$). The total length of hospitalisation was reduced to 12 days, compared to 14 days in the monotherapy group. These parameters are the principal criteria for evaluating the efficacy of each treatment group. The combination of these drugs is particularly notable, as other treatment methods typically focus on a single aspect of the disease. The study provides valuable insights into the role of combination therapy in clinical practice with regard to COVID-19 management

***Keywords**: Azvudine, Lianhua Qingwen capsules, COVID-19, supportive therapy, respiratory infections, traditional Chinese medicine, acute respiratory failure, therapeutic potential*

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1. Introduction

The urgency of this study stems from COVID-19's ongoing global impact on healthcare, economies, and social structures. Despite numerous treatment regimens, effective, safe, and cost-efficient therapies are still needed to enable rapid recovery and reduce healthcare strain. Initially thought to be seasonal pneumonia, COVID-19's possible zoonotic origin was linked to animal-based food and seafood markets. Its symptoms, similar to other respiratory illnesses, complicated identification, particularly during winter when pneumonia is common [1]. Following 44 cases of atypical pneumonia, the need for thorough analysis became clear. The COVID-19 pandemic, caused by SARS-CoV-2, has disrupted public health and global economies. Studies by C.A. Pollard et al. [2] emphasized the pandemic's impact, showing COVID-19 induces an inflammatory immune response and exacerbates comorbidities. While genetic and age factors influencing disease severity are known, comorbidities and genetic variability require further exploration, with no clinical protocols initially proposed.

The urgency for effective antiviral therapy grew as the virus rapidly spread, overwhelming healthcare systems globally and driving the need for treatments to mitigate the pandemic's impact [3]. Research into COVID-19 treatments continues, with further studies needed [4]. FNC, a synthetic agent derived from cytidine, inhibits viral RNA synthesis, preventing replication. Upon oral administration, FNC is phosphorylated intracellularly to its active form, which is incorporated into the viral RNA, terminating the chain and halting genome synthesis. Unlike other nucleoside analogues, FNC accumulates in highly infected pulmonary tissues, maximizing local antiviral efficacy while minimizing systemic toxicity. FNC has minimal activity against host DNA or RNA polymerases, reducing off-target effects. It also contributes to immune homeostasis by limiting T lymphocyte activation, helping prevent the cytokine storm in severe COVID-19 cases. Clinical data show FNC reduces viral load within days, improving outcomes, particularly in moderate COVID-19 infections.

Preclinical studies by [5] demonstrate FNC's effectiveness in reducing viral load and improving outcomes. However, clinical evidence on combining traditional medicines with modern treatments remains limited. Traditional Chinese medicine, including phytotherapy, acupuncture, and dietary therapy, aims to enhance the body's natural abilities [6].

Lianhua Qingwen (LHQW), a traditional Chinese medicine, has been proposed for COVID-19 treatment. It may improve oxygenation, reduce lung inflammation, and alleviate symptoms like fever, cough, and shortness of breath [7]. LHQW's pharmacological effects are primarily through immunomodulatory, anti-inflammatory, and antioxidative properties rather than direct antiviral action. Bioactive compounds like forsythoside A, luteolin, and hesperidin target various host and viral pathways. LHQW inhibits NF-κB activation and reduces pro-inflammatory cytokines (IL-6, IL-1β, TNF-α), attenuating the inflammatory response contributing to lung injury in COVID-19.

LHQW also modulates ACE2 expression and the viral 3CL protease (3CLpro), potentially affecting SARS-CoV-2 entry and replication. In vitro and in vivo studies show LHQW reduces reactive oxygen species and aids mucociliary clearance through expectorant and antipyretic effects. While it does not eliminate the virus, LHQW alleviates respiratory symptoms, restores oxygenation, and accelerates radiological recovery. When combined with antiviral agents like FNC, LHQW enhances therapeutic benefits.

Research on LHQW's components in relation to SARS-CoV-2 3CLpro and ACE2 could improve treatment evaluations [8]. LHQW supports immune function and may reduce disease progression in COVID-19 patients [9], complementing FNC's antiviral action. Studies by [6] and [10] reviewed traditional Chinese medicine's role in symptom reduction but lacked standardized integration protocols with Western medicine. Its widespread use outside Asia remains limited, with few large-scale trials. The combination of FNC and LHQW offers advantages over other treatments. FNC inhibits viral replication, while LHQW addresses inflammation and symptoms. According to [10], combining LHQW with antivirals may mitigate side effects and improve patient well-being. Studies by [11] suggest that their synergy accelerates nucleic acid conversion and improves radiological outcomes. Compared to standard antiviral treatments like molnupiravir and Paxlovid, FNC showed superior results in reducing nucleic acid conversion time and enhancing lung function in severe COVID-19 cases. In the FNC group, the time to negative conversion ranged from 6 to 21 days, averaging 14.11 ± 5.74 days [12]. While FNC shows advantages, comparisons with other treatments, especially regarding potential side effects like molnupiravir's hepatotoxicity, require further large-scale studies.

The purpose of this study is to evaluate the synergistic potential of *FNC* and *LHQW* in terms of their effectiveness in treating coronavirus infection, to investigate the mechanisms of action of the drugs, their impact on immune response regulation, and their role in symptom relief based on available clinical data. The study objectives are to assess their impact on the duration of hospitalisation and the speed of recovery and to analyse the safety profile of these drugs for further application.

2. Planning (methodology) of research

The study protocol describing the different stages of the research is presented in the following flow chart (Fig. 1).

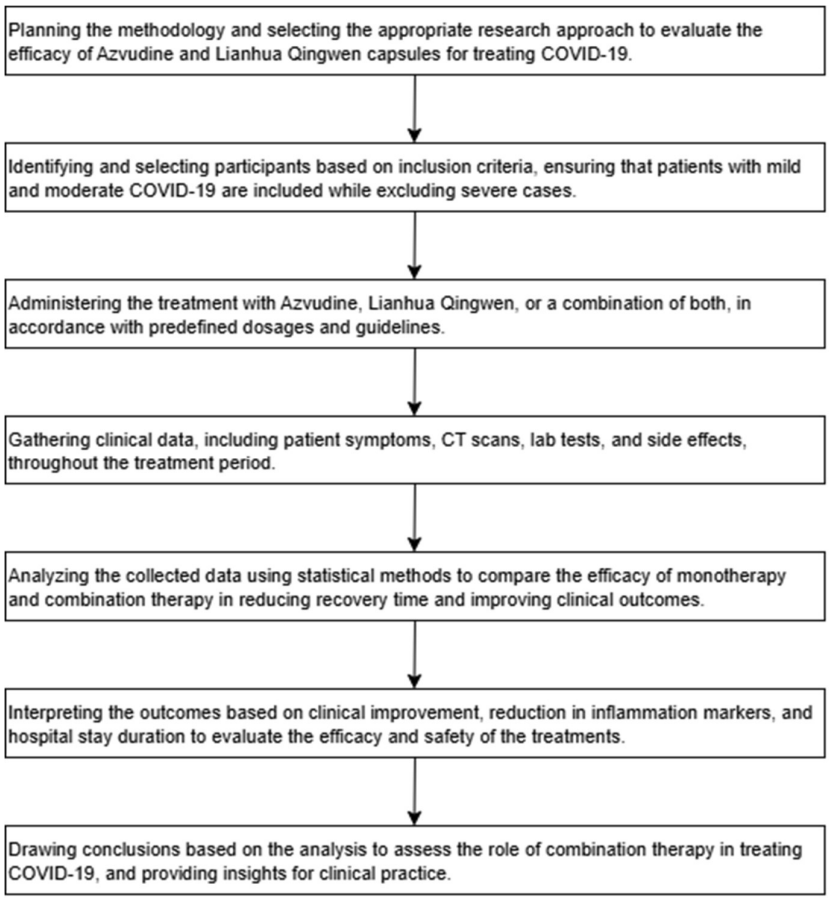

Fig. 1. Study protocol

3. Materials and methods

The study was conducted at a hospital in Zibo, China, from November 2022 to June 2023, treating COVID-19 patients in the infectious diseases department. A total of 307 patients participated, with an average age of 65 ± 16.9 years; 57.3% were men and 42.7% were women. Comorbid conditions included hypertension (35.8%), diabetes (16.6%), and cardiovascular diseases (9.1%), which were considered in the analysis.

Inclusion criteria:

1. Confirmed COVID-19 diagnosis via RT-PCR (Sansure Biotech kit, sensitivity threshold 500 RNA copies/mL).

2. Mild or moderate COVID-19 cases as per Chinese guidelines.

3. Treatment with FNC, LHQW, or their combination.

Exclusion criteria:

1. Severe or critical cases.

2. Pregnant or breastfeeding women.

3. Incomplete medical records.

Patients were divided into three groups: FNC monotherapy, LHQW monotherapy, and FNC + LHQW combination. Treatment doses were as follows: FNC (5 mg daily for 7–14 days), LHQW (4 capsules three times daily for 7–14 days), and the combination (5 mg FNC + 4 capsules LHQW daily for 7–14 days). Data were analyzed for mild and moderate COVID-19 cases.

The study assessed effectiveness using primary parameters such as chest CT scan improvement, blood analysis for CRP, ferritin, D-dimer, clinical symptom improvement, side effect frequency, and RT-PCR-determined NANC duration. Clinical symptoms were monitored through cough severity (0-10 points), body temperature (measured every 6 hours), and a fatigue scale (1–5 points). Comorbidities were also analyzed for their impact on outcomes.

Data analysis was performed using SPSS (version 29.0). Categorical variables were analyzed with chi-square or Fisher's exact test, and continuous variables with ANOVA or the Kruskal-Wallis test. A p-value of <0.05 was considered significant. Ethical approval was obtained from the Research Ethics Committee of Zibo's Fourth People's Hospital and the AIMST University Ethics Committee (AUHEC), October 24, 2022, No. 6859-C.

3. Results

A total of 307 confirmed COVID-19 cases were retrospectively analyzed. Patients were treated under the supervision of infectious disease specialists and pulmonologists for 7–14 days, with clinical and laboratory assessments on days 7 and 14. Therapy adjustments, including antibiotics, were made if no improvement was observed by day 7. Baseline examinations, laboratory tests, and CT scans were conducted at enrolment, and adverse events were monitored throughout. During days 1–3, patients received FNC (5 mg/day), LHQW (four capsules thrice daily), or a combination of both. By day 3, body temperature normalized in 40% (combination group), 30% (LHQW), and 25% (FNC). Fever reduction averaged 1.5°C in the FNC and combination groups, while LHQW primarily improved cough and inflammation.

By days 4–7, clinical improvement was observed in 79.6% (combination), 73% (FNC), and 69.2% (LHQW). Oxygen saturation normalized fastest in the combination group. Follow-up CT scans showed reduced ground-glass opacity in 40% (combination), 28% (FNC), and 25% (LHQW). CRP reductions were highest in the combination group (45%). Mild nausea was reported in a few cases. Statistical analysis included chi-square and Kruskal-Wallis tests.

From days 8–14, 65% of patients regained full respiratory function. Lung lesion regression was highest in the combination group (79.6%), followed by FNC (60%) and LHQW (50%). CT scans on day 14 confirmed lesion reduction in 85% (combination), 65% (FNC), and 55% (LHQW), with CRP levels dropping to 5.1 mg/L in the combination group. LHQW patients showed symptom resolution, though 10% reported mild residual effects. FNC cases required antibiotics in 5% of instances. Adverse events, such as headache and nausea, were mild and manageable, with no therapy discontinuation [6]. Average hospitalization was 14 days, reduced to 12 in the combination group. This group demonstrated faster radiological and clinical recovery, suggesting synergistic effects of FNC and LHQW. Shorter hospital stays improve resource use and reduce transmission risk during outbreaks.

Nucleic acid conversion occurred significantly faster in the combination therapy group, as confirmed by RT-PCR. Elderly patients, particularly those with hypertension (35.8%), diabetes (16.6%), and cardiovascular disease (9.1%), experienced more severe symptoms, longer hospital stays, and required more intensive care. Chi-square analysis ($p < 0.05$) confirmed that these comorbidities significantly worsened outcomes due to systemic inflammation and weakened immunity. The patient distribution across groups was balanced, supporting study validity. Adverse reaction rates were low: 5% (FNC), 3.88% (combination), and 5.77% (LHQW) (Table 2).

Common reactions, such as gastrointestinal disturbances and headaches, were not clinically significant. No serious adverse effects requiring additional interventions were observed during treatment. The results highlight the absence of any perceivable antagonism between *FNC* and *LHQW*, and a positive safety profile supporting the recommendation for drug use. Focusing on patients with a mild course of the disease limits the generalizability of the conclusions for this specific subtype of patients, as they experience fewer complications, lower levels of the inflammatory response, and do not require intensive therapy. The prevalence of comorbid conditions, such as hypertension (27.7%) and diabetes (12.3%), was lower in this group, which influences treatment effectiveness (Table 3).

Since immune response and therapeutic outcomes may vary in patients with more severe disease, these findings cannot be fully extrapolated to all patient categories. The categorization explained variations in clinical and laboratory values. The average age of patients with mild COVID-19 was 52 years, with fewer cases of diabetes, hypertension, and other comorbidities compared to those with moderate disease. This reflects the lower prevalence of mild cases among patients with severe chronic respiratory and cardiovascular conditions. Common symptoms, such as fever and cough, were less prevalent in mild cases, indicating less pronounced symptoms. This data helped determine the most effective therapeutic approaches for mild COVID-19 patients. In moderate cases, the systemic inflammatory process intensifies, with fever (81.4%) and cough (85.1%) being more common. Differences in comorbidities between mild and moderate cases highlight the role of comorbid conditions in complicating disease progression. Hypertension (38.0%) and diabetes (14.8%) were the most prevalent comorbidities in moderate cases, contributing to a more complicated disease course (Table 4).

Table 1

Clinical outcomes of the three study groups (ANOVA test; $p < 0.001$)

Outcome	FNC group	LHQW group	Combination group	*p*-value
Duration of NANC (days)	9.86 ± 2.54	11.49 ± 2.15	7.85 ± 2.52	<0.001*
Time to chest CT improvement (days)	11.14 ± 2.64	12.56 ± 1.81	9.47 ± 3.27	<0.001*
Duration of hospital stay (days)	13.43 ± 2.74	14.80 ± 2.65	12.23 ± 3.53	<0.001*

Source: compiled by the authors.

Table 2

Demographic, clinical, laboratory characteristics, and treatment history of the registered COVID-19 patients (ANOVA, Fisher's exact, chi-square, Kruskal-Wallis tests; $p > 0.05$)

Parameters	Total (n = 307)	FNC (n = 100)	FNC+LHQW (n = 103)	LHQW (n = 104)	p-value
Age (median, range, years)	60.5 (18–92)	61.7 (18–91)	57.8 (21–86)	61.9 (18–92)	0.181
Female	137 (44.6%)	42 (42.0%)	40 (38.8%)	55 (52.9%)	0.103
Male	170 (55.4%)	58 (58.0%)	63 (61.2%)	49 (47.1%)	0.264
Hypertension	110 (35.8%)	39 (39.0%)	41 (39.8%)	30 (28.8%)	0.187
Diabetes	51 (16.6%)	19 (19.0%)	16 (15.5%)	16 (15.4%)	0.737
Chronic liver disease	9 (2.9%)	2 (2.0%)	4 (3.9%)	3 (2.9%)	0.844
Chronic kidney disease	3 (0.98%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1.000
Chronic obstructive lung disease	4 (1.3%)	1 (1.0%)	1 (1.0%)	2 (1.9%)	1.000
Coronary heart disease	28 (9.1%)	7 (7.0%)	10 (9.7%)	11 (10.6%)	0.653
Others	81 (26.4%)	23 (23.0%)	28 (27.2%)	30 (28.8%)	0.622
Fever	244 (79.5%)	76 (76.0%)	86 (83.5%)	82 (78.8%)	0.409
Cough	252 (82.1%)	82 (82.0%)	85 (82.5%)	85 (81.7%)	0.989
Fatigue	136 (44.3%)	44 (44.0%)	45 (43.7%)	47 (45.2%)	0.974
Headache	59 (19.2%)	20 (20.0%)	20 (19.4%)	19 (18.3%)	0.950
Dizziness	31 (10.1%)	10 (10.0%)	11 (10.7%)	10 (9.6%)	0.967
Nasal discharge	35 (11.4%)	11 (11.0%)	12 (11.7%)	12 (11.5%)	0.988
Sore throat	68 (22.1%)	23 (23.0%)	21 (20.4%)	24 (23.1%)	0.870
Nasal congestion	28 (9.1%)	9 (9.0%)	10 (9.7%)	9 (8.7%)	0.965
Expectoration	212 (69.1%)	69 (69.0%)	71 (68.9%)	72 (69.2%)	0.999
Diarrhea	10 (0.3%)	4 (4.0%)	3 (2.9%)	3 (2.9%)	0.852
WBC×10^9/L	5.28 (3.790–6.69)	5.00 (3.705–6.685)	5.01 (3.68–6.60)	5.484 (4.14–6.72)	0.379
CRP (mg/L)	8.41 (2.95–23.95)	9.69 (2.91–32.55)	7.98 (2.81–19.78)	7.95 (3.63–25.88)	0.465
ESR (mm/h)	40.00 (26.00–48.00)	42.50(29.00–49.00)	39.00 (23.00–48.00)	39.00 (26.00–45.00)	0.230
D-dimer (mg/ml)	0.41 (0.310–0.650)	0.42 (0.293–0.688)	0.38 (0.310–0.510)	0.445 (0.310–0.830)	0.345
GPT (IU/L)	21.00 (15.000–31.000)	23.00 (16.000–29.000)	22.00 (15.000–32.000)	19.00 (14.000–29.000)	0.144
GOT (IU/L)	21.00 (16.000–30.000)	20.00 (16.000–30.000)	24.00 (17.000–30.000)	19.00 (14.250–28.000)	0.069
CRE (μmol/L)	64.10 (53.200–74.900)	64.35 (52.975–75.575)	65.00 (54.300–77.600)	62.30 (53.000–69.550)	0.236

Note: WBC – white blood cell; ESR – erythrocyte sedimentation rate; GPT – glutamate pyruvate transaminase; GOT – glutamate oxaloacetate transaminase; CRE – serum creatinine. Source: compiled by the authors.

To assess the impact of treatment on laboratory parameters, the Wilcoxon signed-rank test was performed for paired pre- and post-treatment comparisons across the three groups (Table 5). All groups demonstrated statistically significant improvements (p<0.001) in WBC count, *CRP*, ESR, and D-dimer levels post-treatment. The findings suggest that the combination of *FNC* and *LHQW* may offer enhanced anti-inflammatory effects compared to monotherapy.

WBC levels increased post-treatment in all groups, remaining within the normal range (4–9 × 10^9/L), with a significant increase ($p < 0.001$), indicating immune response activation. Combination therapy helped prevent leukopenia. CRP levels were highest in the FNC group (9.69 mg/L), followed by LHQW (7.95 mg/L) and combination therapy (7.97 mg/L), with LHQW contributing to CRP reduction due to its anti-inflammatory effects. ESR decreased in all groups, with the combination group showing the best result (17.00 mm/h). The combination group also had the most effective reduction in D-dimer (0.38 mg/mL), indicating lower thrombosis risk. PCT levels remained normal in all groups. Liver enzyme levels were normal in all groups, confirming drug safety [13]. FNC effectively reduced viral load and improved clinical symptoms within 5 days. However, its effect on systemic inflammation is limited, necessitating additional anti-inflammatory therapy. Treatment duration was longer in the FNC monotherapy group (15 days) than in the combination group (12 days). FNC does not significantly alleviate secondary symptoms like cough or sore throat.

LHQW, a traditional Chinese medicine with extracts from over 10 medicinal plants, works through multiple therapeutic pathways. Key components like forsythia, luteolin, and hesperidin target organs like the lungs, reducing inflammation by inhibiting NF-κB and cytokines (IL-6, IL-1β, TNF-α), neutralizing free radi-

cals, and providing expectorant, anti-inflammatory, and antipyretic effects. It reduces CRP and ESR, benefiting moderate COVID-19 patients. While it doesn't inhibit viral replication, it complements antiviral therapy without interaction risk, though its efficacy is limited at high viral loads, especially in severe cases [6, 10].

The combination of FNC and LHQW offers a synergistic effect by blocking viral replication, controlling inflammation, and improving symptoms, reducing illness duration. Radiological improvement took an average of 9 days in the combination group, compared to 11 days (FNC) and 13 days (LHQW) monotherapy. The combination group had the shortest hospitalization duration (12 days) and the best laboratory results. However, precise dosing is challenging in resource-limited settings or during epidemics.

Table 3

Baseline demographic, clinical, and laboratory characteristics of patients with mild COVID-19 (ANOVA, Fisher's exact, chi-square, Kruskal-Wallis tests; $p > 0.05$)

Parameters	Total group ($n = 65$)	FNC ($n = 19$)	LHQW ($n = 23$)	LHQW+FNC ($n = 23$)	p-value
Age (years)	52 (34–62)	56 (29–74)	48 (29–56)	52 (38–61)	0.475
Female	27 (41.5%)	8 (42.1%)	9 (39.1%)	10 (43.5%)	0.955
Male	38 (58.5%)	11 (57.9%)	14 (60.9%)	13 (56.5%)	0.993
Hypertension	18 (27.7%)	6 (31.6%)	6 (26.1%)	6 (26.1%)	0.904
Diabetes	8 (12.3%)	3 (15.8%)	1 (4.3%)	4 (17.4%)	0.347
Chronic obstructive lung disease	1 (1.5%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.292
Coronary heart disease	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0.396
Fever	47 (72.3%)	15 (78.9%)	17 (73.9%)	15 (65.2%)	0.599
Cough	46 (70.8%)	13 (68.4%)	17 (73.9%)	16 (69.6%)	0.915
Fatigue	19 (29.2%)	6 (31.6%)	7 (30.4%)	6 (26.1%)	0.915
WBC×10^9/L	5.39 (3.74–6.57)	4.24 (3.34–6.06)	5.68 (5.15–8.01)	5.25 (3.36–6.16)	0.052
CRP (mg/L)	5.01 (3.47–9.55)	5.00 (3.53–21.40)	4.70 (2.70–8.42)	5.29 (3.40–9.02)	0.697
ESR (mm/h)	15.00 (9.00–25.00)	14.00 (7.00–20.00)	19.00 (12.00–30.00)	15.00 (7.00–20.00)	0.305
D-dimer (mg/ml)	0.36 (0.29–0.53)	0.42 (0.29–0.55)	0.38 (0.29–0.62)	0.34 (0.25–0.42)	0.587

Source: compiled by the authors.

Table 4

Baseline demographic, clinical, and laboratory characteristics of patients with moderate COVID-19 (ANOVA, Fisher's exact, chi-square, Kruskal-Wallis tests; $p > 0.05$)

Parameter	Total ($n = 242$)	FNC ($n = 81$)	FNC+LHQW ($n = 80$)	LHQW ($n = 81$)	p-value
Age (median, range, years)	60.5 (18–92)	61.7 (18–91)	57.8 (21–86)	61.9 (18–92)	0.181
Female	137 (43.0%)	42 (42.0%)	40 (38.8%)	55 (52.9%)	0.103
Male	170 (57.0%)	58 (58.0%)	63 (61.2%)	49 (47.1%)	0.134
Hypertension	92 (38.0%)	33 (40.7%)	35 (43.8%)	24 (29.6%)	0.150
Diabetes	43 (14.8%)	16 (19.8%)	15 (18.8%)	12 (14.8%)	0.686
Chronic obstructive lung disease	3 (1.2%)	0 (0.0%)	1 (1.39%)	2 (2.5%)	0.365
Coronary heart disease	27 (11.2%)	7 (8.6%)	10 (12.5%)	10 (12.3%)	0.678
Fever	197 (81.4%)	60 (74.1%)	70 (87.5%)	67 (82.7%)	0.085
Cough	206 (85.1%)	69 (85.2%)	68 (97.1%)	69 (85.2%)	0.999
Fatigue	117 (48.3%)	38 (46.9%)	38 (47.5%)	41 (50.6%)	0.879
WBC ×10^9 /L	5.22 (3.78–6.71)	5.04 (3.74–6.98)	4.99 (3.71–6.76)	5.37 (3.84–6.51)	0.961
CRP (mg/L)	10.55 (2.88–27.40)	11.20 (2.81–33.28)	9.66 (2.79–23.56)	11.20 (4.00–27.90)	0.644
ESR (mm/h)	43.00 (32.00–49.00)	44.00 (37.50–51.50)	43.00 (32.00–48.75)	41.00 (32.00–47.00)	0.076
D-dimer (mg/ml)	0.43 (0.32–0.75)	0.45 (0.31–0.85)	0.40 (0.32–0.56)	0.45 (0.31–1.07)	0.527

Source: compiled by the authors.

Table 5

Test results for laboratory parameters before and after treatment (Wilcoxon test, $p < 0.05$)

Outcome indicators	Before treatment			After treatment		
	FNC	FNC+LHQW	LHQW	FNC	FNC+LHQW	LHQW
WBC×10^9/L	5.00 (3.71–6.69)	5.01 (3.68–6.60)	5.49 (4.14–6.72)	6.61 (5.59–7.66)	7.04 (6.30–8.07)	6.78 (5.21–7.95)
CRP (mg/L)	9.69 (2.91–32.55)	7.98 (2.81–19.78)	7.95 (3.63–28.89)	5.02 (2.95–6.84)	3.11 (1.98–5.58)	3.50 (1.86–5.40)
ESR (mm/h)	42.50 (29.00–49.00)	39.00 (23.00–48.00)	39.00 (26.00–45.00)	25.00 (16.00–35.00)	22.00 (15.00–27.00)	26.50.00 (19.25–33.00)
D-dimer (mg/ml)	0.42 (0.3–0.69)	0.38 (0.31–0.51)	0.45 (0.31–0.83)	0.29 (0.17–0.48)	0.18 (0.09–0.31)	0.36 (0.27–0.49)
p-value	<0.001		–	<0.001		–

Source: compiled by the authors.

Survival distribution was evaluated using the Kaplan-Meier method, with intergroup differences assessed by the Log-rank test. The Cox proportional hazards regression model analyzed independent risk factors for chest CT improvement and hospital stay, calculating hazard ratios (HR) and 95% confidence intervals (CI). Statistical analysis was performed using SPSS 29.0, with significance set at $p < 0.05$, and adjusted for age, gender, and comorbidities.

Kaplan-Meier survival analysis of CT improvement time showed significant differences among groups (log-rank $p < 0.001$) (Fig. 2). The combination therapy group had the fastest CT improvement, followed by the FNC group, with LHQW showing the slowest improvement, suggesting combination therapy accelerates radiological recovery compared to monotherapy.

Kaplan-Meier analysis demonstrated significant differences in hospitalization duration among treatment groups (log-rank $p < 0.001$). Patients receiving combination therapy (*FNC+LHQW*) exhibited a shorter hospital stay compared to monotherapy groups, suggesting a potential benefit of combined treatment in expediting recovery (Fig. 3).

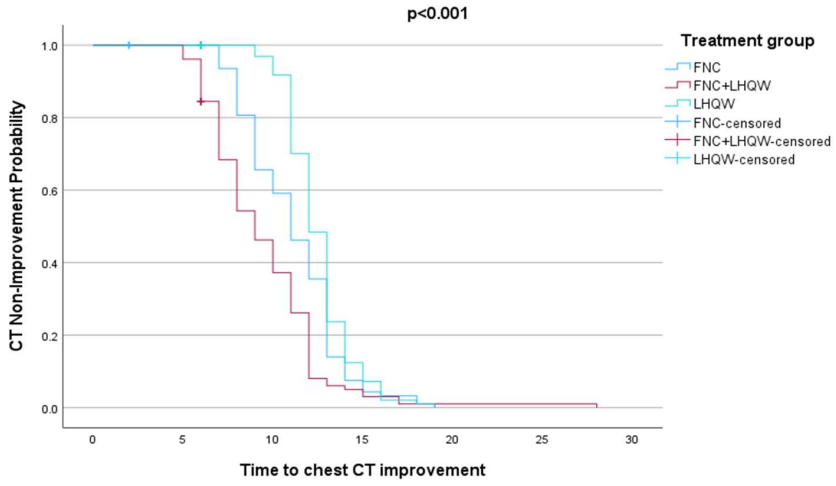

Fig. 2. Comparison of time to improvement and hospitalization among treatment groups.
Source: compiled by the authors

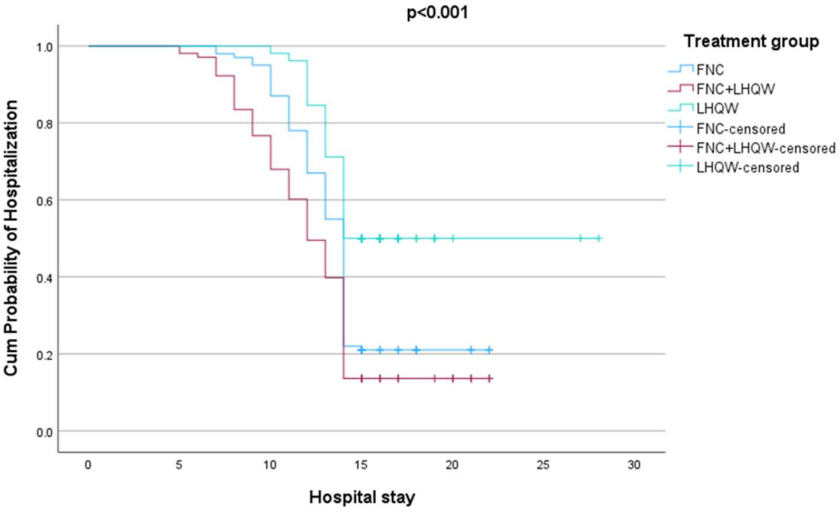

Fig. 3. Comparison of hospitalization time among treatment groups.
Source: compiled by the authors

Cox proportional hazards regression analysis showed that patients with chronic kidney disease (HR = 0.160, 95% CI: 0.038–0.667, $p = 0.012$) and coronary heart disease (HR = 0.587, 95% CI: 0.360–0.956, $p = 0.032$) had significantly longer imaging improvement times, likely due to impaired immunity or reduced viral clearance. Gender, age, hypertension, diabetes, chronic liver disease, and chronic obstructive pulmonary disease had no significant impact ($p > 0.05$). These results suggest that patients with chronic kidney or coronary heart disease may require longer treatment or more intensive interventions for recovery. Cox regression analysis showed that treatment type significantly influenced hospitalization duration ($\chi^2 = 34.255$, $p < 0.001$). Patients receiving FNC monotherapy had a higher risk of prolonged hospitalization (HR=1.484, 95% CI: 1.092–2.016, p=0.012), while those receiving combination therapy (FNC+LHQW) had a significantly lower risk (HR=0.517, 95% CI: 0.363–0.736, $p < 0.001$), indicating that combination therapy helps expedite recovery (Table 6).

Effective antiviral therapy for COVID-19 must address viral replication, inflammation, and symptom relief [6]. The combination of FNC and LHQW targets all three aspects. While LHQW does not have direct antiviral activity like FNC, it helps reduce viral load through antioxidant effects and by lowering excessive T-cell activation, which may facilitate viral spread. The combination provides both direct and indirect effects on the infection: FNC reduces viral load, which diminishes immune stimulation, while LHQW exerts anti-inflammatory effects by inhibiting cytokines. FNC helps prevent excessive immune activation, supporting immune homeostasis, a process enhanced by LHQW. This combination allows for a reduction in FNC dosage without compromising efficacy, thus lowering the risk of side effects. Both medications also reduce vascular inflammation, lowering the risk of thrombosis and other complications [10]. This study evaluated the adverse reactions of *FNC, FNC+LHQW*, and *LHQW* in the treatment of COVID-19 patients (Fig. 4).

There were no statistically significant differences in the incidence of adverse events such as fatigue, dizziness, elevated transaminases, and nausea among the three groups ($p > 0.05$). The findings suggest that the combination therapy did not result in a higher incidence of adverse events compared to monotherapy. This indicates that the combination of *FNC* and *LHQW* is well tolerated in the treatment of COVID-19 patients and does not pose additional safety risks.

Table 6

Results of cox regression analysis

Categories	Time to chest CT improvement					Hospital stay				
	p	Wald	HR	95.0% CI for HR		*p*	Wald	HR	95.0% CI for HR	
				Lower	Upper				Lower	Upper
Gender	0.645	0.212	0.945	0.742	1.203	0.558	0.344	0.922	0.702	1.210
Age	0.234	1.419	0.996	0.988	1.003	0.853	0.034	0.999	0.991	1.007
Hypertension	0.321	0.984	1.150	0.872	1.516	0.631	0.231	1.078	0.793	1.466
Diabetes	0.703	0.145	1.068	0.761	1.499	0.381	0.766	1.182	0.813	1.717
chronic liver disease	0.694	0.155	0.857	0.396	1.851	0.112	2.531	0.393	0.125	1.242
Chronic kidney disease	0.012	6.319	0.160	0.038	0.667	0.245	1.351	0.310	0.043	2.235
Chronic obstructive lung disease	0.238	1.390	0.537	0.191	1.510	0.633	0.228	0.705	0.168	2.957
Coronary heart disease	0.032	4.591	0.587	0.360	0.956	0.037	4.374	0.546	0.310	0.963
Others	0.030	4.687	1.410	1.033	1.924	0.140	2.178	1.296	0.919	1.828
Treatment group	<0.001	35.891	–	–	–	<0.001	34.255	–	–	–
Treatment group (1)	<0.001	16.152	1.822	1.360	2.441	0.012	6.359	1.484	1.092	2.016
Treatment group (2)	0.046	3.966	0.742	0.553	0.995	<0.001	13.390	0.517	0.363	0.736

Notes: Treatment group: FNC, LHQW, and FNC+LHQW; Treatment group (1)*: FNC vs. LHQW; Treatment group* (2)*: FNC+LHQW vs. LHQW. Source: compiled by the authors.*

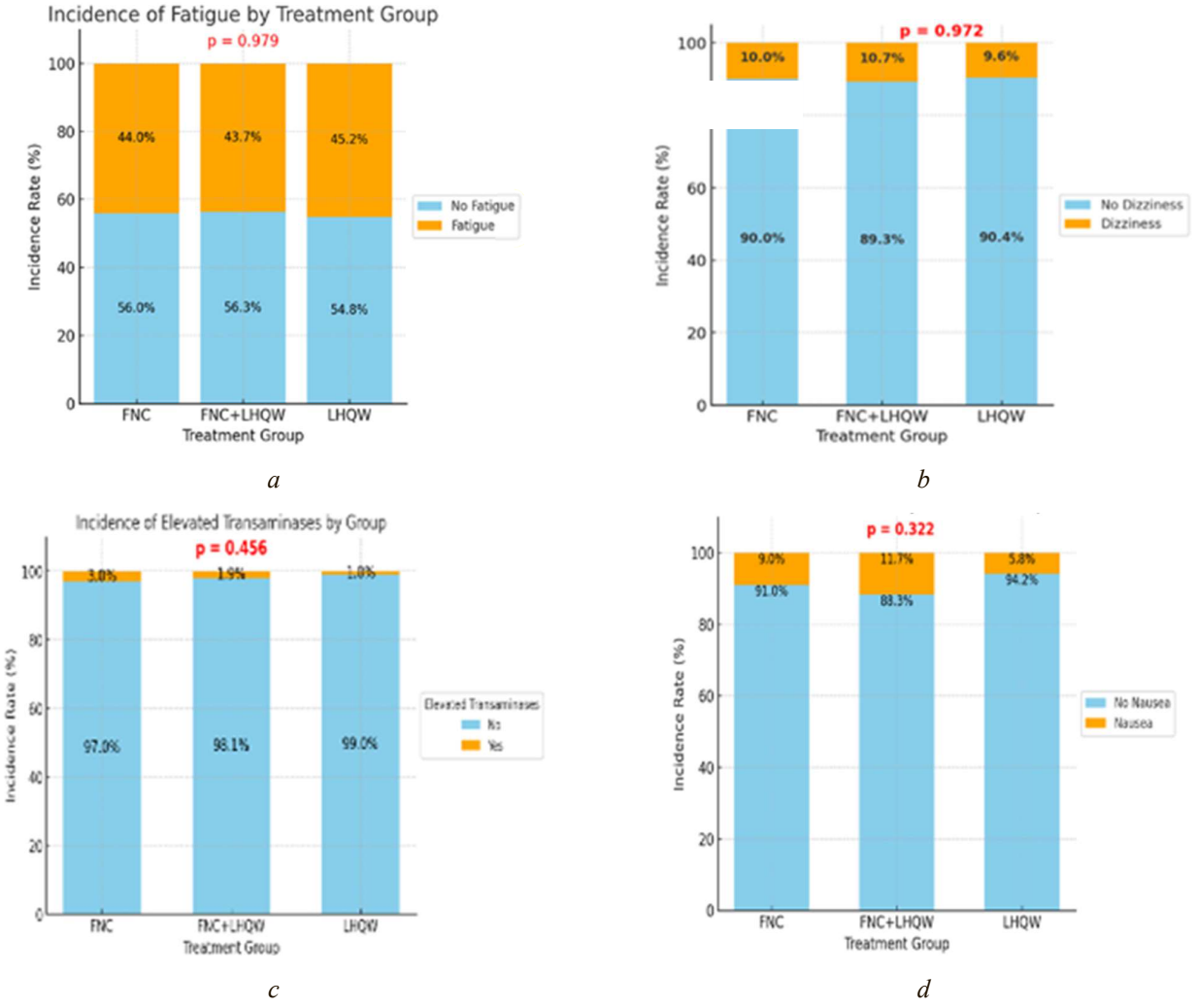

Fig. 4. Incidences of: *a* – fatigue; *b* – dizziness; *c* – elevated transaminases; *d* – nausea among treatment groups. *Source: compiled by the authors*

4. Discussion

This study highlights the benefits of combining antiviral drugs like FNC with adjunct therapies like LHQW for COVID-19 treatment. LHQW targets viral replication, inflammation, and lung damage by interfering with pathways like 3CL, ACE2, COX2, IL-6, and NA, demonstrating anti-inflammatory, antiviral, and immune-regulating effects. [14] support the multi-

target actions of traditional Chinese medicines, though synergy with antiviral agents remains underexplored. [15] found FNC inhibits SARS-CoV-2 replication by 95% at 10 μM. The combination of FNC and LHQW offers a multifaceted approach, leading to faster viral load reduction and improved recovery in the combination group.

The study reflects real-world conditions with diverse patients and disease severities, suggesting that combining FNC and LHQW is more effective for treating mild and moderate COVID-19, reducing hospital stays and healthcare burden. LHQW's antibacterial effect helps control secondary infections, crucial for immunocompromised patients [16]. The combination showed low side effect incidence, safer than other treatments like molnupiravir, which has a 3.70% side effect rate [17]. LHQW reduces inflammation, accelerates viral clearance, and alleviates symptoms like fever, cough, and fatigue [18]. The combination approach lowered FNC dosage, reducing hepatotoxicity and side effects.

As noted by [19], SARS-CoV-2 pathogens share similar characteristics globally, leading to a unified treatment approach. However, treatment strategies differ due to variations in ethnicity, health habits, and medical standards. While Western medicine has contributed significantly to COVID-19 treatment, challenges include the broad-spectrum nature of antiviral drugs, side effects from hormonal therapies, and antibiotic overuse [20]. The Chinese government advocates integrating traditional Chinese medicine with European practices. This study suggests that combining both approaches enhances COVID-19 prevention and treatment.

The findings show that FNC and LHQW combination therapy is significantly more effective for mild and moderate cases than monotherapy, reducing NANC duration, accelerating chest CT improvement, and shortening hospital stays [21]. The FNC+LHQW combination achieved results comparable to Remdesivir, reducing recovery time by 3.5 days, as compared to 4–5 days with Remdesivir [22]. LHQW's anti-inflammatory effects are evident in the significant reduction of IL-6 and CRP [23]. The synergy between FNC and LHQW comes from their complementary mechanisms, with FNC targeting viral replication enzymes to reduce viral load and prevent infection spread [24].

LHQW uses plant extracts that modulate the immune response, alleviate symptoms, and reduce inflammation [25]. Its plant components have anti-inflammatory, antioxidant, and immune-modulatory properties [26]. Patients receiving combination therapy recover more quickly, show symptom reduction, and have shorter hospital stays compared to those on monotherapy [27]. Systematic studies by [28] showed that combining LHQW with European clinical practices enhances clinical efficacy. The combination results in a lower mortality rate compared to Western practices alone, with a clinical effectiveness odds ratio of 2.48 and a mortality rate of 0.31 [29]. These findings highlight the benefits of integrating LHQW with antiviral drugs. FNC combined with supportive agents shows better therapeutic potential [30] and superior effectiveness in improving clinical outcomes and symptoms [31]. The drugs are more effective in moderate cases, though their advantages in severe cases need further confirmation.

Practical relevance. This study informs treatment strategies for mild to moderate COVID-19, especially in resource-limited settings. The combination of FNC and LHQW shortens hospitalization, improves outcomes, and relieves symptoms more rapidly than monotherapy. Integrating modern antivirals with traditional Chinese medicine targets viral replication, inflammation, and immune modulation, potentially easing healthcare burdens during pandemics.

Research limitations. Key limitations include the retrospective design, small sample size, and lack of randomization, all of which restrict causal inference and generalizability. The absence of a randomized controlled trial and focus on mild-to-moderate cases limit broader applicability. Long-term outcomes were not assessed.

Prospects for further research. Future studies should include large-scale, multicenter RCTs, especially in severe cases. Molecular-level investigations into synergistic effects and efficacy against emerging variants are warranted. Research on long-term COVID prevention and the integration of traditional and modern treatments across diverse healthcare settings would further substantiate the approach.

5. Conclusions

The combination of *FNC* and *LHQW* demonstrated greater effectiveness in treating mild to moderate COVID-19 compared to monotherapy. This combination therapy accelerates viral clearance, improves clinical outcomes, and reduces hospitalisation time, offering a new therapeutic approach for treating COVID-19. The *FNC+LHQW* combination yielded the best results, including a reduction in the average time to clinical improvement on chest CT scans to 9.47 ± 3.27 days and a decrease in the duration of hospitalisation to 12.23 ± 3.53 days. In addition, laboratory markers confirmed better control of inflammation in this group. Overall, clinical symptoms such as cough, fever, and shortness of breath disappeared in 90% of cases following treatment.

The therapy demonstrated high safety, with a minimal incidence of side effects (<5%) and no serious complications. Patients tolerated the medication well and showed positive outcomes throughout the treatment period. Its suitability for widespread application, including in patients with comorbidities and the elderly, was confirmed. Preliminary results suggest that the *FNC+LHQW* therapy may reduce the risk of developing "long COVID" due to its comprehensive impact on the virus, inflammation, and immune response. Further studies may confirm the ability of this combination to support sustained recovery without substantial complications. The findings

from this study provide a solid foundation for further research and the development of new therapeutic approaches to combat COVID-19.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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