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.

Journal of Integrative Medicine 19 (2021) 226–231

Contents lists available at ScienceDirect

Journal of Integrative Medicine

journal homepage: www.jcimjournal.com/jim
www.journals.elsevier.com/journal-of-integrative-medicine

Original Research Article

Early therapeutic interventions of traditional Chinese medicine in COVID-19 patients: A retrospective cohort study

Miao-yan Shi [a,1], Shi-qi Sun [a,1], Wei Zhang [a,*], Xing Zhang [a,*], Gui-hua Xu [a], Xuan Chen [a], Zi-jian Su [a], Xiu-ming Song [a], Lu-jiong Liu [a], Yi-bao Zhang [a], Yi-le Zhang [a], Meng Sun [a], Qi Chen [a], Yan Xue [a], Hua Lü [b], Wei-an Yuan [c], Xiao-rong Chen [d], Yun-fei Lu [d]

[a] Department of Respiratory Disease, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
[b] Center for Clinical Effect Evaluation, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
[c] Department of Clinical Pharmacology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
[d] Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China

ARTICLE INFO

Article history:
Received 25 August 2020
Accepted 15 December 2020
Available online 13 January 2021

Keywords:
Coronavirus disease 2019
Early interventions
Traditional Chinese medicine
Conversion time of viral nucleic acid
Inflammatory indicators

ABSTRACT

Objective: To observe the early interventions of traditional Chinese Medicine (TCM) on the conversion time of nucleic acid in patients with coronavirus disease 2019 (COVID-19), and find possible underlying mechanisms of action.

Methods: A retrospective cohort study was conducted on 300 confirmed COVID-19 patients who were treated with TCM, at a designated hospital in China. The patients were categorized into three groups: TCM1, TCM2 and TCM3, who respectively received TCM interventions within 7, 8–14, and greater than 15 days of hospitalization. Different indicators such as the conversion time of pharyngeal swab nucleic acid, the conversion time of fecal nucleic acid, length of hospital stay, and inflammatory markers (leukocyte count, and lymphocyte count and percentage) were analyzed to observe the impact of early TCM interventions on these groups.

Results: The median conversion times of pharyngeal swab nucleic acid in the three groups were 5.5, 7 and 16 d ($P < 0.001$), with TCM1 and TCM2 being statistically different from TCM3 ($P < 0.01$). TCM1 ($P < 0.05$) and TCM3 ($P < 0.01$) were statistically different from TCM2. The median conversion times of fecal nucleic acid in the three groups were 7, 9 and 17 d ($P < 0.001$). Conversion times of fecal nucleic acid in TCM1 were statistically different from TCM3 and TCM2 ($P < 0.01$). The median lengths of hospital stay in the three groups were 13, 16 and 21 d ($P < 0.001$). TCM1 and TCM2 were statistically different from TCM3 ($P < 0.01$); TCM1 and TCM3 were statistically different from TCM2 ($P < 0.01$). Both leucocyte and lymphocyte counts increased gradually with an increase in the length of hospital stay in TCM1 group patients, with a statistically significant difference observed at each time point in the group ($P < 0.001$). Statistically significant differences in lymphocyte count and percentage in TCM2 ($P < 0.001$), and in leucocyte count ($P = 0.043$) and lymphocyte count ($P = 0.038$) in TCM3 were observed. The comparison among the three groups showed a statistically significant difference in lymphocyte percentage on the third day of admission ($P = 0.044$).

Conclusion: In this study, it was observed that in COVID-19 patients treated with a combination of Chinese and Western medicines, TCM intervention earlier in the hospital stay correlated with faster conversion time of pharyngeal swab and fecal nucleic acid, as well as shorter length of hospital stay, thus helping promote faster recovery of the patient. The underlying mechanism of action may be related to improving inflammation in patients with COVID-19.

Please cite this article as: Shi MY, Sun SQ, Zhang W, Zhang X, Xu GH, Chen X, Su ZJ, Song XM, Liu LJ, Zhang YB, Zhang YL, Sun M, Chen Q, Xue Y, Lü H, Yuan WA, Chen XR, Lu YF. Early therapeutic interventions of traditional Chinese medicine in COVID-19 patients: A retrospective cohort study. *J Integr Med.* 2021; 19(3): 226–231.

* Corresponding authors.
E-mail addresses: zhangw1190@sina.com (W. Zhang), zhangxing2012@shutcm.edu.cn (X. Zhang).
[1] They contributed equally to this work.

https://doi.org/10.1016/j.joim.2021.01.002
2095-4964/

1. Introduction

The coronavirus disease pandemic of 2019 has resulted in widespread infection and severe consequences worldwide [1]. According to the guidelines under *the Protocol for Diagnosis and Treatment of 2019 Novel Coronavirus Pneumonia (trial 5th edition)* issued by China's National Health Commission & State Administration of Traditional Chinese Medicine [2], fever, fatigue and dry cough are the main manifestations of the disease, while a small portion of patients show symptoms of nasal congestion, runny nose, sore throat and diarrhea. Blood samples suggest that leucocyte and lymphocyte counts decrease drastically. The disease can progress rapidly to severe and critical stages, but can be effectively controlled with active treatment by Chinese and Western medicines. The inclusion of traditional Chinese medicine (TCM) in the Chinese protocol is based on its successful experience in treating epidemic diseases throughout history [3]. Although instances of hepatotoxicity and nephrotoxicity have occurred when using TCM to treat infectious diseases, in general TCM does not cause serious adverse drug reactions.

TCM had a national usage rate of over 90% in China, and showed outstanding curative effect for coronavirus disease 2019 (COVID-19) [4]. Hanshiyi Formula, a TCM prescription, can significantly reduce the progression to severe disease in patients with mild and moderate COVID-19, which may both prevent and treat the disease [5]. The use of Huoxiang Zhengqi Pill and Lianhua Qingwen Granule combined with Western medicine may have advantages for COVID-19 patients in improving clinical symptoms, reducing utilization rate of antibacterial and antiviral drugs, and improving patient prognosis [6]. Furthermore, TCM has shown rapid clinical improvements. These favorable clinical outcomes promote the recommendation to treat patients with TCM [7].

Based on the high curative effect of TCM in the treatment of COVID-19, this study provides more information for using TCM at specific time periods in the early intervention of the disease, which is different from other published articles. A retrospective study was conducted to observe the early interventions of TCM on the conversion time of nucleic acid of COVID-19 confirmed patients and its correlation with inflammatory indicators such as leucocyte count, and lymphocyte count and percentage.

2. Methods

2.1. Study design and patients

The study included 300 COVID-19 cases diagnosed between January 26 and April 15, 2020 in the Shanghai Public Health Clinical Center and who were treated with TCM.

The diagnostic and clinical classification criteria of COVID-19 were based on the *Protocol for Diagnosis and Treatment of 2019 Novel Coronavirus Pneumonia (trial 5th edition)* [2], which for ease of use, is shortened as "the *Protocol*" in the remainder of this paper.

The diagnostic criteria for confirmed COVID-19 cases included suspected cases with the following etiological or serological evidence at the same time: (1) positive result of real-time fluorescence-based reverse transcriptase-polymerase chain reaction (RT-PCR) assay on novel coronavirus nucleic acid of respiratory or blood specimens; (2) the sequence of the viral genome on respiratory or blood specimens being highly homologous to that of the known novel coronavirus.

The syndrome differentiation and classification of TCM refers to the relevant standards in *Shanghai Traditional Chinese Medicine Protocol for Diagnosis and Treatment of 2019 Novel Coronavirus Pneumonia (trial 2nd edition)* [8].

The inclusion criteria were as follows: (1) laboratory-confirmed COVID-19 cases, according to the *Protocol* and positive confirmation from nucleic acid testing (NAT) of pharyngeal swabs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); (2) male or female patients aged $\geq$ 18 years; (3) patients treated with TCM (decoction or Chinese patent drugs) during hospitalization; (4) patients with pharyngeal swabs or fecal NAT result during hospitalization.

The exclusion criteria were as follows: (1) patients missing the main observation indexes; (2) death during hospitalization, or patients who had more than one hospitalization; (3) respiratory tract bacterial infections due to primary or secondary immunodeficiency, congenital respiratory malformation, congenital heart disease, gastroesophageal reflux or lung malformation; (4) asthma or other chronic airway diseases needing maintenance therapy, acute respiratory tract bacterial infection (i.e., bronchiectasis, tonsillitis, bronchitis, rhinosinusitis and otitis media), and severe pulmonary interstitial diseases; (5) severe systemic diseases (i.e., malignancy, autoimmune diseases, and liver or renal diseases) or surgeries (splenectomy and organ transplantation) that might affect the assessment of efficacy; (6) pregnant or lactating women; (7) participation in other clinical trials within 3 months.

The protocol has been registered with the China Clinical Trial Registry website (www.chictr.org.cn, No. ChiCTR2000029778). The Medical Ethics Committee of Shanghai Public Health Clinical Center approved the study with ethics approval No. YJ-2020-S065-02.

2.2. Treatments

Western medicine treatment refers to the relevant standards in the *Protocol* [2]. It included bed rest, oxygen therapy, and antiviral therapies such as arbidol (2 tablets/time, 3 times/d) or lopinavir/ritonavir (2 tablets/time, 2 times/d). The patients with severe disease continued with monitoring of and treatment with anti-infection, anti-inflammatory, antipyretic medications, and maintaining of electrolyte and acid-base balance.

TCM treatment includes interventions outlined in the *Shanghai Traditional Chinese Medicine Protocol for Diagnosis and Treatment of 2019 Novel Coronavirus Pneumonia (trial 2nd edition)* [8]. Specific decoctions were prescribed according to different TCM syndrome types. Chinese patent medicines used included Tanreqing Capsule, Liushen Pill, Lianhua Qingwen Capsule (Granule) and Shufeng Jiedu Capsule.

2.3. Clinical characteristics and indicators

Data were collected retrospectively from electronically maintained medical records. Baseline characteristics with respect to demographic features, clinical classification, fever on admission, Western medicine treatments (antiviral and antibiotic medications), and underlying diseases were collected for each patient.

The NAT of all pharyngeal swabs for SARS-CoV-2 was found positive in all patients before admission. All patients in the treatment and control groups were tested with pharyngeal swab NAT once a day (at a 24-hour sampling interval). In the early stage of COVID-19, the fecal nucleic acid was not tested for every patient in the Shanghai Public Health Clinical Center. With the widespread use of fecal nucleic acid, subsequently, almost every patient was tested for fecal nucleic acid. If fecal NAT was used, patients in two groups were also tested with fecal nucleic acid once a day (at a 24-hour sampling interval).

If two consecutive RT-PCR results of viral RNA for pharyngeal swabs, at a 24-hour sampling interval, were found negative, the

time of the first detection was used for the conversion time of pharyngeal swab NAT. The first time when fecal NAT turned negative was regarded as "the conversion time of fecal nucleic acid" without needing two consecutive results. The length of hospital stay of both groups was documented simultaneously.

The inflammatory indicators were collected on the 1st, 3rd, 6th and last day of a patient's stay in hospital. In case of any deficiency, these indicators were supplemented with data from one day before and after the earmarked day of collection.

Pharyngeal swab nucleic acid, fecal nucleic acid, and the levels of inflammatory indicators (leucocyte count, and lymphocyte count and percentage) were uniformly investigated by the Department of Clinical Laboratory of Shanghai Public Health Clinical Center.

2.4. Statistical analysis

The original data were collated into Excel files and converted into a database for statistical analysis by SPSS 17.0 (IBM Corporation). The results of inflammatory indicators were analyzed by GraphPad Prism 8.0 software (GraphPad Software, LLC). The numerical variables were first tested for normality, and the variables meeting the normal distribution were calculated as the mean and standard deviation. The analysis of variance was used for comparison between groups. The median and quartile (P_{25}, P_{75}) were calculated for the variables that did not conform to the normal distribution. Kruskal-Wallis test was employed for the comparison of multiple independent samples among three groups. The Bonferroni method was used for pairwise multiple comparisons. Categorical variables were calculated for composition ratio (%), and the chi-square test was used for comparison between groups. For the leucocyte count, and lymphocyte count and percentage, the percentage was obtained by several measurements, and Friedman test was performed on each group to compare the differences at different measurement time points.

3. Results

3.1. Basic information

Three hundred cases of diagnosed COVID-19 included in this study were divided into three groups: TCM1, TCM2 and TCM3, with the intervention times of TCM within 7, 8–14, and greater than 15 days of hospitalization, respectively. This means that TCM1 received TCM treatment at the earliest stage, while TCM3 was relatively the latest in the three groups. Among the 300 cases, 170 were in TCM1, 96 were in TCM2 and 34 were in TCM3.

Among the 300 cases, 158 (52.7%) were males, and 142 (47.3%) were females, aged between 18 and 84 years, with the mean age of 47.54 years. The median time interval between onset of disease and admission into the hospital was 4 (2–7) d.

The three groups were compared in terms of demographic characteristics, fever on admission, Western medicine treatments, underlying diseases, and clinical classification (Tables 1 and 2).

3.2. Conversion time of pharyngeal swab nucleic acid

The median conversion time of pharyngeal swab nucleic acid in the three groups were 5.5, 7 and 16 d, respectively, with a statistically significant difference among the three groups ($P < 0.001$). The conversion time of pharyngeal swab nucleic acid in TCM1 and TCM2 groups were statistically different from that in TCM3 ($P < 0.01$), and in TCM1 ($P < 0.05$) and TCM3 ($P < 0.01$) were statistically different from TCM2 (Table 3).

3.3. Conversion time of fecal nucleic acid

The median conversion times of fecal nucleic acid in the three groups were 7, 9 and 17 d, respectively, and showed statistically significant differences among the three groups ($P < 0.001$). TCM1 was statistically different from TCM3 ($P < 0.01$). TCM1 and TCM3 were statistically different from TCM2 ($P < 0.01$) (Table 4).

3.4. Length of hospital stay

The median lengths of hospital stay of the three groups were 13, 16 and 21 d, respectively, with statistically significant differences observed among the three groups ($P < 0.001$). TCM1 and TCM2 were statistically different from TCM3 ($P < 0.01$). TCM1 and TCM3 were statistically different from TCM2 ($P < 0.01$) (Table 5).

3.5. Inflammatory indicators

There were no statistically significant differences in leucocyte count ($P = 0.110$), lymphocyte count ($P = 0.825$), or lymphocyte percentage ($P = 0.649$) among the three groups at the time of

Table 1
Basic information of the 300 patients with COVID-19.

Baseline characteristic	TCM1 (n = 170)	TCM2 (n = 96)	TCM3 (n = 34)	F/χ^2 value	P value
Male (n [%])[1]	96 (56.5)	41 (42.7)	21 (61.8)	5.935	0.051
Age (mean ± standard deviation, year)[2]	45.93 ± 17.06	48.71 ± 15.29	52.32 ± 16.29	2.501	0.084
Time interval between onset to admission (median [P_{25}, P_{75}], d)[3]	4 (2–8)	4 (2–6.75)	4 (3–7)	2.909	0.234
Fever (n [%])[1]	74 (43.5)	40 (41.7)	16 (47.1)	0.303	0.859
Antiviral medications (n [%])[1]	82 (48.2)	37 (38.5)	14 (41.2)	2.491	0.288
Antibiotics (n [%])[1]	31 (18.2)	20 (20.8)	8 (23.5)	0.624	0.732
Underlying diseases (n [%])[1]	45 (26.5)	28 (29.2)	8 (23.5)	0.461	0.794

Statistical methods: Chi-square test[1], analysis of variance[2] and Kruskal-Wallis test[3]. COVID-19: coronavirus disease 2019; TCM: traditional Chinese medicine.

Table 2
Clinical classification of the 300 patients with COVID-19.

Group	n	Clinical classification, n (%)			
		Mild type	Moderate type	Severe type	Critical type
TCM1	170	14 (8.2)	145 (85.3)	8 (4.7)	3 (1.8)
TCM2	96	2 (2.1)	92 (95.8)	2 (2.1)	0 (0.0)
TCM3	34	0 (0.0)	30 (88.2)	3 (8.8)	1 (2.9)

Data were analyzed by Kruskal-Wallis test ($\chi^2 = 4.709$, $P = 0.095$). COVID-19: coronavirus disease 2019; TCM: traditional Chinese medicine.

Table 3
Comparison of the conversion time of pharyngeal swab nucleic acid among the three groups.

Group	*n*	Conversion time of pharyngeal swabs nucleic acid (d)	χ^2 value	*P* value
TCM1	170	5.5 (2–11)$^{*\triangle\triangle}$	40.382	< 0.001
TCM2	96	7 (4.3–12)$^{\triangle\triangle}$		
TCM3	34	16 (11–20.3)**		

Kruskal-Wallis rank-sum test was used for the comparison among the three groups; Bonferroni method was used for pairwise comparison. $^{*}P < 0.05$, $^{**}P < 0.01$, *vs.* TCM2; $^{\triangle\triangle}P < 0.01$, *vs.* TCM3. TCM: traditional Chinese medicine.

Table 4
Comparison of the conversion time of fecal nucleic acid among the three groups.

Group	*n*	Conversion time of fecal nucleic acid (d)	χ^2 value	*P* value
TCM1	133	7.0 (3.0–12.0)$^{**\triangle\triangle}$	50.904	< 0.001
TCM2	85	9.0 (6.0–14.0)$^{\triangle\triangle}$		
TCM3	33	17.0 (15.0–22.0)**		

Kruskal-Wallis rank-sum test was used for the comparison among the three groups; Bonferroni method was used for pairwise comparison. $^{**}P < 0.01$, *vs.* TCM2; $^{\triangle\triangle}P < 0.01$, *vs.* TCM3. Number of effective observation cases of fecal nucleic acid turning negative. Fecal nucleic acid test was not detected on all the 300 patients involved. TCM: traditional Chinese medicine.

Table 5
Comparison of the length of hospital stay among the three groups.

Group	*n*	Length of hospital stay (d)	χ^2 value	*P* value
TCM1	170	13.00 (10.00–21.00)$^{**\triangle\triangle}$	58.444	< 0.001
TCM2	96	16.00 (13.00–24.50)$^{\triangle\triangle}$		
TCM3	34	21.00 (19.00–28.00)**		

Kruskal-Wallis rank-sum test was used for the comparison among the three groups; Bonferroni method was used for pairwise comparison. $^{**}P < 0.01$, *vs.* TCM2; $^{\triangle\triangle}P < 0.01$, *vs.* TCM3; TCM: traditional Chinese medicine.

admission. The baseline data of the three groups were comparable. Leucocyte and lymphocyte counts increased gradually with the increase of the length of hospital stay in TCM1, and there was a statistically significant difference at each time point in the TCM1 group ($P < 0.001$). There were statistically significant differences in lymphocyte count and percentage in TCM2 ($P < 0.001$), but absent in leucocyte count ($P = 0.239$). There was a statistically significant difference observed in leucocyte count ($P = 0.043$) and lymphocyte count ($P = 0.038$) in TCM3, with no statistical difference in lymphocyte percentage ($P = 0.282$). The comparison among the three groups showed that there was a statistical difference in lymphocyte percentage on the third day ($P = 0.044$) (Table 6, Fig. 1 and Fig. 2).

3.6. Safety

During the application of a combination of Chinese and Western medicines, we did not find any significant liver and kidney damage (alanine transaminase, aspartic transaminase, blood urea nitrogen, or creatinine) pertaining to the use of TCM. During the course of the study, no serious adverse events were documented at any stage.

4. Discussion

The rapid spread of COVID-19 has severely and negatively impacted health and safety on a global scale, and as of yet there are no effective drugs for the treatment of COVID-19. TCM has a long history of efficacy in epidemics, and its valuable, comprehensive therapeutic experience was quickly adapted to be used in this pandemic in the treatment of COVID-19 [9]. TCM strategies have shown clear clinical efficacy in reducing symptoms, promoting virus clearance, and shortening hospitalization time [10]. This study also found that the combined Chinese and Western medicine treatments positively served COVID-19 patients in the Shanghai Public Health Clinical Center, as found in several previous studies [11].

Three hundred cases of COVID-19 who were diagnosed and treated with TCM therapies by the Shanghai Public Health Clinical Center were retrospectively analyzed. Three groups of TCM1, TCM2 and TCM3 were set up with the time of TCM participation within 7 d, 8–14 d, and more than 15 d. Conversion time of pharyngeal swab nucleic acid, conversion time of fecal nucleic acid, hospitalization time, and inflammatory indicators (leucocyte count, and lymphocyte count and percentage) of the three groups were analyzed.

Table 6
Comparison of the inflammatory indicators among the three groups.

Item	Time	TCM1	TCM2	TCM3	Kruskal-Wallis	
					χ^2 value	*P* value
Leucocyte count ($\times 10^9$/L)	Admission day	4.84 (4.01–6.09)	5.14 (4.30–6.23)	5.72 (4.24–7.23)	4.407	0.110
	3rd day	5.00 (4.03–6.35)	5.24 (4.24–6.51)	5.24 (4.07–7.86)	1.998	0.368
	6th day	5.16 (4.26–6.48)	5.54 (4.12–6.71)	5.46 (4.30–6.74)	0.365	0.883
	Discharge day	5.73 (4.64–6.73)	5.87 (4.58–7.00)	5.53 (4.65–7.11)	0.065	0.968
Friedman test	χ^2 value	22.312	4.220	8.147		
	P value	< 0.001	0.239	0.043		
Lymphocyte count ($\times 10^9$/L)	Admission day	1.23 (0.90–1.53)	1.22 (0.85–1.71)	1.28 (0.94–1.79)	0.385	0.825
	3rd day	1.53 (1.20–2.12)	1.37 (1.04–1.88)	1.53 (0.84–1.79)	4.963	0.084
	6th day	1.60 (1.06–2.12)	1.51 (1.03–2.18)	1.61 (0.96–1.92)	0.125	0.939
	Discharge day	1.78 (1.42–2.19)	1.73 (1.44–2.35)	1.70 (1.32–2.22)	0.187	0.911
Friedman test	χ^2 value	72.514	32.541	8.431		
	P value	< 0.001	< 0.001	0.038		
Lymphocyte percentage	Admission day	24.65 (19.90–30.94)	24.12 (18.15–31.48)	24.80 (18.40–35.16)	0.865	0.649
	3rd day	32.01 (24.89–39.25)	28.65 (21.90–35.38)	27.70 (12.50–42.26)	6.254	0.044
	6th day	31.52 (24.82–37.70)	31.41 (24.82–38.11)	29.18 (21.77–39.17)	0.133	0.936
	Discharge day	31.86 (27.11–36.41)	32.47 (26.56–39.01)	33.15 (25.63–38.96)	0.234	0.890
Friedman test	χ^2 value	52.958	25.040	3.814		
	P value	< 0.001	< 0.001	0.282		

Friedman test was performed in each group to compare the difference at different time points. Kruskal-Wallis rank-sum test was used for the comparison among the three groups; TCM: traditional Chinese medicine.

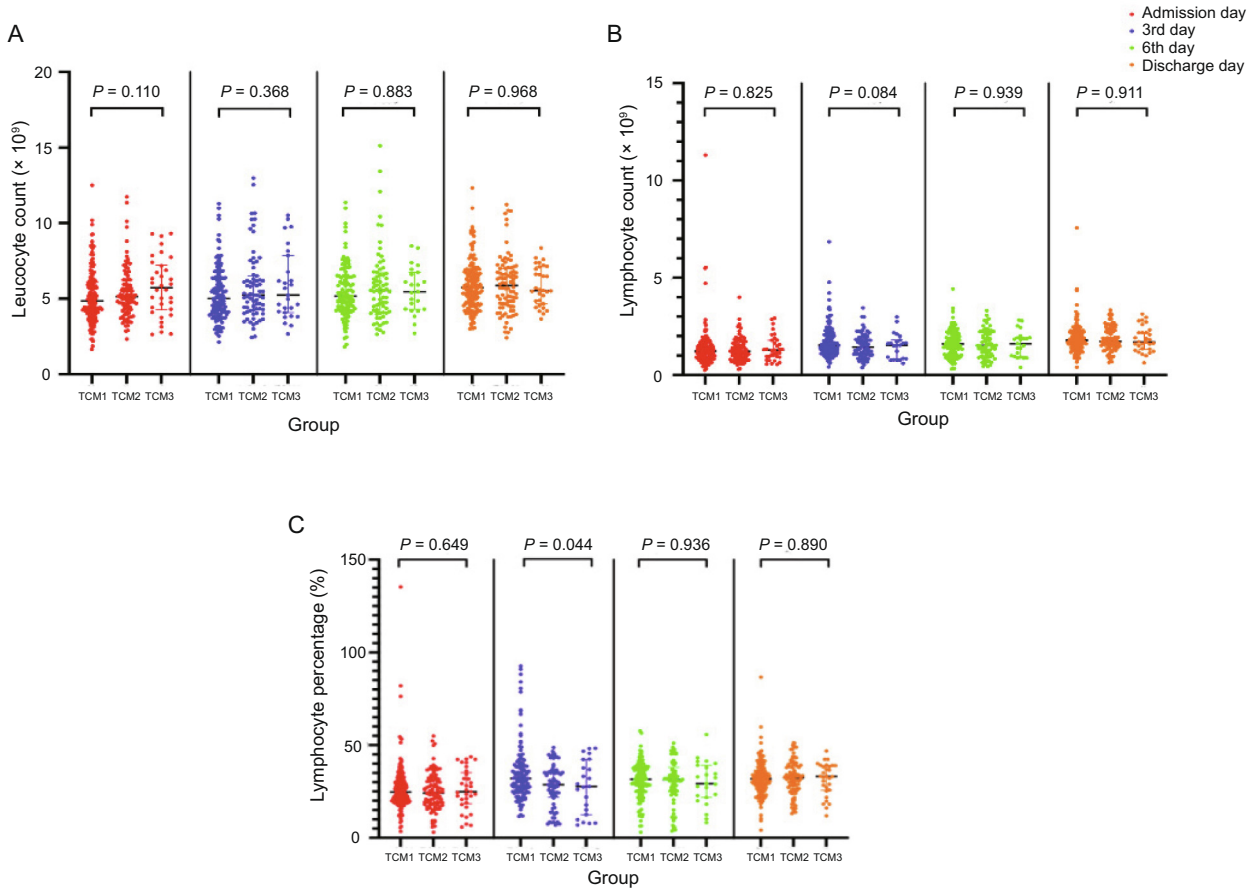

Fig. 1. Comparison of inflammatory indicators showing median value and interquartile range of three groups. (A) comparison of leucocyte count; (B) comparison of lymphocyte count; (C) comparison of lymphocyte percentage. TCM: traditional Chinese medicine.

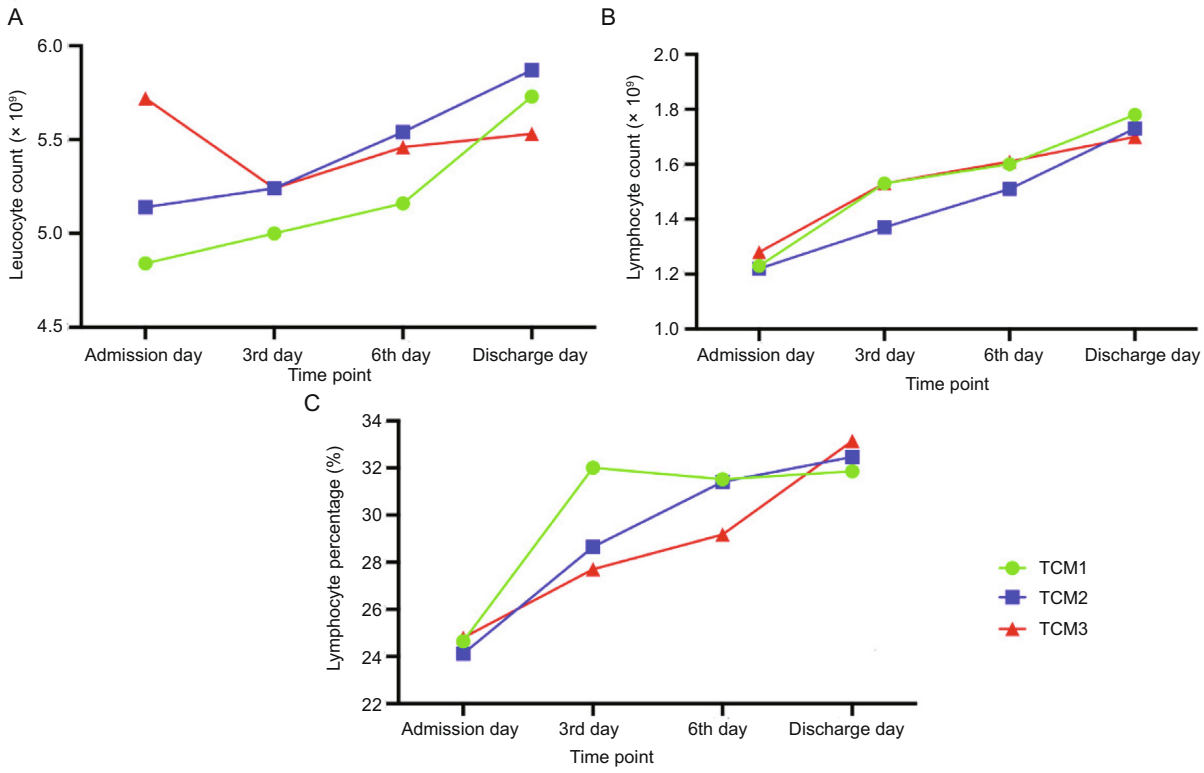

Fig. 2. Dynamic changes of inflammatory indicators in the three groups. (A) dynamic changes of leucocyte count in each group; (B) dynamic changes of lymphocyte count in each group; (C) dynamic changes of lymphocyte percentage in each group. TCM: traditional Chinese medicine.

On comparing the conversion time of pharyngeal swab nucleic acid in the three groups, the results showed that the median times of the three groups were 5.5, 7 and 16 d, respectively, and statistically significant difference among the three groups ($P < 0.001$) was documented. The conversion time of pharyngeal swab nucleic acid of TCM1 was the shortest and that of TCM3 was relatively the longest. This shows that earlier treatment by TCM corresponds with earlier conversion time of pharyngeal swab nucleic acid.

Comparing the conversion time of fecal nucleic acid in the three groups, the results showed that the median times of the three groups were 7, 9 and 17 d, respectively, showing statistically significant differences among the three groups ($P < 0.001$). The conversion time of fecal nucleic acid of TCM1 was the shortest and that of TCM3 was relatively the longest, thus also showing that earlier treatment of TCM correlates with earlier conversion time of fecal nucleic acid.

The COVID-19 virus nucleic acid could be detected in the nasopharyngeal area as well as digestive tract, so there were multiple methods of obtaining NAT, which improves diagnostic accuracy and reduces the false-negative rate, helping to guide clinical treatment and evaluate treatment efficacy [12]. It can be seen that the Shanghai Public Health Clinical Center has specified stricter requirements for the discharge standard of patients with COVID-19, including two consecutive (24-hour sampling interval) negative pharyngeal swab NATs, and at least one negative fecal NAT.

The medial lengths of hospital stay were 13, 16 and 21 d, respectively, showing statistically significant differences among the three groups ($P < 0.001$). Length of hospital stay of TCM1 was the shortest and that of TCM3 was relatively the longest. This observation revealed that TCM treatment earlier in the COVID-19 disease course correlated with a shorter length of hospital stay.

Many other studies have confirmed that inflammatory indicators such as leucocyte and lymphocyte counts can help clinicians predict the severity of patients with COVID-19, and be used as effective indicators to help prevent and control the disease [13–15].

Analysis of inflammatory indicators showed that leucocyte and lymphocyte counts increased gradually with increased length of hospital stay in TCM1 ($P < 0.001$). There were statistically significant differences in lymphocyte count and percentage in TCM2 ($P < 0.001$). There were statistical differences in leucocyte count ($P = 0.043$) and lymphocyte count ($P = 0.038$) in TCM3. The comparison among the three groups showed that there was a statistical difference in lymphocyte percentage on the 3rd day of admission ($P = 0.044$). Treatment of TCM shows potential effects to improve the reduction of leucocyte count, and lymphocyte count and percentage caused by novel coronavirus infection. Earlier TCM intervention directly correlated with more improvements of the lymphocyte percentage.

The current study suffers from several limitations. This was a single-center study, and therefore the findings may not be representative of the general population. Furthermore, it was an observational study whose level of evidence was relatively lower than a randomized controlled trial.

5. Conclusion

This retrospective cohort study showed that earlier intervention of TCM corresponded with faster conversion time of pharyngeal swab and fecal nucleic acid, as well as shorter length of hospital stay. Thus, early intervention with TCM helps to promote more rapid recovery of COVID-19 patients. The underlying mechanisms may be related to improving inflammation in patients with COVID-19. This is a useful study in the larger picture of COVID-19 management, but data from larger, more broad multicenter studies are warranted to confirm the findings.

Funding

This study was supported by Foundation of Shanghai Science and Technology Committee (No. 2041195020002), Shanghai Key Laboratory of Traditional Chinese Clinical Medicine (No. 14DZ2273200) and Shanghai Key Clinical Specialty (No. shslczdzk05101).

Authors' contribution

MYS and SQS contributed equally to this work. WZ and XZ contributed to the research conception and design. MYS and SQS were responsible for data collection and analysis. MYS, SQS, GHX, XC, ZJS, XMS, LJL, YBZ, YLZ, MS, QC, YX, HL, WAY, XRC and YFL participated in data interpretation and manuscript review and writing. All authors contributed to the scientific discussion of the data and of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Omary MB, Eswaraka J, Kimball SD, Moghe PV, Panettieri RA, Scotto KW. The COVID-19 pandemic and research shutdown: staying safe and productive. J Clin Invest 2020;130(6):2745–8.
[2] National Health Commission & State Administration of Traditional Chinese Medicine. Protocol for diagnosis and treatment of 2019 novel coronavirus pneumonia (trial 5th edition). (2020-02-03) [2020-08-11]. http://www.nhc.gov.cn/xcs/zhengcwj/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml [Chinese].
[3] Ni L, Chen L, Huang X, Han C, Xu J, Zhang H, et al. Combating COVID-19 with integrated traditional Chinese and Western medicine in China. Acta Pharm Sin B 2020;10(7):1149–62.
[4] Zhao Z, Li Y, Zhou L, Zhou X, Xie B, Zhang W, et al. Prevention and treatment of COVID-19 using traditional Chinese medicine: a review. Phytomedicine 2020:153308.
[5] Tian J, Yan S, Wang H, Zhang Y, Zheng Y, Wu H, et al. 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. Pharmacol Res 2020;161:105127.
[6] Xiao M, Tian J, Zhou Y, Xu Xi, Min X, Lv Yi, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: a randomized controlled trial. Pharmacol Res 2020;161:105126.
[7] Ren X, Shao XX, Li XX, Jia XH, Song T, Zhou WY, et al. Identifying potential treatments of COVID-19 from traditional Chinese medicine (TCM) by using a data-driven approach. J Ethnopharmacol 2020;258:112932.
[8] Shanghai Municipal Health Commission. Shanghai traditional Chinese medicine protocol for diagnosis and treatment of 2019 novel coronavirus pneumonia (trial 2nd edition). (2020-02-24) [2020-08-11]. http://wsjkw.sh.gov.cn/zyygz2/20200224/a1f1aab9745e4490867cb4aaf40eaad0.html [Chinese].
[9] Wang WY, Xie Y, Zhou H, Liu L. Contribution of traditional Chinese medicine to the treatment of COVID-19. Phytomedicine 2021;85:153279.
[10] Zhao ZH, Zhou Y, Li WH, Huang QS, Tang ZH, Li H. Analysis of traditional Chinese medicine diagnosis and treatment strategies for COVID-19 based on "*The Diagnosis and Treatment Program for Coronavirus Disease—2019*" from Chinese authority. Am J Chin Med 2020;48(5):1035–49.
[11] Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends 2020;14(1):64–8.
[12] Wu J, Liu J, Li S, Peng Z, Xiao Z, Wang X, et al. Detection and analysis of nucleic acid in various biological samples of COVID-19 patients. Travel Med Infect Dis 2020;37:101673.
[13] Feng XD, Li SS, Sun Q, Zhu J, Chen B, Xiong MM, et al. Immune-inflammatory parameters in COVID-19 cases: a systematic review and meta-analysis. Front Med (Lausanne) 2020;7:301.
[14] Ferrari D, Motta A, Strollo M, Banfi G, Locatelli M. Routine blood tests as a potential diagnostic tool for COVID-19. Clin Chem Lab Med 2020;58(7):1095–9.
[15] Zheng ZH, Peng F, Xu BY, Zhao JJ, Liu HH, Peng JH, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81(2):e16–25.