Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pharmacological Research 178 (2022) 106174

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Timely treatment and higher compliance to traditional Chinese medicine: New influencing factors for reducing severe COVID-19 based on retrospective cohorts in 2020 and 2021

Ying Zhang [a], Yangyang Liu [b], Ming Li [c], Shaohua Feng [c], Xiuyang Li [d], Zezheng Gao [e,f], Yingying Yang [e], Xiaolin Tong [g,*]

[a] School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing100029, China
[b] The Affiliated Hospital to Changchun University of Chinese Medicine, 1478 Gongnong Street, Changchun, Jilin Province 130021, China
[c] Tonghua Central Hospital, Tonghua 134099, China
[d] Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
[e] Department of Endocrinology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
[f] Institute of Metabolic Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
[g] Changchun University of Chinese Medicine, Changchun, Jilin Province 130021, China

ARTICLE INFO

Keywords:
Mild COVID-19
Moderate COVID-19
The proportion to severe status
Traditional Chinese medicine
Cohort study
E-value

ABSTRACT

Objective: From the beginning of 2020, our study team formulated a traditional Chinese medicine (TCM) prescription named Sanhanhuashi formula (SHHS) to treat COVID-19 patients. Then we conducted several studies to explore the effectiveness of SHHS formula and other influencing factors on prognosis of disease. The purpose of this study was to describe the trends of patients' characters from 2020 to 2021 based on two separate cohorts, and to explore the influencing factors on incidence of severe COVID-19 conditions, especially the contributions of timely treatment and higher compliance to SHHS formula.

Methods: A retrospective cohort study was conducted in Wuhan, Hubei province and Tonghua, Jilin province. Participants were hospitalized mild to moderate COVID-19 consecutive enrolled patients in Wuhan hospital of traditional Chinese and western medicine (from Feb 13, 2020 to March 8, 2020) and Tonghua central hospital (from Jan 17, 2021 to Feb 5, 2021). Age, sex, time waiting to be hospitalized, medical history, initial symptoms, concomitant medication, and severity of disease were collected. Univariate and multivariate logistic regression were used to explore the associations between various exposures and the outcome, ie. the proportion of patients who were converted to severe status. E-values and its lower control limit (LCL) were calculated for sensitivity analysis.

Results: Totally, 176 COVID-19 patients in two hospitals were enrolled. 81 patients were from Wuhan hospital of traditional Chinese and western medicine and 95 from Tonghua central hospital. 42 patients used SHHS formula arrival or exceed 7 days, and 2 (4.8%) progressed to severe condition. Among 134 patients who were exposed SHHS less than 7 days, 18 (13.4%) were converted to severe situation. Compared with those diagnosed in 2020, cases in 2021 were characterized as lower rates of initial symptoms (88.9% vs 35.8%, $P < 0.001$) and concomitant medications ever widely used, eg. antiviral medicine (71.6% vs 43.2%, $P < 0.001$), antibiotics (61.7% vs 13.7%, $P < 0.001$) and Chinese patent medicine (76.5% vs 44.2%, $P < 0.001$). They also waited less time for hospitalization (median: 12 vs 2 days, $P < 0.001$). The final multivariate logistic regression model showed that age (> 60 yrs) (OR: 3.943; 95% CI: 1.402–11.086; $P = 0.009$; E-value = 7.35, LCL:2.15), diagnosis year (OR: 0.165; 95% CI: 0.050–0.551; $P = 0.003$; E-value=11.6, LCL: 3.03) and SHHS exposure (OR: 0.118; 95% CI: 0.014–0.992; $P = 0.049$; E-value = 16.43, LCL:1.1) were independent risk factors for predicting severe status.

Conclusions: The profile of COVID-19 patients has changed after one year. In addition to age, diagnosis year and SHHS exposure are two new factors to predict the prognosis of disease. The patients diagnosed in 2021 were mainly benefited from timely treatment. Subsequently, adhere to use SHHS formula a quite longer time reduced the number of severe cases. Therefore, both the current epidemic prevention and control measures and

* Correspondence to: Changchun University of Chinese Medicine, China.
E-mail addresses: yingzhang@bucm.edu.cn (Y. Zhang), 996439299@qq.com (Y. Liu), 339558371@qq.com (M. Li), shiyiyuan9@163.com (S. Feng), leexiuyang@126.com (X. Li), zzgaobucm@163.com (Z. Gao), wyhcyyy@126.com (Y. Yang), tongxiaolin@vip.163.com (X. Tong).

https://doi.org/10.1016/j.phrs.2022.106174
Received 12 January 2022; Received in revised form 22 February 2022; Accepted 7 March 2022
Available online 11 March 2022

increasing compliance to traditional Chinese medicine are effective ways to reducing severe cases and improving public health.

1. Introduction

At the end of December 2019, the Coronavirus disease (COVID-19) epidemic emerged in Wuhan (Hubei Province, China) [1], and then spread rapidly around the world. Globally, as of January 7, 2022, there have been more than 298 million confirmed cases, including over 5 million deaths reported to WHO [2]. Owing to excellent management strategies and quickly social responses to foreign imported cases, the epidemic has been under well control in China. The cumulative confirmed cases in China was around 133 thousand, including 5699 deaths [2]. Because Mild or moderate was the initial status in majority of confirmed cases, to effective control the progress of disease will remarkably reduce the incidence of severe COVID-19, hereby the deaths.

As the location with the first outbreak, Wuhan is a first-line big city with a high population density. At the early time, due to limited medical resources, patients could not be diagnosed until some typical symptoms appeared. It's not worthy of doubt, there was relatively high prevalence of various initial symptoms in hospitalized patients at the beginning of 2020. Tonghua city, located in the northeastern China's Jilin province, with more than two-thirds of mountainous areas and its population ranked 5th in Jilin. In January 12, 2021, epidemic of COVID-19 outbroke in Tonghua and mainly spread by asymptomatic carriers. Then the city government announced lockdown in January 18. The tight control mode on the patients with confirmed or suspected COVID-19, and close contacts of the confirmed cases, ensured a large number of mild to moderate cases were treated in time, reducing the possibility of becoming severe cases. Therefore, the proportion of severe cases dropped significantly.

Our team is one of the first medical teams to aid coronavirus control in Wuhan in 2020. we formulated a traditional Chinese medicine (TCM) prescription named Cold-damp Plague Formula (Hanshiyi) to prevent exacerbations of the epidemic [4,5]. In previous cohort study of 17 quarantine stations, the results showed Hanshiyi formula (decoction or granule), renamed Sanhanhuashi (SHHS) formula in 2021, could significantly reduce the progression to severe condition in patients with mild to moderate COVID-19 [5]. But, we still don't know whether there will be notable difference when patients' compliance differs. There is also lack of quantitative evidences to show the changes of severity proportion over years. Furthermore, the analysis of whether the contributions of SHHS formula to curb disease progress will change under strictly controlled medical environments, is still needed.

Therefore, we conducted this study with the purpose to describe the trends of patients' characters from 2020 to 2021 based on two separate cohorts, and to explore the influencing factors on incidence of severe COVID-19, especially the contributions of timely treatment and higher compliance of SHHS formula.

2. Methods

2.1. Study design and participants

This study is a retrospective cohort study conducted in Wuhan, Hubei province and Tonghua, Jilin province. Participants were hospitalized mild to moderate COVID-19 consecutive patients in Wuhan hospital of traditional Chinese and western medicine (from Feb 13, 2020 to March 8, 2020) and Tonghua central hospital (from Jan 17, 2021 to Feb 5, 2021). All of the participants were aged over 18 years old and ever exposed to SHHS formula, more or less. There were no any restrictions on dosage or duration of using SHHS. Data on age, sex, time waiting to be hospitalized, medical history, initial symptoms, concomitant medication, and severity of disease were collected.

The diagnosis of COVID-19 patients was conducted by Wuhan hospital of traditional Chinese and western medicine, and Tonghua central hospital. The diagnosed criteria were according to the *Diagnosis and Treatment Guideline for COVID-19* released by the National Health Commission of the People's Republic of China [6].

This study was approved by the institutional ethics board of Hubei Provincial Hospital of Traditional Chinese Medicine (No. HBZY2020-C27–01) and Changchun University of Chinese Medicine (CCZYFYLL2021–001). The study was also a sub task of the Special Project for Emergency of the Ministry of Science and Technology (2020YFC0845000).

2.2. Data collection

Data of consecutive hospitalized patients in two hospitals were exported from HIS (hospital information system) system to a standard electronic database. Clinical coordinating staffs from Guang'anmen hospital and Changchun University of Chinese Medicine, along with data management associates in Beijing University of Chinese Medicine completed the query generating and data cleaning, after rounds of communicating with clinicians to verify the information and ensure the accuracy of the data. The analysis and reporting of the results of the study were in accordance with the STORBE guideline [7].

2.3. Exposures

All of the patients were ever prescribed SHHS formula (decoction or granule), the exposure level was categorized into high and low, which implied using time arrival 7 days or not. The patients in Wuhan and Tonghua were collected in 2020 and 2021, respectively. In China, the epidemic in 2021 differs from 2020, not only on virus mutations, but also the public health strategies. Therefore, patients in two hospitals who were diagnosed in different years were also exposed to different treatment, social and policy environments.

2.4. Outcomes

The outcome of the cohorts was the proportion of mild to moderate COVID-19 patients who were converted to severe or death status. The baseline covariates included age, sex, time waiting to be hospitalized, medical history, initial symptoms, concomitant medication, year of diagnosis and exposure level of SHHS. Univariate regression analysis and multivariate logistic regression were used to analyze the factors that influenced the prognosis of disease. Interaction(s) between factors were considered to add into the model when any combinations could increase the statistical power.

2.5. Statistical analysis

Data management and statistical analyses in this study were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, US) and SPSS 20.0 (IBM SPSS Inc., Chicago, IL, US). Two-sided test was used, and a P-values < 0.05 were considered statistically significant. Numerical variables were summarized as mean ($\pm$SD) and median (IQR). The data of the categorical variables was described as counts and percentages.

According to the characteristics of the variables, the t-test / Wilcoxon rank-sum test was used to compare continuous data between groups, and the chi-square test / Fisher's exact test for categorical data. To construct the univariate and multivariate model, the proportion of patients who were converted to severe status was the dependent variable, age, sex, medical history, initial symptoms, concomitant medicines, year

of diagnosis and level of SHHS exposure were the independent variables. To select the independent variables which could enter the model, likelihood ratio forward method was used the construct the final model. We calculated the E-values and its lower control limit (LCL) as a sensitivity analysis to quantify the potential for unmeasured confounding bias on observed associations between exposures and outcomes [8–10]. The E-value is the minimum strength of association required between an unmeasured confounder and exposure and between confounder and outcome, conditional on measured covariates, to explain away the observed exposure-outcome association [10]. A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate, therefore, the larger E-value means more robust of the observed associations. E-value is a sensitivity analysis without any assumptions and the calculation is straightforward. E-values for each exposure were calculated using an online calculator (website: www.evalue-calculator.com, accessed on January 1, 2021) [11].

3. Results

3.1. Demographic and patient characteristics

Totally, 176 COVID-19 patients in two hospitals were enrolled. 81 patients were from Wuhan hospital of traditional Chinese and western medicine and 95 from Tonghua central hospital. The severity of all included patients was mild or moderate. Due to the characters of epidemic in China, one city has relatively a little possibility to encounter outbreak once again over a year. For most situations, the cases were scattered in different cities and years. Therefore, patients in two hospitals could represent more differences than similarities on virus type, treatments and management strategies.

42 patients used SHHS formula arrival or exceed 7 days, and 2 (4.8%) of them was converted to severe status. Among 134 patients who were exposed SHHS less than 7 days, 40 (29.9%) had become severe situation (see Fig. 1).

In the included patients, 90 (51.1%) were female, and 39 (48.1%) were diagnosed in 2021. The median age was 55.5 years old. There was no statistical difference between year groups on age, proportion of over 60 years old and sex ($P > 0.05$). Patients with medical history were 88 (50.0%), of which the most common medical history were hypertension (46, 26.1%), diabetes (21, 11.9%) and coronary heart disease (19, 10.8%). The proportion of gastrosis was decreased from year 2020 to 2021 (8.6% vs 0.0%, $P = 0.011$) and the differences on other diseases between year groups were not statistically significant ($P > 0.05$). Among all the patients, 106 (60.2%) had initial symptoms and there was statistical significance on the decrease of proportion after one year (88.9% vs 35.8%, $P < 0.001$). The proportion of patients with fever (25.9% vs 9.5%, $P < 0.001$), headache or fatigue (24.7% vs 2.1%, $P < 0.001$), expectoration (58.0% vs 25.3%, $P < 0.001$), heart and lung symptoms (35.8% vs 7.4%, $P < 0.001$), gastrointestinal symptoms (29.6% vs 2.1%, $P < 0.001$), mental symptoms (34.6% vs 0.0%, $P < 0.001$) and cacation disorders (16.1% vs 4.2%, $P = 0.008$) was lower in 2021 than 2020 (see Table 1 and Fig. 2).

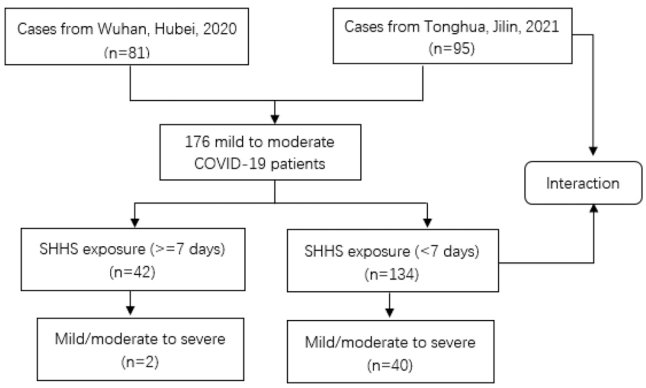

Fig. 1. Flowchart of enrollment.

The patients were administered multiple medication during treating COVID-19, medicines most used included Chinese patent medicine (104, 59.1%), antiviral treatment (99, 56.3%), antibiotics (63, 35.8%) and antifebrile (29, 16.5%) etc. 47 (26.7%) patients used medicine for their concomitant diseases. There was a remarkable decline after one year on using medicine of antiviral (71.6% vs 43.2%, $P < 0.001$), antibiotics (61.7% vs 13.7%, $P < 0.001$) and Chinese patent medicine (76.5% vs 44.2%, $P < 0.001$); an increase on using antifebrile (4.9% vs 26.3%, $P < 0.001$) and hormone (2.5% vs 10.5%, $P = 0.035$). Time from typical symptoms emerged or disease confirmed to hospitalization was shortened remarkably (median: 12 vs 2 days, $P < 0.001$). The exposure time of SHHS was nearly equal (27.2% vs 21.1%) between years ($P > 0.05$) (see Table 1).

3.2. Prognosis

Our primary outcome was the proportion of mild/moderate COVID-19 patients turning to severe status. There was no death observed in hospitalization period in either hospital. The variations on sex, concomitant diseases, initial symptoms and SHHS exposure didn't differ the incidence of severe status ($P > 0.05$). The difference of age category (>60 yrs or not) (18.6% vs 6.6%, $P = 0.014$) and diagnosis year (18.5% vs 5.3%, $P = 0.006$) could significantly influence the rate of severe cases (Table 2).

Univariate and multivariate logistic regression were used to evaluate the influencing factors on the proportion of mild to moderate COVID-19 patients turning to severe status. The dependent variable was the proportion of severe status. Age (>60 yrs or not), sex, medical history, initial symptoms, SHHS exposure (>7days or not) and diagnosis year (2020 vs 2021) entered the exploratory model as independent variables. After using forward likelihood ratio model selection procedure, there were three variables and one interaction item (see Fig. 3) included in the final model. The results showed that age (> 60 yrs) (OR: 3.943; 95% CI: 1.402–11.086; $P = 0.009$; E-value = 7.35, LCL:2.15), diagnosis year (OR: 0.165; 95% CI: 0.050–0.551; $P = 0.003$; E-value = 11.6, LCL: 3.03) and SHHS exposure (OR: 0.118; 95% CI: 0.014–0.992; $P = 0.049$; E-value = 16.43, LCL:1.1) were independent risk factors of predicting severe status (Table 3).

4. Discussions

4.1. Findings of this study

This cohort study showed several meaningful findings. The first, there was notable downtrend on initial symptoms (88.9–35.8%) and usage of several concomitant medicines, such as antiviral treatment (71.6–43.2%) and antibiotic (61.7–13.7%). The decrease of initial symptoms might largely owe to the screening strategies to suspected case and close contacts of confirmed cases. In 2021, most of the cases had been detected and then closely observed and treated before typical symptoms emerged under the strict control strategies in Tonghua city. It's worth mentioning that mental symptoms disappeared in 2021, implying psychological stability was improved among confirmed cases compared with those in 2020. The accumulating clinical experiences and evidences of diagnosis and treating COVID-19 made the prescriptions more targeted other than broad medicating in the beginning stage in 2020. In addition, lower symptoms prevalence also reduced usages of some combined medicines. The second, we found remarkable decrease on the incidence of severe cases from 2020 to 2021. These might be the results of multiple control measures in 2021, for example, virus mutations, timely treatment, longer isolation or hospitalization time etc. The third and the most, the final model demonstrated three factors could dependently influence the proportion of mild/moderate

Table 1
Demographic and Patient Characteristics.

	All patients (n = 176)	Diagnosis year		Statistics	*P*-value
		2020 (n = 81)	2021 (n = 95)		
Age					
Mean ± SD	53.65 ± 16.43	52.96 ± 14.35	54.24 ± 18.07	Z = −0.540	0.589
Median(IQR)	55.50 (27.50)	56.00 (25.00)	55.00 (31.00)		
≤ 60 yr	106 (60.2%)	48 (59.3%)	58 (61.1%)	χ^2= 0.059	0.809
> 60 yr	70 (39.8%)	33 (40.7%)	37 (38.9%)		
Sex					
Female	90 (51.1%)	39 (48.1%)	51 (53.7%)	χ^2= 0.536	0.464
Medical history					
Medical history	88 (50.0%)	39 (48.1%)	49 (51.6%)	χ^2= 0.206	0.650
Hypertension	46 (26.1%)	21 (25.9%)	25 (26.3%)	χ^2= 0.003	0.953
Diabetes	21 (11.9%)	7(8.6%)	14 (14.7%)	χ^2= 1.546	0.214
Coronary heart disease	19 (10.8%)	6(7.4%)	13 (13.7%)	χ^2= 1.789	0.181
Gastrosis	7(4.0%)	7(8.6%)	0(0.0%)	χ^2= 6.437	0.011
Stroke	3(1.7%)	2(2.5%)	1(1.1%)	χ^2= 0.019	0.889
Hepatopathy	3(1.7%)	1(1.2%)	2(2.1%)	χ^2= 0.000	1.000
Cancer	1(0.6%)	0(0.0%)	1(1.1%)	–	1.000
Initial symptoms					
Initial symptoms	106 (60.2%)	72 (88.9%)	34 (35.8%)	χ^2= 51.463	< 0.001
Fever	30 (17.1%)	21 (25.9%)	9(9.5%)	χ^2= 8.370	0.004
Sweating	2(1.1%)	2(2.5%)	0(0.0%)	-[a]	0.210
Headache or fatigue	22 (12.5%)	20 (24.7%)	2(2.1%)	χ^2= 20.392	< 0.001
Expectoration	71 (40.3%)	47 (58.0%)	24 (25.3%)	χ^2= 19.499	< 0.001
Nasopharynx symptoms	14(8.0%)	9 (11.1%)	5(5.3%)	χ^2= 2.042	0.153
Heart and lung symptoms	36 (20.5%)	29 (35.8%)	7(7.4%)	χ^2= 21.725	< 0.001
Taste	3(1.7%)	0(0.0%)	3(3.2%)	χ^2= 1.059	0.304
Gastrointestinal symptoms	26 (14.8%)	24 (29.6%)	2(2.1%)	χ^2= 26.308	< 0.001
Mental symptoms	28 (15.9%)	28 (34.6%)	0(0.0%)	χ^2= 39.052	< 0.001
Cacation disorders	17(9.7%)	13 (16.1%)	4(4.2%)	χ^2= 7.023	0.008
Concomitant medication					
Antiviral treatment	99 (56.3%)	58 (71.6%)	41 (43.2%)	χ^2= 14.377	< 0.001
Antibiotics	63 (35.8%)	50 (61.7%)	13 (13.7%)	χ^2= 43.912	< 0.001
Antifebrile	29 (16.5%)	4(4.9%)	25 (26.3%)	χ^2= 14.519	< 0.001
Interferon	9(5.1%)	1(1.2%)	8(8.4%)	χ^2= 3.290	0.070
Hormone medicine	12(6.8%)	2(2.5%)	10 (10.5%)	χ^2= 4.468	0.035
Chinese patent medicine	104 (59.1%)	62 (76.5%)	42 (44.2%)	χ^2= 18.908	< 0.001
Other medicine	132 (75.0%)	59 (72.8%)	73 (76.8%)	χ^2= 0.374	0.541
Medicine for concomitant disease	47 (26.7%)	26 (32.1%)	21 (22.1%)	χ^2= 2.231	0.135
Hospitalization waiting[b]					
Mean±SD	8.70 ± 10.60	15.62 ± 12.26	2.81 ± 2.27	Z = −9.311	< 0.001
Median(IQR)	5.00 (10.00)	12.00 (16.50)	2.00 (3.00)		
LOS (days)[c]					
Mean±SD	18.14 ± 7.27	17.37 ± 6.87	18.80 ± 7.56	Z = −1.071	0.284
Median(IQR)	16.50 (8.00)	17.00 (11.50)	16.00 (7.00)		
SHHS exposure (>=7 days)	42 (23.9%)	22 (27.2%)	20 (21.1%)	χ^2= 0.898	0.343

[a] Fisher exact test.
[b] Time from symptoms emerged or disease confirmed to be hospitalized.
[c] LOS: length of hospital stay.

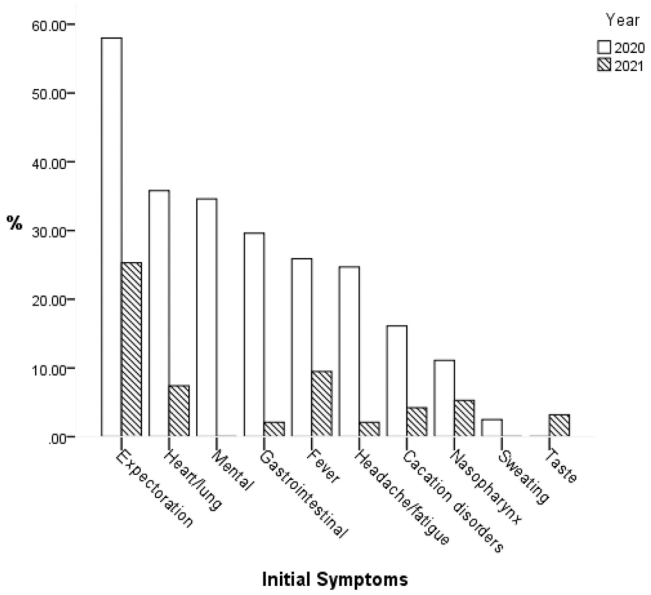

Fig. 2. The downtrend of initial symptoms from 2020 to 2021.

Table 2
Evaluation of severity conversion.

	Mild/moderate to severe		Statistics	*P*-value
	Yes (n = 20)	No (n = 156)		
Sex				
Male	10 (11.6%)	76 (88.4%)	χ^2= 0.012	0.914
Female	10 (11.1%)	80 (88.9%)		
Age (years)				
≤ 60	7 (6.6%)	99 (93.4%)	χ^2= 5.995	0.014
> 60	13 (18.6%)	57 (81.4%)		
Concomitant disease				
Yes	12(13.6%)	76(86.4%)	χ^2= 0.903	0.342
No	8(9.1%)	80(90.9%)		
Initial symptoms				
Yes	13(12.3%)	93(87.7%)	χ^2= 0.215	0.643
No	7(10.0%)	63(90.0%)		
SHHS exposure (>=7 days)				
Yes	2(4.8%)	40(95.2%)	χ^2= 1.604	0.205
No	18(13.4%)	116(86.6%)		
Diagnosis year				
2020	15(18.5%)	66(81.5%)	χ^2= 7.627	0.006
2021	5(5.3%)	90(94.7%)		

patients to severe conditions. The risk progressing to severe for the older, especially over 60 years old, was nearly fourfold (OR = 3.943) to younger patients. The progressing risk for cases diagnosed in 2021 decreased 83.5% (OR = 0.165) compared with those diagnosed in 2020. Although all the patients had ever taken SHHS formula, the results further found the exposure level was a potential predictor for severity status. Using SHHS with higher compliance (>= 7 days) could decrease

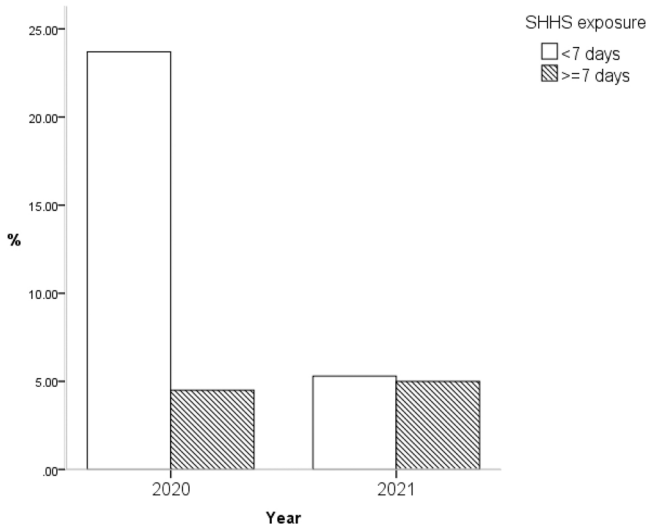

Fig. 3. The downtrend of severe incidence from 2020 to 2021 and interaction between year and SHHS exposure.

Table 3
Univariate and final multivariate regression model.

Factors	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	*P*-value	OR (95%CI)
Age (ref:<= 60 years old)	0.019	3.226(1.217,8.551)	0.009	3.943(1.402,11.086)
SHHS exposure (ref: <7days)	0.140	0.322(0.072,1.451)	0.049	0.118(0.014,0.992)
Diagnosis year (ref: 2020)	0.009	0.244(0.085,0.706)	0.003	0.165(0.050,0.551)

Notes: The model includes age, SHHS exposure, year and the interaction between year and SHHS exposure.

progressing risk by 88.2% (OR = 0.118) compared to those with poor compliance.

4.2. Comparisons with previous studies

The population in this study have several similarities with patients in our previous cohort which was conducted in 17 quarantine stations [5], for example, average age (53.65 vs. 48.49 yrs), female proportion (51.1% vs. 51.9%) and medical history (50.0% vs. 46.3%). These make it possible to repeatedly validate the effectiveness of SHHS formula for mild to moderate COVID-19. An observational study our team completed in 2020 [12], explored comprehensive intervention might be a protective factor for recurrent positive RT-PCR. SHHS formula is one part of the whole comprehensive intervention, which also included Baduanjin exercise, foot baths, moxibustion etc. At the same period, we conducted a randomized controlled trial (RCT) concluded that the use of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules combined with western medicine had clinical advantages for COVID-19 patients in improving clinical symptoms [13]. This finding confirmed the former findings that Huo Xiang (Pogostemonis Herba) could effectively inhibit the replication of influenza A (H1N1) virus [14]. Huoxiang is also one of the constituents of SHHS formula. Consistent with our previous study [5], we found the older was still an important factor for prognosis of disease, implying differential preventive and treatment measures are needed to older population. The median of LOS in this study was 16.5 days, much longer than situations reported in outside of China which was 5 days for LOS median [15]. The most possible reason might be the unified management measures in China which generally require confirmed cases should be isolated or stayed in hospital at least 14 days.

4.3. Strengths and limitations

Our study has many strengths. The first, this study might be the first attempt to explore the influence of epidemic control measures and medical environments on characters of patients and their prognosis by comparing the cohorts from 2020 to 2021. The second, other than the findings in previous study which have proved the potential benefits for COVID-19 patients from using SHHS [5], we further evaluated the effectiveness of higher compliance to SHHS (ie. longer exposure time) which will be helpful to guide clinical prescriptions. The third, E value [9], a novel method, was calculated to explore the robust of the associations. For age and diagnosis year, the E value was large enough, which it's unlikely any unmeasured factors could explain away the observed associations. However, the LCL of E value for SHHS exposure level is around 1 (LCL = 1.1). We should consider whether there might exist any unobserved confoundings in this study could threaten current association, for example, different combined medicines or virus types. Although we got a quite strong association (OR = 0.118) in the model, further studies with larger sample size are still warranted.

The main limitation of our study was its sample size. Generally, small sample size will cause lower power to detect a statistical significance, hence a higher possibility of type II error. We used model selection procedure, instead of including all of the co-variates in the model. The interaction between diagnosis year and SHHS exposure was also introduced to the final model to increase the statistical power. The second, we also found the associations of age and severe condition in our study was quite large (OR=3.943), one possible reason might relate to the special epidemic background in Tonghua city, its outbreak mainly started from the super spreader, an asymptomatic carrier, took part in a gathering which many older people were involved. Nevertheless, the prevention and treatment in older population are more challenging. The third, with the approval of "three TCM formula and three Chinese patent drugs" by China food and drug administration, there might be an increase both on patients' expectation and acceptance to TCM. In real world, patients might use other TCMs besides SHHS formula, but we could only mostly focus the SHHS, due to the complexity of the prescription data. Finally, some studies revealed the relationship between overweight (eg. BMI) and the severe outcomes. However, the data of weight and height was seriously missing in the hospitalization database, which made this analysis unpractical. Highly depending on the retrospectively collected data is also a common limitation for all retrospective studies.

5. Conclusions

The profile of COVID-19 patients has changed after one year. The reducing of severe cases could be the joint effects of multiple factors. In addition to age, diagnosis year and SHHS exposure are two new factors to predict the prognosis of disease. In this study, the patients diagnosed in 2021 were mainly benefited from timely treatment. Subsequently, adhere to use SHHS formula a quite longer time reduced the number of severe cases. Therefore, both the current epidemic prevention and control measures and increasing compliance to traditional Chinese medicine are effective ways to reducing severe cases and improving public health.

Compliance and ethics

We declare no competing interests. This study was approved by the institutional ethics board of Hubei Provincial Hospital of Traditional Chinese Medicine (No. HBZY2020-C27-01) and Changchun University of Chinese Medicine (CCZYFYLL2021–001).

Acknowledgments

This work was funded by the Special Project for Emergency of the Ministry of Science and Technology of PR. China (2020YFC0845000) and Special Project for Emergency Research on the Prevention and Control of COVID-19 by Traditional Chinese Medicine of National Administration of Traditional Chinese Medicine of PR. China (2022ZYLCYJ01–4). We acknowledge all volunteers and health-care workers in the Wuhan, Hubei province and Tonghua, Jilin province.

References

[1] H. Lu, C.W. Stratton, Y.W. Tang, Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle, J. Med. Virol. 92 (4) (2020) 401–402.
[2] World health organization. WHO Coronavirus (COVID-19) dashboard. ⟨https://covid19.who.int⟩. (accessed on Jan 10, 2022).
[4] X.L. Tong, X.Y. Li, L.H. Zhao, et al., Discussion on traditional chinese medicine prevention and treatment strategies of coronavirus disease 2019 (COVID-19) from the perspective of cold-dampness pestilence, J. Tradit. Chin. Med. 61 (06) (2020) 465–470+553.
[5] J. Tian, S. Yan, H. Wang, Y. Zhang, Y. Zheng, H. Wu, X. Li, Z. Gao, Y. Ai, X. Gou, L. Zhang, L. He, F. Lian, B. Liu, X. Tong, Hanshiyi Formula, an approved medicine for Sars-CoV2 infection in China, reduced the proportion of mild and moderate COVID-19 patients turning to severe status: a cohort study, Pharm. Res. 161 (2020), 105127.
[6] E. Von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gotzsche, J. P. Vandenbroucke, The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, BMJ 335 (7624) (2007) 806–808.
[7] National Health Commission of the People's Republic of China, National Administration of Traditional Chinese Medicine of the People's Republic of China, Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management, People's Medical Publishing House, 2020.
[8] P. Ding, T.J. VanderWeele, Sensitivity analysis without assumptions, Epidemiology 27 (3) (2016) 368–377.
[9] T.J. VanderWeele, P. Ding, Sensitivity analysis in observational research: introducing the E-value, Ann. Intern. Med. 167 (4) (2017) 268–274.
[10] S. Haneuse, T.J. VanderWeele, D. Arterburn, Using the E-value to assess the potential effect of unmeasured confounding in observational studies, JAMA 321 (6) (2019) 602–603.
[11] M.B. Mathur, P. Ding, C.A. Riddell, T.J. VanderWeele, Web site and R package for computing E-values, Epidemiology 29 (5) (2018) e45–e47.
[12] S. He, J. Tian, X. Li, Y. Zhou, M. Xiao, Y. Zhang, X. Min, X. Li, D. Jin, Q. Zhang, Y. Zheng, J. Ke, Q. Li, J. Tao, P. Song, H. Wang, Y. Lv, Q. Ding, S. Tang, J. Lin, Z. Jiang, Z. Zhang, J. Song, F. Lian, X. Tong, Positive RT-PCR test results in 420 patients recovered from COVID-19 in Wuhan: an observational study, Front. Pharm. 11 (2020), 549117.
[13] M. Xiao, J. Tian, Y. Zhou, X. Xu, X. Min, Y. Lv, M. Peng, Y. Zhang, D. Yan, S. Lang, Q. Zhang, A. Fan, J. Ke, X. Li, B. Liu, M. Jiang, Q. Liu, J. Zhu, L. Yang, Z. Zhu, K. Zeng, C. Li, Y. Zheng, H. Wu, J. Lin, F. Lian, X. Li, X. Tong, Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: a randomized controlled trial, Pharm. Res. 161 (2020), 105126.
[14] X.L. Wu, D.H. Ju, J. Chen, B. Yu, K.L. Liu, J.X. He, C.Q. Dai, S. Wu, Z. Chang, Y. P. Wang, X.Y. Chen, Immunologic mechanism of Patchouli alcohol anti-H1N1 influenza virus may through regulation of the RLH signal pathway in vitro, Curr. Microbiol. 67 (4) (2013) 431–436.
[15] E.M. Rees, E.S. Nightingale, Y. Jafari, N.R. Waterlow, S. Clifford B., C.A. Pearson, C.W. Group, T. Jombart, S.R. Procter, G.M. Knight, COVID-19 length of hospital stay: a systematic review and data synthesis, BMC Med. 18 (1) (2020) 270.