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## Hanshiyi Formula, a medicine for Sars-CoV2 infection in China, reduced the proportion of mild and moderate COVID-19 patients turning to severe status: A cohort study

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### ABSTRACT

We formulated a traditional Chinese medicine (TCM) prescription, Hanshiyi Formula (HSYF), which was approved and promoted by the Wuhan Municipal Health Commission for treating mild and moderate coronavirus disease 2019 (COVID-19). We aimed to evaluate the effect of HSYF on the progression to severe disease in mild and moderate COVID-19 patients. We conducted a retrospective cohort study of patients with mild and moderate COVID-19 in a quarantine station in Wuchang District, Wuhan. Using the real-time Internet information collection application and Centers for Disease Control for the Wuchang District, patient data were collected through patient self-reports and follow-ups. HSYF intervention was defined as the exposure. The primary outcome was the proportion of patients who progressed to a severe disease status, and a stratification analysis was performed. Univariate and multivariate regression analyses were performed to identify influencing factors that may affect the outcome. Further, we used propensity score matching (PSM) to assess the effect of HSYF intervention on the conversion of mild and moderate to a severe disease status. Totally, 721 mild and moderate COVID-19 patients were enrolled, including 430 HSYF users (exposed group) and 291 non-users (control group). No cases in the exposed group and 19 (6.5 %,  $P < 0.001$ ) cases in the control group progressed to severe disease, and the difference between the two groups (exposed group-control group) was  $-6.5$  % [95 % confidence interval (CI):  $(-8.87$  %,  $-4.13$  %)]. Univariate regression analysis revealed sex (male), age, fever, cough, and fatigue as risk factors for progression to severe disease. After PSM, none of the HSYF users and 7 (4.7 %,  $P = 0.022$ ) non-users transitioned to severe disease, and the difference between the two groups (exposed group-control group) was  $-4.7$  % [95 % CI:  $(-8.2$  %,  $-1.2$  %)]. Multivariate regression analysis revealed that sex (male) [OR: 3.145; 95 % CI: 1.036–9.545;  $P = 0.043$ ] and age ( $> 48$  years) [odds ratio (OR): 1.044; 95 % CI: 1.001–1.088;  $P = 0.044$ ] were independent risk factors for conversion to severe disease. Therefore, HSYF can significantly reduce the progression to severe disease in patients with mild and moderate COVID-19, which may effectively prevent and treat the disease. However, further larger clinical studies are required to verify our results.

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## 1. Introduction

At the end of December 2019, a series of coronavirus disease 2019 (COVID-19) cases emerged in Wuhan (Hubei Province, China), and the number of diagnosed cases have rapidly increased since then [1]. In the early stage of the epidemic, a large number of patients with mild and moderate COVID-19 were diagnosed and treated in quarantine stations. Identifying effective treatments for early intervention can improve the prognosis of patients with mild and moderate COVID-19, which can also help control the epidemic progression and reduce the medical burden.

Wuchang District is located at the center of Wuhan, with a high population density. It was one of the most severely affected areas with many confirmed COVID-19 cases. For a large number of patients with mild and moderate COVID-19 in the quarantine station, the Wuhan Municipal Health Commission adopted a combination of Chinese herbal medicines and used Internet data to tackle the pandemic.

Our study group formulated a traditional Chinese medicine (TCM) prescription, named Hanshiyi Formula (HSYF), to prevent the exacerbation of the epidemic. This was approved and promoted by the Wuhan Municipal Health Commission for the treatment of mild and moderate COVID-19 patients in 17 quarantine stations [2,3]. Data was collected from the real-time Internet information collection application (Yuge medical system), which was convenient for physicians to communicate with isolated patients in real time, dynamically monitor changes in the patient's condition, observe the efficacy of HSYF in mild and moderate COVID-19 patients, and adjust the treatment plan if necessary.

In guiding the treatment of mild and moderate COVID-19 patients, we found that after HSYF intervention, patients with mild and moderate disease experienced rapid resolution of symptoms and fewer patients transitioned to a severe disease status. Therefore, we compared the clinical data of mild and moderate COVID-19 patients treated with HSYF with patients who were diagnosed but were not treated with HSYF. Data were collected from the database of Wuhan Wuchang District Disease Control Center (CDC) as well as from the real-time Internet information collection application, to evaluate the effect of HSYF on the proportion of COVID-19 patients who progressed from a mild and moderate to severe disease status.

## 2. Methods

### 2.1. Study design and participants

In this retrospective cohort study conducted in the Wuchang District, Wuhan, data were collected from mild and moderate COVID-19 patients

in 17 quarantine stations in Wuchang District, Wuhan before March 10, 2020. The exposed group included patients who were administered HSYF for more than 2 days. If there is no adverse effect or disease progression, HSYF can be taken continuously until recovery. The control group included patients who were diagnosed with COVID-19 but were not administered HSYF (including decoction, granules, etc.) at the same time. Data on age, sex, disease duration, medical history, initial symptoms, concomitant medication, and outcomes of the two groups were collected, and the difference in the proportion of mild to moderate COVID-19 patients who transitioned to a severe status were analyzed (Fig. 1).

The diagnosis of COVID-19 patients was made by the designated tertiary hospital in Wuchang District, Wuhan. The diagnostic criteria was according to the Diagnosis and Treatment Guideline for COVID-19 released by the National Health Commission of the People's Republic of China [4]. The study included patients who met the criteria of mild and moderate COVID-19, the mild COVID-19 patients usually presented mild clinical symptoms, with no radiological manifestations of pneumonia; the moderate COVID-19 patients had fever and respiratory symptoms, with radiological manifestations of pneumonia. Severe and critical patients were excluded.

This study was approved by the institutional ethics board of Hubei Provincial Hospital of Traditional Chinese Medicine (No. HBZY2020-C01-01) and was registered with [chictr.org.cn](http://chictr.org.cn) (ChiCTR2000029601).

### 2.2. Data collection

Data from the exposure group was first provided by the patients, who scanned the QR code on the medication box and entered data on the real-time Internet information collection application. After downloading and sorting the data, if there were mistakes or lack of relevant information, a medical staff member followed up the patients by telephone, and if necessary, contacted the staff of the community health service station to verify the information to ensure accuracy and completeness of the data. Data from the control group were provided by the Wuhan Wuchang District CDC database. Data of mild and moderate COVID-19 patients diagnosed at the same time were screened and downloaded, and a telephone follow-up was conducted by a medical staff member to ensure accuracy and completeness of the data. All data were collected using a standard electronic database. In order to ensure the accuracy of the data and avoid bias, data were verified by two researchers (A and B), and a third researcher (C) resolved any dispute between the first two researchers. The results of the study were analyzed and reported in accordance with the STROBE guidelines.

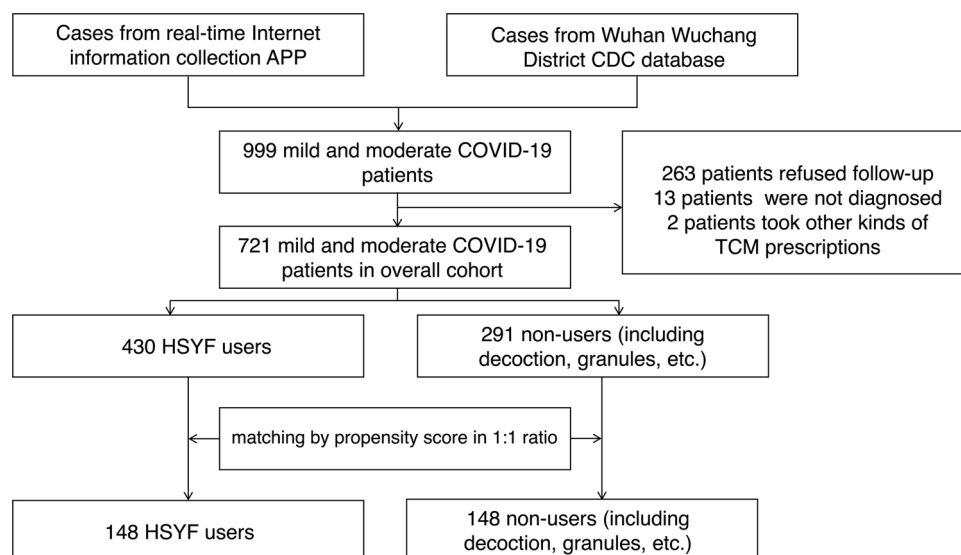


Fig. 1. Flow chart of the observational research.

**Table 1**  
Demographic and Patient Characteristics.

	All patients	Exposed group	Control group	Statistics	P-value
<b>Age</b>					
Mean ± SD	48.49 ± 14.362	43.79 ± 12.099	55.44 ± 14.641	Z=-10.789	< 0.001
0-14yr	6(0.8 %)	4(0.9 %)	2(0.7 %)		
15-49yr	377(52.3 %)	286(66.5 %)	91(31.3 %)	X <sup>2</sup> =-10.724	< 0.001
50-64yr	224(31.1 %)	120(27.9 %)	104(35.7 %)		
≥65yr	114(15.8 %)	20(4.7 %)	94(32.3 %)		
≤48yr	365(50.6 %)	277(64.4 %)	88(30.2 %)	X <sup>2</sup> = 81.105	< 0.001
> 48yr	356(49.4 %)	153(35.6 %)	203(69.8 %)		
<b>Sex</b>					
Female	374(51.9 %)	229(53.3 %)	145(49.8 %)	X <sup>2</sup> =0.817	0.366
<b>Medical history</b>					
Medical history	334(46.3 %)	208(48.4 %)	126(43.3 %)	X <sup>2</sup> =1.796	0.180
Hypertension	122 (16.9 %)	64(14.9 %)	58(19.9 %)	X <sup>2</sup> =3.145	0.076
Coronary heart disease	33(4.6 %)	16(3.7 %)	17(5.8 %)	X <sup>2</sup> =1.788	0.181
Diabetes	51(7.1 %)	27(6.3 %)	24(8.2 %)	X <sup>2</sup> =1.023	0.312
Bronchial asthma	24(3.3 %)	19(4.4 %)	5 (1.7 %)	X <sup>2</sup> =3.933	0.047
Chronic obstructive pulmonary disease	9(1.2 %)	5(1.2 %)	4(1.4 %)	X <sup>2</sup> < 0.001	1.000
Hyperlipidemia	48(6.7 %)	16(3.7 %)	32(11.0 %)	X <sup>2</sup> = 14.784	< 0.001
Fatty liver	57(7.9 %)	36(8.4 %)	21(7.2 %)	X <sup>2</sup> =0.318	0.573
Gallbladder disease	17(2.4 %)	11(2.6 %)	6(2.1 %)	X <sup>2</sup> =0.186	0.667
Thyroid disease	15(2.1 %)	13(3.0 %)	2(0.7 %)	X <sup>2</sup> =4.649	0.031
Stroke	2(0.3 %)	0.0 %)	2(0.7 %)		0.163
Chronic glomerulonephritis	6(0.8 %)	6(1.4 %)	0.0 %)	X <sup>2</sup> =2.578	0.108
Cancer	6(0.8 %)	2(0.5 %)	4(1.4 %)	X <sup>2</sup> =0.812	0.368
Hepatitis	15(2.1 %)	12(2.8 %)	3(1.0 %)	X <sup>2</sup> =2.638	0.104
Tuberculosis	3(0.4 %)	2(0.5 %)	1(0.3 %)	X <sup>2</sup> < 0.001	1.000
Other diseases	103(14.3 %)	72(16.7 %)	31(10.7 %)	X <sup>2</sup> =5.259	0.022
<b>Initial symptoms</b>					
Initial symptoms	608(84.3 %)	359(83.5 %)	249(85.6 %)	X <sup>2</sup> =0.567	0.451
Fever	369(51.2 %)	176(40.9 %)	193(66.3 %)	X <sup>2</sup> = 44.787	< 0.001
Cough	199(27.6 %)	78(18.1 %)	121(41.6 %)	X <sup>2</sup> = 47.724	< 0.001
Diarrhea	150(20.8 %)	113(26.3 %)	37(12.7 %)	X <sup>2</sup> = 19.380	< 0.001
Fatigue	137(19.0 %)	31(7.2 %)	106(36.4 %)	X <sup>2</sup> = 96.256	< 0.001
Conjunctivitis	1(0.1 %)	1(0.2 %)	0.0 %)		1.000
Other symptoms	136(18.9 %)	21(4.9 %)	115 (39.5 %)	X <sup>2</sup> = 136.031	< 0.001
<b>Concomitant medication</b>					
Antiviral treatment	518(71.8 %)	315(73.3 %)	203(69.8 %)	X <sup>2</sup> =1.049	0.306
Oseltamivir	324(44.9 %)	167(38.8 %)	157(54 %)	X <sup>2</sup> = 16.024	< 0.001
Lopinavir	10(1.4 %)	5(1.2 %)	5(1.7 %)	X <sup>2</sup> =0.091	0.763
Aciclovir	13(1.8 %)	3(0.7 %)	10(3.4 %)	X <sup>2</sup> =7.352	0.007
Ribavirin	34(4.7 %)	31(7.2 %)	3(1.0 %)	X <sup>2</sup> = 14.744	< 0.001
Arbidol	261(36.2 %)	192(44.7 %)	69(23.7 %)	X <sup>2</sup> = 32.949	< 0.001
Other antiviral drugs	73(10.1 %)	69(16.0 %)	4(1.4 %)	X <sup>2</sup> = 41.056	< 0.001
Antibiotics					
Antibiotics	407(56.4 %)	246(57.2 %)	161(55.3 %)	X <sup>2</sup> =0.250	0.617
Amoxicillin	85(11.8 %)	68(15.8 %)	17(5.8 %)	X <sup>2</sup> = 16.595	< 0.001
Cephalosporin	96(13.3 %)	63(14.7 %)	33(11.3 %)	X <sup>2</sup> =1.648	0.199
Levofloxacin	74(10.3 %)	46(10.7 %)	28(9.6 %)	X <sup>2</sup> =0.218	0.641
Moxifloxacin	196(27.2 %)	133(30.9 %)	63(21.6 %)	X <sup>2</sup> =7.552	0.006
Clarithromycin	72(10.0 %)	30(7.0 %)	42(14.4 %)	X <sup>2</sup> =10.734	0.001
Other antibiotics	41(5.7 %)	26(6.0 %)	15(5.2 %)	X <sup>2</sup> =0.257	0.612
Chinese patent medicine					
Chinese patent medicine	452 (62.7 %)	259 (60.2 %)	193 (66.3 %)	X <sup>2</sup> =2.752	0.097
Lianhua Qingwen capsule	400 (55.5 %)	221 (51.4 %)	179 (61.5 %)	X <sup>2</sup> =7.191	0.007
Xiaochaihu granule	12 (1.7 %)	11 (2.6 %)	1 (0.3 %)	X <sup>2</sup> =3.935	0.047
Shuanghuanglian oral solution	19 (2.6 %)	16 (3.7 %)	3 (1.0 %)	X <sup>2</sup> =4.895	0.027
Huoxiang Zhengqi preparation	56 (7.8 %)	1 (0.2 %)	55 (18.9 %)	X <sup>2</sup> = 84.425	< 0.001
Cough syrup	50 (6.9 %)	41 (9.5 %)	9 (3.1 %)	X <sup>2</sup> =11.160	0.001
Banlangen preparation	24 (3.3 %)	22 (5.1 %)	2 (0.7 %)	X <sup>2</sup> =10.579	0.001
Ganmao Qingre granule	21 (2.9 %)	21 (4.9 %)	0	X <sup>2</sup> = 14.638	< 0.001
Other Chinese patent medicines	53 (7.4 %)	22 (5.1 %)	31 (10.7 %)	X <sup>2</sup> =7.812	0.005

2.3. Outcomes

The primary outcome of this study was the proportion of mild and moderate COVID-19 patients who progressed to a severe disease status. We also analysed factors that may affect the outcome, including the patient's age, sex, disease duration, medical history, initial symptoms, concomitant medication, and grouping. Propensity score matching (PSM) was used to further assess the effect of HSYF intervention on the conversion from mild and moderate COVID-19 to a severe status.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS 20.0 software (SPSS Inc., Chicago, IL, United States). Two-sided tests were used, and P-values < 0.05 were considered statistically significant. Numerical variables are summarized as mean (±SD). The data of the categorical variables are described as numbers and percentages.

The t-test/Wilcoxon rank-sum test was used to compare the ages between the two groups. The chi-square test/Fisher's exact test was used to compare the sex, medical history, initial symptoms, and concomitant

medication between the two groups to calculate the rate difference and 95 % confidence interval (CI). Using the proportion of patients who transitioned to a severe status as the dependent variable, the effects of age, sex, disease duration, medical history, initial symptoms, concomitant antiviral drugs, antibiotics, Chinese patent medicines, and grouping were analyzed by univariate and multivariate logistic regression. For factors with a statistical significance in the univariate regression analysis, a logistic regression was performed to match the two groups of patients by propensity score in a 1:1 ratio, and the difference in the primary outcome between the two groups was evaluated.

### 3. Results

#### 3.1. Demographic and patient characteristics

By March 10, 2020, we enrolled 999 mild and moderate COVID-19 patients from 17 quarantine stations in the Wuchang District. After further screening, 263 patients who refused follow-up, 13 patients who were not diagnosed, and two patients who took other types of TCM prescriptions were excluded. Finally, 721 patients were included in our study cohort, including 430 HSYF users and 291 non-users (including decoction, granules, etc.). Among all patients enrolled in this study, 347 (48.1 %) were men and 374 (51.9 %) were women. The median age of the patients was 48 years old. The median age of the exposed group was significantly lower than that of the control group ( $P < 0.001$ ). We found that 46.3 % of patients had a medical history, which included hypertension (16.9 %), fatty liver (7.9 %), and diabetes (7.1 %). A significantly higher proportion of patients in the exposed group had a history of bronchial asthma (4.4 % vs 1.7 %,  $P = 0.047$ ) and thyroid disease (3.0 % vs 0.7 %,  $P = 0.031$ ) compared with the control group, while the proportion of patients with hyperlipidemia (3.7 % vs 11 %,  $P < 0.001$ ) was higher in the control group than the exposed group. Among all patients, 84.3 % had experienced initial COVID-19 symptoms. The number of patients with diarrhea in the exposed group was significantly higher than that in the control group (26.3 % vs 12.7 %, respectively,  $P < 0.001$ ), and the number of patients with fever (40.9 % vs 66.3 %,  $P < 0.001$ ), cough (18.1 % vs 41.6 %,  $P < 0.001$ ), and fatigue (7.2 % vs 36.4

%,  $P < 0.001$ ) was significantly lower in the exposed group than in the control group.

The patients were administered multiple medications during the treatment. There were no differences in the number of patients receiving antiviral drugs, antibiotics, and Chinese patent medicines between the two groups. In terms of antiviral treatment, ribavirin (7.2 % vs 1.0 %,  $P < 0.001$ ) and arbidol (44.7 % vs 23.7 %,  $P < 0.001$ ) were the most commonly administered medications in the exposed group, while oseltamivir (38.8 % vs 54.0 %,  $P < 0.001$ ) and acyclovir (0.7 % vs 3.4 %,  $P = 0.007$ ) were the most commonly administered medication in the control group. In terms of antibiotics, amoxicillin (15.8 % vs 5.8 %,  $P < 0.001$ ) and moxifloxacin (30.9 % vs 21.6 %,  $P = 0.006$ ) were most commonly used in the exposed group, while clarithromycin (7.0 % vs 14.4 %,  $P = 0.001$ ) were most commonly used in the control group. In terms of Chinese patent medicines, the patients in the exposed group were usually administered Xiaochaihu granules (2.6 % vs 0.3 %,  $P = 0.047$ ), Shuanghuanglian oral solution (3.7 % vs 1.0 %,  $P = 0.027$ ), cough syrup (9.5 % vs 3.1 %,  $P = 0.001$ ), Banlangen preparation (5.1 % vs 0.7 %,  $P = 0.001$ ), and Ganmao Qingre granules (4.9 % vs 0 %,  $P < 0.001$ ), while the patients in the control group were administered Lianhua Qingwen capsule (51.4 % vs 61.5 %,  $P = 0.007$ ), and Huoxiang Zhengqi preparation (0.2 % vs 18.9 %,  $P < 0.001$ ) (as shown in Table 1). The majority of onset times in the two groups were from January 23 to February 18 (76.1 % vs 80.8 %).

#### 3.2. The proportion to severe status

Our primary outcome was the proportion of COVID-19 patients who progressed from mild and moderate COVID-19 to a severe disease status. There were no cases of progression to severe disease in the exposed group, while 19 cases (6.5 %,  $P < 0.001$ ) in the control group progressed to severe disease. The difference between the two groups in terms of progression to severe disease (exposed group-control group) was -6.5 % [95 % CI: (-8.87 %, -4.13 %)]. Stratification analysis showed that, excluding diarrhea, there were significant differences between the two groups in terms of sex, age (>48 years), medical history, initial symptoms (fever, cough, diarrhea, fatigue), concomitant medication, etc., (P

**Table 2**  
Efficacy evaluation.

	All patients	Exposed group	Control group	Statistics	P-value
<b>The proportion to severe status</b>					
The proportion to severe status	19(2.6 %)	0	19(6.5 %)	$X^2 = 28.835$	< 0.001
<b>Sex</b>					
Male	14(4.0 %)	0	14(9.6 %)	$X^2 = 20.084$	< 0.001
Female	5(1.3 %)	0	5(3.4 %)	$X^2 = 8.004$	0.005
<b>Age</b>					
Age ≤ 48yr	3(0.8 %)	0	3(3.4 %)	$X^2 = 9.521$	0.002
Age > 48yr	16(4.5 %)	0	16(7.9 %)	$X^2 = 12.627$	< 0.001
<b>Underlying disease</b>					
Yes	7(2.1 %)	0	7(5.6 %)	$X^2 = 9.251$	0.002
No	12(3.1 %)	0	12(7.3 %)	$X^2 = 16.662$	< 0.001
<b>Initial symptoms</b>					
Yes	19(3.1 %)	0	19(7.6 %)	$X^2 = 28.277$	< 0.001
No	0	0	0		
<b>Fever</b>					
Yes	16(4.3 %)	0	16(8.3 %)	$X^2 = 15.252$	< 0.001
No	3(0.9 %)	0	3(3.1 %)	$X^2 = 7.842$	0.005
<b>Cough</b>					
Yes	12(6.0 %)	0	12(9.9 %)	$X^2 = 6.575$	0.010
No	7(1.3 %)	0	7(4.1 %)	$X^2 = 11.744$	0.001
<b>Diarrhea</b>					
Yes	1(0.7 %)	0	1(2.7 %)		0.247
No	18(3.2 %)	0	18(7.1 %)	$X^2 = 23.196$	< 0.001
<b>Fatigue</b>					
Yes	10(7.3 %)	0	10(9.4 %)	$X^2 = 1.915$	0.166
No	9(1.5 %)	0	9(4.9 %)	$X^2 = 16.639$	< 0.001
<b>Chinese patent medicine</b>					
Yes	13(2.9 %)	0	13(6.7 %)	$X^2 = 17.962$	< 0.001
No	6(2.2 %)	0	6(6.1 %)	$X^2 = 8.085$	0.004

< 0.05); therefore, these factors were accounted for in the subsequent analysis (Table 2).

The univariate logistic regression analysis showed that sex (male), age (>48 years), fever, cough, and fatigue were risk factors for progression to a severe status. We further performed a multivariate logistic regression analysis to adjust for the above risk factors. The results showed that after adjusting for all factors, sex (male) (OR: 3.145; 95 % CI: 1.036–9.545; P = 0.043) and age (>48 years) (OR: 1.044; 95 % CI: 1.001–1.088; P = 0.044) were independent risk factors for progression to a severe disease status (Table 3).

Considering the difference in sample size between the two groups and the imbalance in confounding factors, the risk factors analyzed in the univariate logistic regression analysis were used as variables for 1:1 PSM (caliper = 0.25σ), and the number of patients in both groups were 148. Among them, no patients in the exposed group progressed to severe disease, and seven patients in the control group progressed to severe disease (4.7 %) (P = 0.022). The difference between the two groups in terms of progression to severe disease (exposed group-control group) was -4.7 % [95 % CI: (-8.2 %, -1.2 %)] (Table 4).

#### 4. Discussion

The global prevalence of COVID-19 has brought tremendous medical pressure worldwide. According to data from Johns Hopkins University in the United States, by April 3, 2020, the number of COVID-19 cases exceeded 1 million globally. Furthermore, the number of diagnosed cases in the United States were over 240,000, and that in Italy and Spain were over 110,000, with the number of newly diagnosed cases still rising [5]. With a large number of people in close contact with mild/moderate COVID-19 patients, all countries have adopted community control and home quarantine measures to prevent the spread of the epidemic. However, during home quarantine, problems such as cross-infection and cluster outbreaks in the community have emerged due to the lack of strict community supervision as well as the need to purchase necessities and travel for hospital consultations. In addition, mild and moderate COVID-19 patients who were under home quarantine lacked effective intervention strategies without the guidance from physicians, which may have resulted in problems such as the progression from mild and moderate to severe disease [6,7]. In such patients, an effective large-scale community intervention strategy could reduce this conversion to severe disease and reduce the number of severe and critical COVID-19 patients, thus significantly improving and controlling the COVID-19 epidemic.

For mild and moderate COVID-19 patients, antiviral, antibiotic, and symptomatic supportive treatments are most commonly used. However, most of the antiviral drugs used to treat COVID-19 currently are based on previous treatments for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and influenza A, and uncertainties on the efficacy and side effects of these drugs remain problematic. One case report stated that a patient was cured with remdesivir [8]. In another clinical study, lopinavir-ritonavir had no clinical benefit on the treatment of patients with severe COVID-19, and adverse gastrointestinal events were identified [9]. Furthermore, Abidol and lopinavir-ritonavir did not improve COVID-19 symptoms or shorten the conversion of the viral nucleic acid to a negative result in a clinical study of 134 patients [10]. The adverse reactions and side effects of related antiviral drugs, such as hypocalcemia, hemolytic anemia, hypomagnesemia, as well as those that emerged during the treatment of SARS by ribavirin cannot be ignored [11]. Hydroxychloroquine and chloroquine were urgently approved by the Food and Drug Administration to treat COVID-19, but chloroquine drugs (hydroxychloroquine and chloroquine phosphate) can cause adverse reactions such as dizziness, headache, vertigo, loss of appetite and nausea [12].

Our study showed that under the conditions of home quarantine, TCM is effective in reducing the progression of mild and moderate COVID-19 to severe disease, which can serve as a reference for the

**Table 3**  
Univariate and multivariate regression analysis.

Factors	Univariate analysis		Multivariate analysis				
	P-value	OR(95 %CI)	P-value	OR(95 %CI)			
Age	<0.001	1.073 (1.034,1.113)	< 0.001 <sup>1</sup>	1.072 (1.034,1.112)			
			< 0.001 <sup>2</sup>	1.083 (1.041,1.125)			
			0.006 <sup>3</sup>	1.060 (1.017,1.104)			
			0.004 <sup>4</sup>	1.063 (1.019,1.109)			
			0.005 <sup>5</sup>	1.063 (1.019,1.108)			
			0.005 <sup>6</sup>	1.063 (1.019,1.109)			
			0.044 <sup>7</sup>	1.044 (1.001,1.088)			
			0.027 <sup>1</sup>	3.241 (1.141,9.203)			
			0.027 <sup>2</sup>	3.258 (1.144,9.284)			
			0.034 <sup>3</sup>	3.207 (1.091,9.427)			
Sex(Ref = female)	0.031	3.103(1.106, 8.707)	0.038 <sup>4</sup>	3.165 (1.064,9.414)			
			0.036 <sup>5</sup>	3.263 (1.083,9.832)			
			0.036 <sup>6</sup>	3.284 (1.084,9.948)			
			0.043 <sup>7</sup>	3.145 (1.036,9.545)			
			0.052 <sup>2</sup>	0.371 (0.137,1.009)			
			0.152 <sup>3</sup>	0.463 (0.161,1.329)			
			0.095 <sup>4</sup>	0.397 (0.134,1.175)			
			0.092 <sup>5</sup>	0.393 (0.133,1.165)			
			0.099 <sup>6</sup>	0.397 (0.132,1.188)			
			0.162 <sup>7</sup>	0.454 (0.150,1.372)			
Medical history (Ref = no)	0.404	0.669 (0.260,1.719)	0.033 <sup>3</sup>	4.119 (1.125,15.08)			
			0.037 <sup>4</sup>	4.035 (1.090,14.943)			
			0.036 <sup>5</sup>	4.053 (1.096,14.986)			
			0.036 <sup>6</sup>	4.062 (1.097,15.037)			
			0.179 <sup>7</sup>	2.461 (0.663,9.142)			
			0.024 <sup>3</sup>	3.355 (1.172,9.601)			
			0.045 <sup>4</sup>	2.996 (1.027,8.738)			
			0.042 <sup>5</sup>	3.040 (1.040,8.886)			
			0.042 <sup>6</sup>	3.041 (1.039,8.897)			
			0.159 <sup>7</sup>	2.150 (0.742,6.234)			
Cough	0.001	4.721 (1.831,12.172)	0.152 <sup>3</sup>	0.219 (0.027,1.753)			
			0.131 <sup>4</sup>	0.199 (0.024,1.619)			
			0.129 <sup>5</sup>	0.197 (0.024,1.608)			
			0.129 <sup>6</sup>	0.195 (0.024,1.607)			
			0.185 <sup>7</sup>	0.235 (0.028,2.000)			
			0.185 <sup>3</sup>	2.061 (0.708,5.998)			
			0.133 <sup>4</sup>				
			Diarrhea	0.126	0.206 (0.027,1.557)	0.129 <sup>5</sup>	
						0.129 <sup>6</sup>	
						0.185 <sup>7</sup>	
Fatigue	0.001	5.031 (2.003,12.634)				0.185 <sup>3</sup>	
						0.133 <sup>4</sup>	

(continued on next page)



Table 3 (continued)

Factors	Univariate analysis		Multivariate analysis	
	P-value	OR(95 %CI)	P-value	OR(95 %CI)
Antiviral treatment (Ref = no)	0.103	3.410 (0.781,14.895)		2.310 (0.776,6.880)
			0.123 <sup>5</sup>	2.387 (0.791,7.201)
			0.125 <sup>6</sup>	2.377 (0.786,7.192)
			0.327 <sup>7</sup>	1.710 (0.585,5.000)
			0.058 <sup>4</sup>	4.439 (0.951,20.730)
			0.055 <sup>5</sup>	4.948 (0.964,25.389)
			0.056 <sup>6</sup>	4.944 (0.963,25.378)
Antibiotics (Ref = no)	0.291	1.694 (0.636,4.507)	0.061 <sup>7</sup>	4.691 (0.930,23.644)
			0.694 <sup>5</sup>	0.795 (0.254,2.488)
			0.684 <sup>6</sup>	0.788 (0.249,2.491)
Chinese patent medicine (Ref = no)	0.602	1.298 (0.487,3.456)	0.950 <sup>7</sup>	0.964 (0.308,3.016)
			0.906 <sup>6</sup>	1.069 (0.352,3.246)
Grouping (Ref = control group)	0.992	/	0.758 <sup>7</sup>	1.187 (0.398,3.545)
			0.992 <sup>7</sup>	

- 1) The model includes age and sex.
- 2) The model includes age, gender and medical history.
- 3) The model includes age, sex, medical history and initial symptoms.
- 4) The model includes age, gender, medical history, initial symptoms and antiviral drugs.
- 5) The model includes age, gender, medical history, initial symptoms, antiviral drugs and antibiotics.
- 6) The model includes age, gender, medical history, initial symptoms, antiviral drugs, antibiotics and Chinese patent medicine.
- 7) The model includes age, gender, medical history, initial symptoms, antiviral drugs, antibiotics, Chinese patent medicine and grouping.

prevention of the disease. As a key point of COVID-19 prognosis, there have only been a few studies assessing the proportion of mild and moderate COVID-19 patients who have progressed to a severe disease status currently. In attempting to prevent and control the epidemic in China, TCM has been widely used. Some studies revealed that TCM can reduce the clinical symptoms of fever and cough in mild and moderate patients [13,14] and improve relevant imaging indexes [15]. However, these studies usually had small sample sizes, and did not assess the proportion of mild and moderate patients who progressed to a severe disease status.

In this retrospective cohort study, the results showed that the main influencing factors for the progression of mild and moderate COVID-19 to severe disease included sex (male), age, fever, cough, and fatigue,

Table 4 Propensity score matching (PSM).

Variables		Before PSM		P-value	After PSM		P-value
		Exposed group n = 430	Control group n = 291		Exposed group n = 148	Control group n = 148	
Age	Mean ± SD	43.79 ± 12.099	55.44 ± 14.641	< 0.001	47.80 ± 12.656	48.97 ± 14.618	0.407
	Median(Q1,Q3)	44.00 (35,52)	57.00 (46,68)		49.50(39,57)	50.50(37,59)	
Sex(Ref = female)		201(46.7 %)	146(50.2 %)	0.366	83(56.1 %)	75(50.7 %)	0.351
Fever		176(40.9 %)	193(66.3 %)	< 0.001	71(48 %)	78(52.7 %)	0.416
Cough		78(18.1 %)	121(41.6 %)	< 0.001	126(85.1 %)	115(77.7 %)	0.100
Fatigue		31(7.2 %)	106(36.4 %)	< 0.001	133(89.9 %)	134(90.5 %)	0.845

which are consistent with other studies [16–18]. After excluding the effects of the above factors, we found that the HSYF intervention can effectively reduce the conversion of mild and moderate COVID-19 to severe disease, providing evidence on the effectiveness of TCM. Thus, TCM can be an option in addition to antibiotic therapy, antiviral treatment, and supportive oxygen therapy for the treatment of mild and moderate COVID-19 patients.

HSYF administered in the study mainly contains the following Chinese materia medica: Ma Huang (Ephedrae Herba), Shi Gao (Gypsum fibrosum), Xing Ren (Armeniacae Semen), Qiang Huo (Notopterygii Rhizoma seu Radix), Ting Li Zi (Lepidii/Descurainiae Semen), Guan Zhong (Cynanchi Rhizoma), Di Long (Pheretima), Xu Chang Qing (Cynanchi paniculati Radix), Huo Xiang (Pogostemonis Herba), Pei Lan (Eupatorii Herba), Cang Zhu (Atractylodis Rhizoma), Yun Ling (Poria), Sheng Bai Zhu (Atractylodis macrocephalae Rhizoma), Jiao Shan Zha (Crataegi Fructus), Jiao Shen Qu (Massa medicata fermentata), Jiao Mai Ya (Hordei Fructus germinatus), Hou Po (Magnoliae officinalis Cortex), Jiao Bing Lang (Arecae Semen), Wei Cao Guo (Tsaoko Fructus), and Sheng Jiang (Zingiberis Rhizoma recens). In TCM theory, these prescriptions can improve the patients' healthy qi and dispel evil factors. Ma Huang (Ephedrae Herba), Shi Gao (Gypsum fibrosum), Xing Ren (Armeniacae Semen), Ting Li Zi (Lepidii/Descurainiae Semen) focus on improving asthma symptoms in the lung; Yun Ling (Poria), Sheng Bai Zhu (Atractylodis macrocephalae Rhizoma), Jiao Shan Zha (Crataegi Fructus), Jiao Shen Qu (Massa medicata fermentata), Jiao Mai Ya (Hordei Fructus germinatus), Hou Po (Magnoliae officinalis Cortex), Jiao Bing Lang (Arecae Semen), and Wei Cao Guo (Tsaoko Fructus) help strengthen the healthy qi; Huo Xiang (Pogostemonis Herba), and Pei Lan (Eupatorii Herba) can dispel the evil factors. Studies have shown that many Chinese components of HSYF can exert antiviral effects and improve respiratory symptoms. In terms of the antiviral components, methyl ephedrine, L-ephedrine, and D-pseudoephedrine are present in Ma Huang (Ephedrae Herba), which can significantly inhibit the in vitro proliferation of influenza A (H1N1) virus [19]. Patchouli alcohol in Huo Xiang (Pogostemonis Herba) can effectively inhibit the replication of H1N1 virus [20]; Hou Po (Magnoliae officinalis Cortex) can alter the cell cycle and promote H1N1 infected cells into the S phase [21]; the magnolol extract can inhibit the secretion of CD44 and CD54, reduce the levels of inflammatory factors IL-1β, IL-6, and TNF-α, and relieve inflammation [22]. The active ingredients of Wei Cao Guo (Tsaoko Fructus) inhibit the binding region of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S-protein to human ACE2, and control the replication of SARS-CoV-2 in the human body [23]. In addition to its antiviral effect, Ma Huang (Ephedrae Herba) is a widely used Chinese herbal medicine for respiratory diseases, and it also stimulates β receptors of the bronchial smooth muscle, expands the bronchus, exerts anti-inflammatory effects [24], and can stimulate central nervous system excitability, and regulate body temperature [25]. This plays an important role in improving the symptoms of COVID-19, including fever, cough, shortness of breath, and other respiratory symptoms.

The clinical benefits and risks need to be balanced for the treatment of mild and moderate COVID-19. The lack of understanding on the efficacy, side effects, and other risks associated with current antiviral treatments make it difficult to be used as a conventional intervention for mild and

moderate COVID-19 patients. However, the results of our study provide evidence on the effectiveness of TCM for the treatment of mild and moderate COVID-19. TCM treatment has the advantage of being widely used and inexpensive, making it convenient for mild and moderate COVID-19 patients isolated in the large-scale community to quickly recover. Furthermore, our study used a real-time Internet information collection application to collect data, which enabled physicians to communicate with the patients in real time and dynamically monitor changes in the patient's condition. Thus, self-quarantined patients did not need to go to the hospital for a consultation, which prevented cross-infection.

Although the results of our study are significant and provides insight on the use of TCM treatment for mild and moderate COVID-19, there are still some limitations. Firstly, our study was a retrospective study rather than a prospective, randomized clinical trial (RCT) due to the current situation. In the future, we aim to conduct RCTs and experiments to further verify the efficacy and mechanism of HSYF. Secondly, as a retrospective cohort study, some baseline factors between the exposed group and the control group were not completely accounted for, and the age of the exposed group was significantly younger than that of the control group, which may be related to our data collection method. Using a real-time Internet information collection application is a more acceptable method in the younger population, and imbalances in baseline data such as sex, age, and medical history could have introduced bias, which may have affected the results of the study. Nevertheless, we have corrected these possible influencing factors during our analysis. In order to improve the reliability of the study results, a cohort study with a larger sample size or RCTs is necessary.

## 5. Conclusion

HSYF can significantly reduce the progression of mild and moderate COVID-19 to a severe disease status, which has a positive effect on the prevention and treatment of the disease. However, future clinical studies with a larger sample size are needed to further verify our results.

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## Declaration of Competing Interest

Authors declare no competing interests. Jiangsu Kanion Pharmaceutical Co., Ltd. provided the medications for the study, while they did not participate in research design, data collection, data analysis, data interpretation, nor article writing.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.phrs.2020.105127>.

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