Future Integrative Medicine **2024** vol. 3(2) | 99–105
DOI: 10.14218/FIM.2023.00106

Original Article

Effect of Lianhua Qingwen on Depression and Anxiety in COVID-19 Patients with Asymptomatic or Mild Symptoms

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Received: December 26, 2023 | **Revised:** April 08, 2024 | **Accepted:** May 15, 2024 | **Published online:** June 28, 2024

Abstract

Background and objectives: Patients with corona virus disease 2019 (COVID-19) face not only physical strains but also significant psychological stress, highlighting the importance of addressing their mental health concerns. This study aimed to evaluate the impact of Lianhua Qingwen on the psychological well-being of asymptomatic and mildly symptomatic COVID-19 patients, providing empirical evidence to guide clinical practices.

Methods: Conducted in eight shelter hospitals in Shanghai, the study employed a cluster randomization method to allocate patients equally into either the Lianhua Qingwen group or the control group. The Lianhua Qingwen group received oral doses of four capsules or one packet of granules three times daily for 14 days. In contrast, the control group received standardized treatment according to the diagnostic and treatment plan, excluding Lianhua Qingwen. Mental health was assessed using the Self-rating Depression Scale and Self-rating Anxiety Scale, with symptom reporting on the 7th and 14th days, accompanied by nucleic acid test result screenshots. A follow-up investigation on new disease occurrence was conducted six months post-discharge.

Results: Among the 2,652 valid questionnaire respondents, the Lianhua Qingwen group accounted for 1,665 cases, characterized by a higher proportion of females (32.7% vs. 26.9%), younger age (44.8 vs. 46.2 years), lower percentages of asymptomatic infections (27.6% vs. 38.5%), higher baseline Patient Health Questionnaire-9 scores (2.7 vs. 1.9), and higher Generalized Anxiety Disorder 7 scores (1.9 vs. 1.4). Further multivariate logistic regression analysis explored factors influencing the alleviation of depressive and anxiety symptoms during follow-up, revealing that Lianhua Qingwen use was an independent factor in reducing anxiety (odds ratio = 1.37, 95% confidence interval 1.14–1.65, $p = 0.001$) and depression (odds ratio = 1.42, 95% confidence interval 1.19–1.69, $p < 0.0001$). Lianhua Qingwen increased the likelihood of reducing anxiety by 37% and depression by 42%.

Conclusions: Lianhua Qingwen significantly alleviated anxiety and depression symptoms in COVID-19 patients, suggesting its potential therapeutic efficacy in mitigating these conditions.

Keywords: Lianhua Qingwen; Corona virus disease 2019; COVID-19; Anxiety; Depression; Mental health; Traditional Chinese medicine.

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How to cite this article: Ruan M, Zhang J, Zhang W, Sheng C, Wang R, Tian J, *et al*. Effect of Lianhua Qingwen on Depression and Anxiety in COVID-19 Patients with Asymptomatic or Mild Symptoms. *Future Integr Med* 2024;3(2):99–105. doi: 10.14218/FIM.2023.00106.

Introduction

The corona virus disease 2019 (COVID-19) pandemic, caused by the novel coronavirus, represents a recently emerged infectious disease characterized by acute respiratory symptoms.[1,2] As of 2022, many provinces and cities in China, including Shanghai and Jilin, have reported confirmed cases and asymptomatic carriers of

COVID-19. Patients infected with the virus also face significant psychological pressure, making it crucial to pay attention to their mental health.[3,4]

Lianhua Qingwen is a patented drug developed based on traditional Chinese medicine (TCM) theory for the treatment of colds and influenza (National Drug Approval Number Z20040063). It was the first new drug approved through the rapid approval channel of the National Medical Products Administration during the SARS outbreak in China. Lianhua Qingwen is the only Chinese medicine that has won the second prize in the National Science and Technology Progress Award for the treatment of colds and influenza. It is also the inaugural Chinese medicinal formulation to undergo clinical trials for the management of influenza in the United States under the auspices of the U.S. Food and Drug Administration. Since the onset of the COVID-19 pandemic, Lianhua Qingwen has been extensively utilized across numerous epicenters within China, encompassing designated hospitals and temporary treatment facilities in Hubei Province. Over 70 million individuals have employed this formulation as a prophylactic and therapeutic measure against the outbreak. Within the Chinese healthcare system, comprehensive clinical evaluations, including prospective and retrospective studies, alongside fundamental experimental research focusing on the efficacy of Lianhua Qingwen in combating COVID-19, have been initiated and are currently underway. Among them: (1) Prospective clinical studies: A multicenter, randomized, controlled, prospective clinical study of Lianhua Qingwen in the treatment of COVID-19 patients (284 cases) and a multicenter, randomized, controlled, prospective clinical study of Lianhua Qingwen in the treatment of suspected COVID-19 patients (240 cases) were jointly conducted by 20 hospitals in nine provinces in China. The results showed that Lianhua Qingwen could improve clinical symptoms such as fever, fatigue, and cough, significantly improve lung computed tomography features, shorten the duration and treatment time of symptoms, and improve the clinical cure rate when used as an adjuvant to routine treatment.[5] (2) Retrospective clinical studies showed: Lianhua Qingwen effectively alleviated symptoms such as fever, cough, sputum, and shortness of breath in confirmed and suspected patients, and shortened the duration of fever.[6–8] (3) Basic experimental studies: The latest research at the National Key Laboratory of Respiratory Diseases, Guangzhou Medical University,[9] confirmed that Lianhua Qingwen had inhibitory effects on cell lesions caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection in VeroE6 cells *in vitro*. After treatment with Lianhua Qingwen, the expression of viral particles in cells was significantly reduced, and the messenger RNA overexpression of inflammatory factors tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein-1, and interferon γ inducible protein-10 was significantly inhibited in a dose-dependent manner. The Institute of Medical Experimental Animals of the Chinese Academy of Medical Sciences confirmed that Lianhua Qingwen effectively inhibited weight loss in mice with a COVID-19 model and had certain improvement effects on lung inflammatory damage and clinical symptoms.[10] Lianhua Qingwen has been included in the "New Coronavirus Infection Pneumonia Diagnosis and Treatment Plan" (trial version IV/V/VI/VII/VIII/IX) issued by the National Health Commission and the recommendation list of medical institutions and TCM bureaus in 20 provinces such as Hubei, Beijing, and Shanghai. It has become the most recommended Chinese patent medicine with the highest frequency of recommendations in China's fight against COVID-19.[11] This study aimed to evaluate the effect of Lianhua Qingwen on depression and anxiety in patients with asymptomatic or mild COVID-19 infections, providing evidence to support the clinical medication.

Materials and methods

This study has been approved by the Ethics Committee of Ruijin Hospital, which is affiliated with Shanghai Jiao Tong University School of Medicine (Approval number: 2022-65). All participants provided written informed consent prior to recruitment. The study adhered strictly to the ethical standards set forth in the Declaration of Helsinki (as revised in 2013).

Subjects of the study

This study was conducted in eight makeshift hospitals in Shanghai, employing a cluster randomization approach. The clusters were the hospitals (with approximately 3,500 patients each, totaling 14 hospitals), and they were randomly assigned to the Lianhua Qingwen group or the control group at a 1:1 ratio. Data on the baseline and discharge-related information of patients from both groups were collected to evaluate the effectiveness, safety, and impact on depressive and anxious emotions of Lianhua Qingwen in asymptomatic and mildly infected individuals.

Inclusion criteria

1. Confirmed asymptomatic or mildly diagnosed COVID-19 cases by pathogenic testing, in accordance with the "Diagnosis and Treatment Plan for COVID-19 (Trial Version 9)";
2. Able to receive standardized and homogeneous treatment according to the group's size;
3. Aged 18 years or older (inclusive), with no gender restrictions;
4. Voluntarily signed a written informed consent form before the study began.

Exclusion criteria

1. Confirmed common, severe, or critical COVID-19 cases by pathogenic testing and clinical manifestations or signs;
2. Pregnant or lactating women;
3. Individuals with allergies, such as a history of allergy to two or more medications or foods, or known allergy to the drug's components.

Research methods

The trial was divided into two groups: the Lianhua Qingwen group and the control group. Patients in the Lianhua Qingwen group received four capsules or 1 bag of Lianhua Qingwen per dose, three times a day, for a total of 14 days. Patients in the control group received standardized and homogeneous treatment according to the diagnosis and treatment plan, without receiving Lianhua Qingwen. Data collection for informed consent, past medical history, and personal history was conducted by scanning quick response code for electronic signatures and filling out questionnaires. Depression symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) scale,[12,13] while anxiety symptoms were assessed using the Generalized Anxiety Disorder 7 (GAD-7) scale.[14,15] Psychiatric specialists were consulted if necessary for collaborative assessment. Symptoms were reported at seven days (mid-term) and 14 days (discharge). New disease occurrence was investigated six months after discharge (open follow-up). Adverse events were collected, and their relationship with the study medication was determined.

Statistical methods

All statistical tests employed bilateral testing, with *p*-values less

Table 1. Baseline characteristics

	Using Lianhua Qingwen group (n = 1,665)	Without Lianhua Qingwen group (n = 987)	*p*
Male	1,120 (67.3)	721 (73.1)	0.002
Age	44.8 ± 14.4	46.2 ± 15.2	0.02
COVID-19 vaccination	2.3 ± 0.9	2.3 ± 3.0	0.27
Asymptomatic infection	459 (27.6)	380 (38.5)	<0.0001
Smoking	321 (19.3)	215 (21.8)	0.12
Drink	205 (12.3)	135 (13.7)	0.31
Hypertension	217 (13.0)	132 (13.4)	0.81
Diabetes	64 (3.8)	43 (4.4)	0.54
Hyperlipemia	59 (3.5)	22 (2.2)	0.06
Hepatic disease	36 (2.2)	18 (1.8)	0.67
Coronary heart disease	35 (2.1)	26 (2.6)	0.42
Stroke	21 (1.3)	8 (0.8)	0.34
Asthma	29 (1.7)	10 (1.0)	0.18
PHQ-9 code	2.7 ± 4.8	1.9 ± 4.0	<0.0001
GAD-7 code	1.9 ± 3.9	1.4 ± 3.5	<0.0001

COVID-19, corona virus disease 2019; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire-9.

than or equal to 0.05 considered statistically significant (unless otherwise specified). Categorical variables were described as counts and percentages, while continuous variables were described as medians and interquartile ranges. Chi-square tests were employed to discern differences between subgroups. Subsequently, a multivariate logistic regression analysis was conducted to calculate the adjusted odds ratio (OR) and the 95% confidence interval (CI), with adjustments made for potential confounding variables such as gender and age.

Results

Basic situation

A total of 5,330 questionnaires were collected at baseline from the eight makeshift hospitals in Shanghai, including 2,666 participants in the experimental group and 2,664 participants in the control group. After six months of follow-up via telephone, a total of 2,652 valid questionnaires were completed.

Of these 2,652 patients, 1,841 were male and 811 were female, with an average age of 45.3 ± 14.7 years. The proportion of patients using Lianhua Qingwen was 62.8% (1,665/2,652). Compared with the non-Lianhua Qingwen group, the Lianhua Qingwen group had more female patients (32.7% vs. 26.9%), a younger average age (44.8 vs. 46.2 years), a lower proportion of asymptomatic infections (27.6% vs. 38.5%), and higher baseline PHQ-9 (2.7 vs. 1.9) and GAD-7 scores (1.9 vs. 1.4). There were no differences in vaccination status, smoking and drinking habits, or underlying diseases between the two groups ($p \geq 0.06$, see Table 1).

The patient's condition of depression and anxiety at baseline

Table 2 shows the severity of anxiety and depressive symptoms in participants based on baseline characteristics, as measured by the GAD-7 and PHQ-9 scales.[16,17] The GAD-7 scale suggests that those with scores of 0–4 do not have anxiety, 5–9 have mild anxiety, 10–14 have moderate anxiety, 15–21 have severe anxiety, and 22–27 have extremely severe anxiety. The PHQ-9 scale suggests that those with scores of 0–4 do not have depression, 5–9 have mild depression, 10–14 have moderate depression, 15–19 have moderately severe depression, and 20–27 have severe depression. The average GAD-7 score of the 2,652 participants was 1.70 ± 3.79, and the average PHQ-9 score was 2.40 ± 4.51. A total of 121 (4.56%) participants reported moderate or higher levels of anxiety symptoms, and 164 (6.18%) participants reported moderate or higher levels of depressive symptoms. Among the 1,665 participants using Lianhua Qingwen, 87 (5.23%) reported moderate or higher levels of anxiety symptoms, and 146 (6.11%) reported moderate or higher levels of depressive symptoms. Among the 987 participants not using Lianhua Qingwen, 34 (3.44%) reported moderate or higher levels of anxiety symptoms, and 18 (6.84%) reported moderate or higher levels of depressive symptoms.

Analysis of factors influencing the alleviation of depression and anxiety symptoms in patients at the six-month follow-up

Among the 1,665 patients using Lianhua Qingwen, 20.78% showed a decrease in PHQ-9 score levels at the six-month follow-up post-discharge, indicating alleviation of depressive symptoms, while 2.04% exhibited an increase in PHQ-9 score levels, suggesting worsening of depressive symptoms. Among the 987 patients not using Lianhua Qingwen, 15.10% experienced a reduction in PHQ-9 score levels, signifying relief from depression, and 2.73% had elevated PHQ-9 scores, indicating intensified depressive symptoms. In the group of 1,665 patients using Lianhua Qingwen, 17.06% reported a decline in GAD-7 score levels at the six-month follow-up post-discharge, denoting reduced anxiety symptoms, whereas 1.26% displayed increased GAD-7 scores, reflecting heightened anxiety symptoms. In the cohort of 987 patients not utilizing Lianhua Qingwen, 11.05% saw a decrease in GAD-7 scores, implying lessened anxiety and 1.11% had higher GAD-7 scores, indicating augmented anxiety symptoms (Fig. 1).

Table 2. The scores of anxiety and depression symptoms in all subjects and subgroups at baseline

	Anxiety (GAD-7)		Depression (PHQ-9)	
	$\bar{x}$ (s)	The number of patients with a score of more than 10 (%)	$\bar{x}$ (s)	The number of patients with a score of more than 10 (%)
All the crowd (2,652)	1.70 (3.79)	121 (4.56)	2.40 (4.51)	164 (6.18)
Gender				
Female (811)	1.91 (3.85)	39 (4.81)	2.70 (4.74)	58 (7.15)
Male (1,841)	1.60 (3.76)	82 (4.45)	2.27 (4.40)	106 (4.89)
Age				
18–29 (452)	2.46 (4.66)	33 (7.30)	3.55 (5.41)	45 (9.96)
30–45 (901)	1.84 (3.80)	42 (4.66)	2.67 (4.59)	61 (6.77)
46–59 (917)	1.45 (3.51)	38 (4.14)	1.94 (3.99)	42 (4.58)
≥60 (382)	1.05 (3.01)	8 (2.09)	1.53 (3.97)	16 (4.19)
Using Lianhua Qingwen group				
Yes (1,665)	1.90 (3.94)	87 (5.23)	2.69 (4.75)	123 (7.39)
No (987)	1.35 (3.47)	34 (3.44)	1.91 (4.01)	41 (4.15)
COVID-19 vaccination				
Yes (2,389)	1.70 (3.82)	112 (4.69)	2.42 (4.53)	146 (6.11)
No (263)	1.63 (3.46)	9 (3.42)	2.27 (4.28)	18 (6.84)
Asymptomatic infection				
Yes (839)	1.15 (3.39)	26 (3.10)	1.69 (4.42)	44 (5.24)
No (1,813)	1.95 (3.93)	95 (5.24)	2.73 (4.51)	120 (6.62)
Hypertension				
Yes (349)	1.49 (3.63)	14 (4.01)	2.03 (4.44)	18 (5.16)
No (2,303)	1.73 (3.81)	107 (4.65)	2.46 (4.52)	146 (6.34)
Diabetes				
Yes (107)	1.19 (3.49)	3 (2.80)	1.86 (4.50)	5 (4.67)
No (2,545)	1.72 (3.80)	118 (4.64)	2.43 (4.51)	159 (6.25)
Hyperlipemia				
Yes (81)	2.53 (4.62)	5 (6.17)	3.00 (5.76)	6 (7.41)
No (2,571)	1.67 (3.76)	116 (4.51)	2.38 (4.46)	158 (6.15)

COVID-19, corona virus disease 2019; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire-9.

We conducted a multivariate logistic regression analysis to investigate the factors associated with the mitigation of depression and anxiety symptoms in patients during follow-up. The regression model incorporated variables such as age, gender, use of Lianhua Qingwen, COVID-19 vaccination status, asymptomatic infection, smoking, alcohol consumption, and underlying diseases. The results indicated that age (OR = 0.78, 95% CI 0.73–0.84, $p < 0.0001$), use of Lianhua Qingwen (OR = 1.37, 95% CI 1.14–1.65, $p = 0.001$), asymptomatic infection (OR = 0.48, 95% CI 0.39–0.59, $p < 0.0001$), alcohol consumption (OR = 1.32, 95% CI 1.01–1.73, $p = 0.04$), hyperlipidemia (OR = 1.76, 95% CI 1.06–2.93, $p = 0.03$), coronary heart disease (OR = 2.66, 95% CI 1.49–4.74, $p = 0.001$), and stroke (OR = 2.33, 95% CI 1.05–5.21, $p = 0.04$) were independent factors associated with a reduction in anxiety symptoms. Meanwhile, age (OR = 0.77, 95% CI 0.72–0.82, $p < 0.0001$), use of Lianhua Qingwen (OR = 1.42, 95% CI 1.19–1.69, $p < 0.0001$), asymptomatic infection (OR = 0.39, 95% CI 0.32–0.49, $p < 0.0001$), alcohol consumption (OR = 1.32, 95% CI 1.03–1.70, $p = 0.03$), liver disease (OR = 1.95, 95% CI 1.10–3.45, $p = 0.02$), and coronary heart disease (OR = 3.52, 95% CI 1.99–6.24, $p < 0.0001$) were independent factors associated with a decrease in depressive symptoms. Notably, the use of Lianhua Qingwen was associated with a 37% increase in the likelihood of reduced anxiety symptoms and a 42% increase in the likelihood of alleviated depressive symptoms (Table 3).

Discussion

Patients infected with the novel coronavirus not only face physical pressure but also immense psychological stress.[18–21] There-

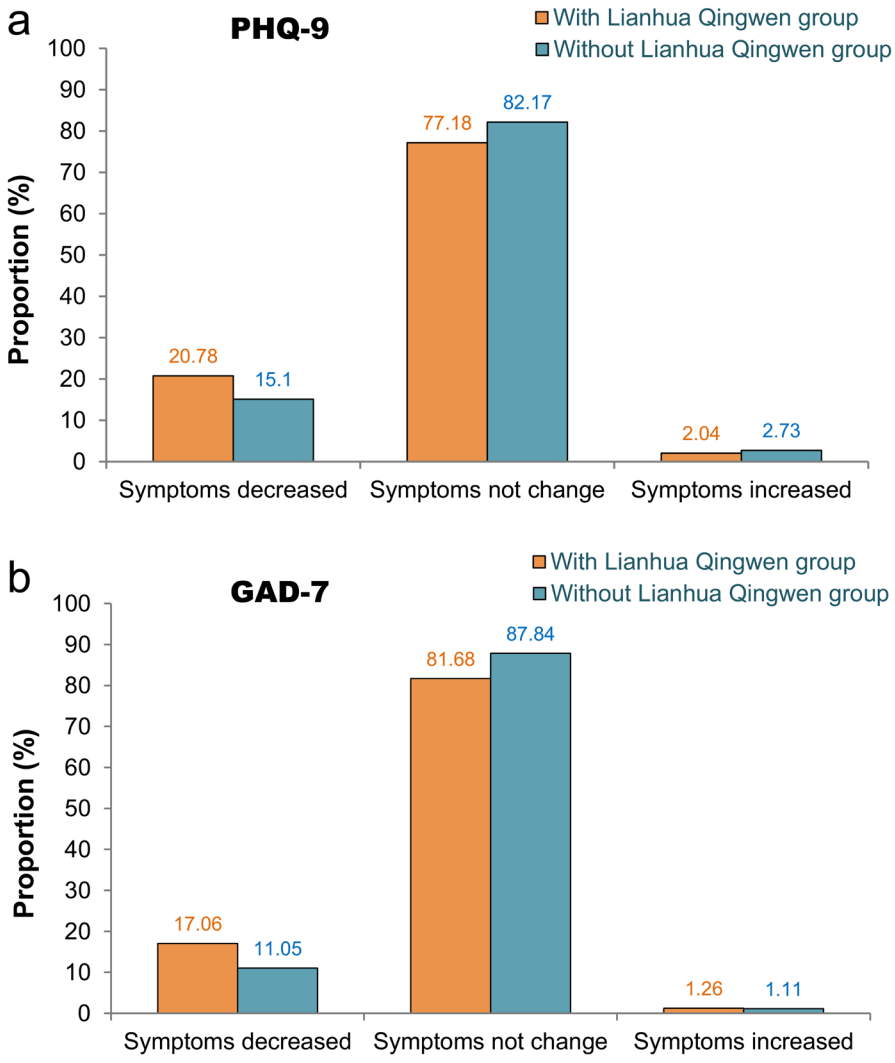

Fig. 1. Distribution of changes in PHQ-9 and GAD-7 scores at follow-up. As determined by the PHQ-9 questionnaire, patients with decreased symptoms during the six-month follow-up period in the using Lianhua Qingwen group were higher than those in the without Lianhua Qingwen group (20.78% vs 15.10%). Meanwhile, the patients with decreased symptoms in the using Lianhua Qingwen group were higher than those in the without Lianhua Qingwen group (17.06% vs 11.05%), as determined by the GAD-7 questionnaire. GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire-9.

fore, we cannot overlook their mental health concerns. Numerous studies have indicated a significant rise in the prevalence of anxiety and depression as the COVID-19 pandemic persists. These psychological issues can negatively impact patients' recovery and quality of life, so it is essential to take proactive measures to support their mental well-being.[22] While treating individuals infected with the virus, we must also pay attention to whether the medications used have any positive effects on anxiety and depression.[23,24] In this investigation, the administration of Lianhua Qingwen was observed to substantially ameliorate symptoms associated with anxiety and depression in individuals afflicted by the novel coronavirus. The reason behind this may be related to patients' level of trust in TCM. Chinese patients may have a higher level of trust in TCM due to the influence of traditional Chinese culture. Lianhua Qingwen, as a TCM medication promoted by the government during the epidemic, can increase patients' sense of security and improve their anxiety and depressive emotions. Future studies could include a placebo control group to better validate this hypothesis.

In TCM classics, there are no specific disease names for anxiety and depression. However, based on their symptomatic manifestations, states of anxiety and depression can be categorized under conditions such as "depressed spri" and "visceral irritability", often related to the liver, heart, and lungs.[25] The initial stage of the disease is usually associated with the liver, typically caused by emotional imbalances and qi stagnation. Prolonged liver qi stagnation can transform into heat, which, being a yang pathogen, may harm the liver blood. Insufficient liver blood can then lead to kidney essence depletion. After the COVID-19 infection, when lung heat becomes excessive, it can affect the liver wood element, leading to physical discomfort and significant psychological stress from societal pressures, resulting in liver depression turning into fire and emotional discomfort. Some studies indicate that in TCM formulas treating insomnia with accompanying depression and anxiety, cold-natured herbs account for more than one-third of the ingredients.[26] The text "Symptoms, Causes, Pulse Diagnosis, and

Table 3. Analysis of influencing factors for the improvement of anxiety and depression symptoms during follow-up

	Reduction of anxiety (GAD-7)		Reduction of depression (PHQ-9)	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Using Lianhua Qingwen	1.37 (1.14–1.65)	0.001	1.42 (1.19–1.69)	<0.0001
Female	1.20 (0.98–1.46)	0.08	1.18 (0.98–1.42)	0.09
Age	0.78 (0.73–0.84)	<0.0001	0.77 (0.72–0.82)	<0.0001
COVID-19 vaccination	0.88 (0.64–1.21)	0.44	0.84 (0.62–1.12)	0.24
Asymptomatic infection	0.48 (0.39–0.59)	<0.0001	0.39 (0.32–0.47)	<0.0001
Smoking	0.84 (0.66–1.07)	0.15	1.12 (0.90–1.39)	0.33
Drink	1.32 (1.01–1.73)	0.04	1.32 (1.03–1.70)	0.03
Hypertension	0.99 (0.74–1.34)	0.97	0.96 (0.73–1.27)	0.79
Diabete	0.74 (0.44–1.24)	0.25	1.08 (0.69–1.70)	0.72
Hyperlipemia	1.76 (1.06–2.93)	0.03	1.37 (0.83–2.25)	0.22
Hepatic disease	1.39 (0.78–2.48)	0.26	1.95 (1.10–3.45)	0.02
Coronary heart disease	2.66 (1.49–4.74)	0.001	3.52 (1.99–6.24)	<0.0001
Stroke	2.33 (1.05–5.21)	0.04	0.81 (0.42–1.67)	0.63
Asthma	1.01 (0.49–2.10)	0.98	0.83 (0.90–1.39)	0.61

CI, confidence interval; COVID-19, corona virus disease 2019; GAD-7, Generalized Anxiety Disorder 7; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9.

Treatment" suggests: "The causes of liver fire leading to sleeplessness could be due to anger damaging the liver, causing liver qi to become depressed and leading to restless nights", highlighting that liver depression turning into the fire and disturbing the heart spirit is a primary cause of insomnia and anxiety. Lianhua Qingwen formula mainly consists of herbs that clear heat and detoxify, ventilate the lungs, and purge heat, targeting the stage of viral respiratory tract infections where heat toxin attacks the lungs. It can alleviate symptoms such as cough, fatigue, chest tightness, and shortness of breath, thereby improving patients' sleep quality and mental state. These effects contribute to alleviating symptoms of depression and anxiety in patients. Moreover, clearing lung heat can moderate the subsequent metal energy, allowing liver qi to relax and resolve qi stagnation.[27,28]

Although preliminary studies have shown that Lianhua Qingwen is effective in reducing symptoms of anxiety and depression, further clinical research is needed to validate its efficacy. Such studies should include larger sample sizes, randomized controlled trials, and long-term follow-up observations. Only through rigorous scientific investigation can we better understand the clinical value of Lianhua Qingwen in treating individuals infected with COVID-19 and those with mild cases of the disease.

Conclusions

Lianhua Qingwen, as a TCM, has shown potential in treating individuals infected with COVID-19 and those with mild cases of the disease. It can also significantly improve anxiety levels among COVID-19 patients. Although current research is still limited, further clinical studies and a deeper understanding will allow us to better evaluate its efficacy and safety.

Acknowledgments

None.

Funding

This work was supported by Combine Traditional Chinese And Western Medicine Flagship Hospital Construction, ZY(2021-2023)-0205-01.

Conflict of interest

No potential conflict of interest was reported by the authors.

Author contributions

Conceptualization (MR, JJZ, WZ), methodology (MR, JJZ, WZ, CSS, RSW, JYT), investigation (MR, JJZ, WZ, CSS, RSW, JYT), Formal Analysis (MR, JJZ, WZ), writing - original draft (MR, JJZ, WZ), writing - review & editing (CSS, RSW, JYT, WRZ, HLG), visualization (MR, JJZ, WZ), project administration (WRZ, HLG), and study supervision (CSS, RSW, JYT). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethics statement

This study has been approved by the Ethics Committee of Ruijin Hospital, which is affiliated with Shanghai Jiao Tong University School of Medicine (Approval number: 2022-65). All participants provided written informed consent prior to recruitment. The study adhered strictly to the ethical standards set forth in the Declaration of Helsinki (as revised in 2013).

Data sharing statement

The fundamental details regarding the test subjects, along with the comprehensive scale scores utilized to uphold the discoveries of this research, can be accessed from the respective author at wil-

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