Science in One Health 2 (2023) 100049

Contents lists available at ScienceDirect

Science in One Health

journal homepage: www.journals.elsevier.com/science-in-one-health

Full length article

Efficacy of traditional Chinese medicine on shortening the negative conversion time of SARS-CoV-2 ribonucleic acid in patients with mild COVID-19: a retrospective cohort study

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Traditional Chinese medicine
Negative conversion time

ABSTRACT

Background: The holistic view of the 'The unity of man and nature' promotes the development and application of traditional Chinese medicine (TCM). Despite the absence of modern pharmacological therapies with robust efficacy against coronavirus disease 2019 (COVID-19), TCM has exhibited potential utility for treating the disease in clinical practice.

Methods: A retrospective cohort study was conducted to investigate the therapeutic effect of TCM treatment intensity (TCMTI) in patients with mild COVID-19. A total of 6120 laboratory-confirmed patients with mild COVID-19 were recruited from temporary isolation facilities. The primary outcome measure was severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid conversion time. In addition, restricted cubic spline models were employed to elucidate nonlinear relationships.

Results: The median age (range) of the study participants was 43.0 (2.0–75.0) years, with a median hospitalization duration of 9.7 (4.1–22.5) days. The median time for achieving SARS-CoV-2 ribonucleic acid negativity was 6.67 days. The restricted cubic spline models revealed a remarkable nonlinear association between TCMTI and the time-to-ribonucleic acid negativity. After adjusting for potential confounders, the high TCMTI group exhibited a markedly shorter median time to SARS-CoV-2 ribonucleic acid negativity and reduced hospitalization duration ($P < 0.001$) than the low TCMTI group. Moreover, the mean time to achieve SARS-CoV-2 ribonucleic acid negativity was shortened by 1.909 days ($P < 0.001$) in the high-TCMTI group compared to the low-TCMTI group.

Conclusion: This study suggests that early initiation and intensified use of TCM may accelerate the time required to achieve SARS-CoV-2 ribonucleic acid negativity in patients with COVID-19, bearing considerable implications for public health.

1. Introduction

The continuous evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has exacerbated the global impact of the coronavirus disease 2019 (COVID-19) pandemic on public health [1,2], resulting in increased morbidity and mortality worldwide [3–5]. Mutations in the SARS-CoV-2 genome have given rise to several variants, including the Alpha, Beta, Gamma, Delta, and Omicron variants [2,6,7]. Novel chemically synthesized drugs have been developed, and the scope of existing pharmaceuticals for COVID-19 treatment has expanded in recent years [8,9]. For example, nirmatrelvir/ritonavir, remdesivir, and molnupiravir have received emergency use authorizations for managing mild or moderate COVID-19 symptoms in patients with underlying medical conditions [10–12]. These therapeutic strategies primarily mitigate the progression from moderate to severe illness, thereby reducing hospitalization and mortality rates [13,14]. Furthermore, COVID-19 vaccines are pivotal for controlling the pandemic and reducing mortality [12,15–17]. However, immunological investigations have demonstrated reduced neutralization of Omicron compared to earlier variants in both vaccine-induced and monoclonal antibody sera [15,16]. Accessibility to COVID-19 treatment remains limited in resource-constrained areas and emergency situations [5,16].

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https://doi.org/10.1016/j.soh.2023.100049
Received 8 October 2023; Accepted 27 October 2023
Available online 31 October 2023

One Health entails comprehensive and lifelong health, safeguarding human well-being [18]. This approach encompasses 1) human and animal health: One Health seeks to enhance the health of all life on Earth, extending concern beyond humans. It integrates human medicine, veterinary medicine, and environmental science to improve the survival and quality of life of humans and animals, ultimately achieving optimal health for humans, animals, and ecosystems [18,19]. Zoonotic diseases pose considerable risks to humans and animals, as exemplified by outbreaks of SARS, H7N9 avian influenza, H1N1 swine flu, Ebola virus, and COVID-19 [20]; 2) universal health: universal health ensures that every individual can access essential healthcare services at any time and place without incurring heavy financial burdens [18].

The holistic view of the 'Heaven-and-Man Oneness' promotes the development and application of traditional Chinese medicine (TCM) [21]. Chinese herbal medicine is frequently co-prescribed with modern pharmaceuticals to treat infections presented with acute respiratory symptoms [22]. When adjunctively administered with standard treatments, TCM can expedite viral clearance, reduce hospitalization duration, and accelerate the resolution of clinical symptoms [23–28]. Consequently, the 9th edition of "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" published by the Chinese National Health Commission, has incorporated several TCM regimens as standard treatment approaches for mild to moderate COVID-19 cases [22].

There is limited research investigating the relationship between TCM treatment intensity (TI; TCMTI) and therapeutic efficacy. This study aimed to assess the clinical effectiveness of TCMTI in patients with COVID-19 exhibiting mild or moderate symptoms.

2. Methods

2.1. Study design and setting

The retrospective cohort study used administrative data from four wards (A, B, C, and D) of a temporary hospital converted from Shanghai Jinshan Fangcang Hospital between April 15 and May 31, 2022. Data of patients infected with SARS-CoV-2 were integrated into the electronic medical record system and key statistical databases of the temporary hospital using unique anonymous identifiers. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies [29].

2.2. Participants

The severity of COVID-19 was classified into mild, moderate, severe, and critical based on laboratory examinations, clinical characteristics, and chest imaging (chest radiography and/or computed tomography [CT]) [30]. Mild COVID-19 was defined as SARS-CoV-2 infection positive with mild clinical symptoms (including fever, dry cough, fatigue, vomiting, body aches, and loss of appetite) and no radiographic evidence of pneumonia, according to the 'Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Version 9)' issued by National Health Commission of the People's Republic of China [30]. Confirmation of SARS-CoV-2 infection was determined by meeting one of the following virological or serological criteria: 1) positive results for SARS-CoV-2 RNA, as determined via real-time reverse transcription-polymerase chain reaction (RT-PCR) from throat and/or nasal swabs and 2) positive results for both IgG and IgM antibodies against SARS-CoV-2 antigen, determined through enzyme-linked immunosorbent assay (ELISA) [30]. Throat swabs or nasopharyngeal aspirates were collected daily from each patient during hospitalization.

The inclusion criteria for the study participants were as follows: 1) individuals definitively diagnosed with SARS-CoV-2 infection who were admitted to the designated temporary medical facility; 2) patients with COVID-19 who met the diagnostic criteria for mild or moderate manifestations of the disease; 3) individuals who provided informed consent; and 4) those possessing the capacity for autonomy.

Patients were excluded from the study based on any of the following criteria: 1) incapacity for self-care or cooperation in self-assessment and professional evaluation; 2) exacerbation of disease progression or mortality occurring within 48 h of admission to the temporary medical facility; 3) manifestation of severe psychiatric disorders; 4) recent exposure to severe psychological trauma; 5) presentation of severe cardiovascular, hepatic, renal, and neurological disorders, or other profound medical diagnoses; 6) participation in concurrent clinical trials for the management of COVID-19 or the discontinuation of medication during the course of alternative clinical trials; 7) patients with interrupted treatment.

2.3. Exposure variables and assessment

The primary analysis entailed modeling TCM treatment as a continuous exposure variable. To assess treatment duration, we defined TCMTI of total prescribed TCM therapy relative to the length of hospitalization (days) for each patient, as delineated in Formula (1). In subsequent analyses, the exposure variable was discretized into a categorical variable using an optimal threshold value determined using a systematic grid search method. Consequently, all patients were stratified into two distinct groups: high and low TCMTI.

$$\text{TCMTI} = \text{Total days of TCM treatment/Total length of hospital stay} \quad (1)$$

2.4. Covariates

Key baseline covariates identified as potential prognostic factors encompassed the following: 1) demographic attributes, including age, sex, and marital status; 2) risk factors, such as the month of patient recruitment, food allergies, COVID-19 vaccine administration, volunteer status, and underlying medical conditions and comorbidities (tumors, hypertension, diabetes, cardiovascular ailments, chronic obstructive pulmonary disease, and pulmonary infections).

Post-baseline covariates included the use of medications targeting respiratory, circulatory, and digestive system disorders, including prescription drug details for antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and other pharmaceutical agents administered throughout hospitalization. When patients with COVID-19 presented with the aforementioned underlying medical conditions and comorbidities, medical prescriptions were crafted by the attending physicians and dispensed daily within the temporary hospital. The TI for each medication was computed as the ratio of the number of days of medication administration to the overall duration of hospitalization, which was calculated individually for each medication category.

2.5. Intervention

The primary independent variable was TCMTI, which was examined in both continuous and dichotomous forms (high vs. low TCMTI groups). Some TCM treatments were administered to patients with COVID-19 based on their physical symptoms, constitution, and characteristics (Table S1). The TCM treatment protocols for each patient adhered to the "Guidelines on Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial 9th Edition)" [22,30]. Additionally, basic symptomatic treatment and general healthcare measures (including fever reduction, cough alleviation, mucus dissolution, pain relief, and anti-asthma interventions) were provided based on the clinical manifestations of the patients. Medications for underlying medical conditions were administered to patients with COVID-19 when deemed necessary.

2.6. Definition and therapeutic efficacy evaluation

The primary outcome was the time taken for a negative conversion of SARS-CoV-2 RNA, defined as the duration (days) between the date of

admission to the temporary hospital and the date of the first instance of two consecutive negative test results. Negative conversion was confirmed when a patient with COVID-19 had at least two consecutive negative results from RT-PCR testing with a minimum interval of 24 h between tests. SARS-CoV-2 RNA were considered negative when the cycle threshold (*Ct*) values of both the ORF1ab and N genes were > 35 [30].

The secondary efficacy endpoint was the duration of hospitalization for patients with COVID-19, defined as the time interval (days) between hospital admission and discharge. The discharge criteria required laboratory evidence of SARS-CoV-2 clearance, which was confirmed by negative RT-PCR tests conducted on nasopharyngeal swab samples collected at intervals of at least 24 h [30].

2.7. Statistical analyses

The probability of SARS-CoV-2 RNA turning negative on Day 7 in relation to TCMTI was visually assessed, and a mathematical analysis was conducted to identify a cutoff point using threshold regression using the method of estimation and hypothesis testing for threshold regression (R package chngpt, version 2021.5–12) [31]. Furthermore, continuous TCMTI data were utilized in restricted cubic spline (RCS) regression models. The potential cutoffs for TCMTI were explored using the RCS model with four knots representing the 5th, 35th, 65th, and 95th percentiles [32,33]. Ultimately, the determined cutoff value was 0.65 (Supplementary Material 1).

Survival curves were constructed for both high and low TCMTI groups using the Kaplan–Meier method. The proportional hazards assumption was validated through graphical assessments by plotting log (-log (survival)) against log (survival time) and was confirmed using the Schoenfeld residuals method [22]. In cases where the proportionality assumption was not met, an approach based on time splitting was considered for Cox proportional hazard multivariate analysis; hazard ratios (*HRs*) and 95 % confidence intervals (*CIs*) were calculated. Multiple models were used to explore this association, including The least absolute shrinkage and selection operator (lasso) Cox regression, restricted mean survival time (RMST), and Cox regression models with RCS using four knots (at the 5th, 35th, 65th, and 95th percentiles of TCMTI) as previously described [33,34]. Linear regression models (LRMs) were used to assess the relationship between the TCMTI and logarithmically transformed hospitalization days. Additionally, RCS LRMs with four knots positioned at the 5th, 35th, 65th, and 95th percentiles of the TCMTI distribution were performed. To control for potential confounders, covariates related to both the TCMTI and the logarithmic transformation of hospitalization duration, was adjusted by four models with increasing numbers of covariates.

Sensitivity analyses were performed for both the measured and unmeasured confounders using Model 4. The measured confounders were evaluated through inverse probability of treatment weight (IPTW) logistic regression models using propensity scores. Standardized mean differences (SMDs) were utilized to assess covariate balance, with SMD values ≤ 0.10 indicating acceptable balance. The approach for unmeasured confounders was consistent with that applied by Lin et al [35]. Two synthetic variables were created and assigned different levels: gamma, which can be interpreted as the direct effect of unmeasured confounders on the time to SARS-CoV-2 RNA negativity and TCMTI; and delta, which can be interpreted as the association between unmeasured confounders and the exposure indicator. Values for gamma and delta ranged from 0.00 to 1.00 in increments of 0.25. Upon refitting the results after introducing the hypothesized unmeasured confounders, the recalibrated estimates were confounded by additional factors with different observed correlations.

All statistical analyses were conducted using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria, https://cran.r-project.org/). Two-tailed tests were used for all statistical assessments, and the significance level was set at $P < 0.05$.

3. Results

3.1. COVID-19 patient characteristics

The study recruited 6120 patients with COVID-19 from a temporary hospital between April and May 2022. No loss to follow-up or deaths occurred during the follow-up period. The median age of all patients with mild COVID-19 was 43.0 years (range: 2.0–75.0 years), whereas the median duration of TCM use was 2.0 days (range: 0.0–15.0 days). The median TCMTI was 0.23 (range: 0.00–1.00). Furthermore, the median time to SARS-CoV-2 RNA negativity was 6.67 days (range: 6.64–6.69 days), whereas the median length of hospitalization was 9.70 days (range: 4.10–22.50 days). The logarithmic transformed median length of hospitalization was 2.28 (range: 1.40–3.24).

The patients with mild COVID-19 comprised 1854 women (30.3%), 3928 married individuals (64.2%), 1188 individuals who were unvaccinated against COVID-19 (19.4%). Furthermore, 64 participants (1.0%) had a history of food allergies and 648 (11.6%) had underlying comorbidities. Additionally, 569 (9.3%), 205 (3.3%), and 250 (4.1%) received pharmacological treatment for the respiratory, circulatory, and digestive systems, respectively. Similarly, 260 (4.3%) and 404 (6.6%) participants received antibiotic and NSAIDs treatment, respectively (Table S2). A significant nonlinear positive correlation was found between the logarithmically transformed hospitalization duration and negative conversion time of SARS-CoV-2 RNA ($P < 0.001$) (Fig. 1).

3.2. Association between TCMTI and the time to negative conversion of SARS-CoV-2 RNA

3.2.1. The cox proportional hazards model was used to investigate the association between TCMTI and the time it takes for SARS-CoV-2 RNA to turn negative

Several factors were significantly associated with time to SARS-CoV-2 RNA negativity, including age, sex, patient recruitment time, temporary hospital ward, vaccination status, and marital status, as well as respiratory system, circulatory system, antibiotic, digestive system, NSAIDs, and other pharmacological TIs (all $P < 0.001$. Table 1). However, no significant linear correlation was observed between TCMTI and the time to SARS-CoV-2 RNA negativity ($HR = 0.873$, 95% *CI*: 0.756–1.007, $P = 0.062$). The likelihood ratio test indicated that the nonlinear model was significantly better than the linear model ($\chi^2 = 701.223$, $P < 0.001$). Additionally, a smoothing plot showed a significant nonlinear correlation between the TCMTI and time to SARS-CoV-2 RNA negativity (Fig. S1, Table S3).

Multiple statistical methods were used to determine the cut-off point for the association between the probability of SARS-CoV-2 RNA negativity by day 7 after admission and TCMTI in patients with COVID-19. The cutoff value for this relationship was also set at 0.65. Moreover, a linear relationship was observed between the day 7 survival probability and TCMTI when the TCMTI was >0.65 (Fig. S1). Therefore, all patients with COVID-19 were categorized into low (< 0.65, $n = 5725$) and high (≥ 0.65, $n = 395$) TCMTI groups.

3.2.2. RCS cox regression was utilized to explore the association between TCMTI and time to SARS-CoV-2 RNA negativity

The inverse relationship between TCMTI and the negative conversion time of SARS-CoV-2 RNA exhibited a nonlinear pattern (Table 2, Fig. 2). In all adjusted models, increased TCMTI (as a continuous variable) was consistently associated with a decrease in the negative conversion time of SARS-CoV-2 RNA at TCMTI ≥ 0.65. These associations were statistically significant across all models (all $P < 0.001$, Fig. 2).

3.2.3. A time-dependent cox model was used to explore the association between TCMTI (high vs. low TCMTI groups) and the negative conversion time of SARS-CoV-2 RNA

The association between TCMTI (high vs. low TCMTI groups, Table S4) and the time to SARS-CoV-2 RNA negativity was analyzed

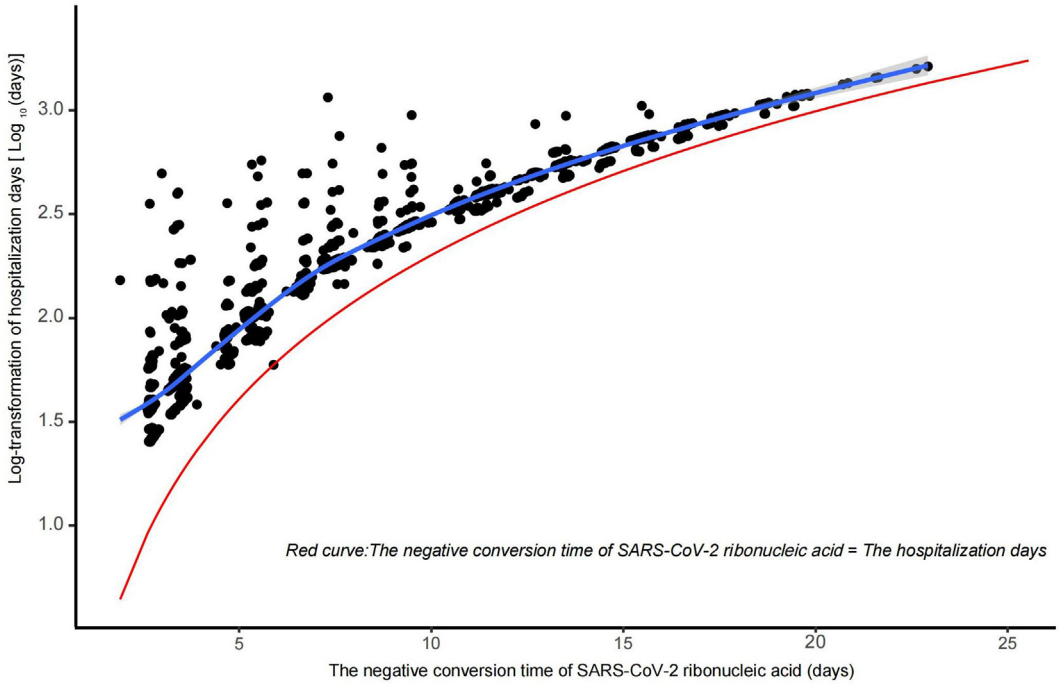

Fig. 1. The correlation between log-transformation of hospitalization days and the negative conversion time of SARS-CoV-2 RNA. Abbreviations: RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 1
Predictors for SARS-CoV-2 RNA negative conversion at Day 7 after entering the shelter hospital was explored with univariate cox proportional risk regression model.

Variables	Univariate analysis	
	HR (95 % *CIs*)	*P*-value
Age	0.986 (0.984, 0.988)	<0.001
Gender (female vs. male (reference))	1.074 (1.012, 1.140)	<0.001
Volunteer (Yes vs. No (reference))	1.025 (0.955, 1.100)	0.499
Patient recruitment time (month 5 vs. month 4 (reference))	0.384 (0.327, 0.452)	<0.001
Food allergy (Yes vs No (reference))	0.780 (0.590, 1.031)	0.081
Hospital ward in temporary hospital		
A ward (reference)	–	–
B ward	1.207 (1.098, 1.326)	<0.001
C ward	1.746 (1.602, 1.904)	<0.001
D ward	1.274 (1.169, 1.389)	<0.001
Marital status		
Unknown (reference)	–	–
Single	1.407 (1.162, 1.705)	<0.001
Married	1.125 (0.931, 1.360)	0.221
Comorbidities		
Endocrine system disease (reference)	–	–
Digestive system disease	0.953 (0.607, 1.496)	0.834
Circulatory system disease	1.045 (0.800, 1.366)	0.746
Other system	0.910 (0.649, 1.276)	0.584
None	1.166 (0.910, 1.496)	0.225
Vaccine inoculation		
1 dose (reference)	–	–
2 doses	0.940 (0.805, 1.098)	0.433
3 doses	0.820 (0.705, 0.955)	0.011
None	0.875 (0.746, 1.026)	0.101
Medicine treatment intensity		
TCMTI	0.873 (0.756, 1.007)	0.062
Respiratory system drugs treatment intensity	0.083 (0.045, 0.155)	<0.001
Circulatory system drugs treatment intensity	0.188 (0.081, 0.432)	<0.001
Antibiotics treatment intensity	0.175 (0.068, 0.455)	<0.001
Digestive system drugs treatment intensity	0.045 (0.014, 0.137)	<0.001
NSAIDs treatment intensity	0.020 (0.007, 0.056)	<0.001
Other drugs treatment intensity	0.531 (0.160, 1.760)	0.301

Notes: univariate analysis model. Abbreviations: CIs: confidence intervals. NSAIDs: non-steroidal anti-inflammatory drugs. RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity.

using Kaplan–Meier survival curves (Fig. 3). The median days to SARS-CoV-2 RNA negativity were 8.47 [range: 1.90–25.54] and 5.24 [range: 2.65–21.50] days in the low and high TCMTI groups, respectively. The median time to SARS-CoV-2 RNA negativity was shorter in the high TCMTI group than in the low TCMTI group ($\chi^2 = 103.988$, $P < 0.001$).

The Schoenfeld residual proportional hazards test indicated a violation of the proportional hazards assumption ($\chi^2 = 21.643$, $P < 0.001$), as

Table 2
RSC models were conduced to explore the association between TCMTI and the negative conversion time of SARS-CoV-2 RNA.

Item	Models	Coefficient (95 % *CIs*)	*P*-value
TCMTI'	Nonlinear model 0	9.387 (8.421, 10.354)	<0.001
TCMTI″		−88.552 (−95.649, −81.454)	<0.001
TCMTI‴		166.504 (153.602, 179.406)	<0.001
TCMTI'	Nonlinear model 1	9.701 (8.726, 10.673)	<0.001
TCMTI″		−88.668 (−95.806, −81.530)	<0.001
TCMTI‴		165.918 (152.942, 178.894)	<0.001
TCMTI'	Nonlinear model 2	9.832 (8.791, 10.872)	<0.001
TCMTI″		−100.381 (−108.062, −92.700)	<0.001
TCMTI‴		188.062 (174.098, 202.025)	<0.001
TCMTI'	Nonlinear model 3	9.839 (8.798, 10.881)	<0.001
TCMTI″		−100.361 (−108.05, −92.672)	<0.001
TCMTI‴		188.006 (174.028, 201.984)	<0.001
TCMTI'	Nonlinear model 4	10.445 (9.390, 11.500)	<0.001
TCMTI″		−102.820 (−110.549, −95.090)	<0.001
TCMTI‴		191.943 (177.899, 205.988)	<0.001

Notes: 1) Model 0 only included TCMTI. Model 1 was adjusted for gender and age. Model 2 was further adjusted for marital status, patient recruitment time, volunteer and wards. Model 3 was further adjusted for various comorbidities (hypertension, diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease, pulmonary infection, and so on) and food allergy. The fully Model 4 further adjusted for all post-line covariants, it included respiratory drug TI, circulatory drug TI, antibiotic TI, digest drug TI, NSAIDs drug TI and others drug TI. 2) TCMTI', TCMTI″ and TCMTI″ are three new variables producted by restricted cubic splines with four konts (at the 5th, 35th, 65th, and 95th percentiles) of the TCMTI distribution, these are producted by formula 1 and formula 2 (Supplementary material 2). Abbreviations: *CIs*: confidence intervals. NSAIDs: non-steroidal anti-inflammatory drugs. RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity. TI: treatment intensity.

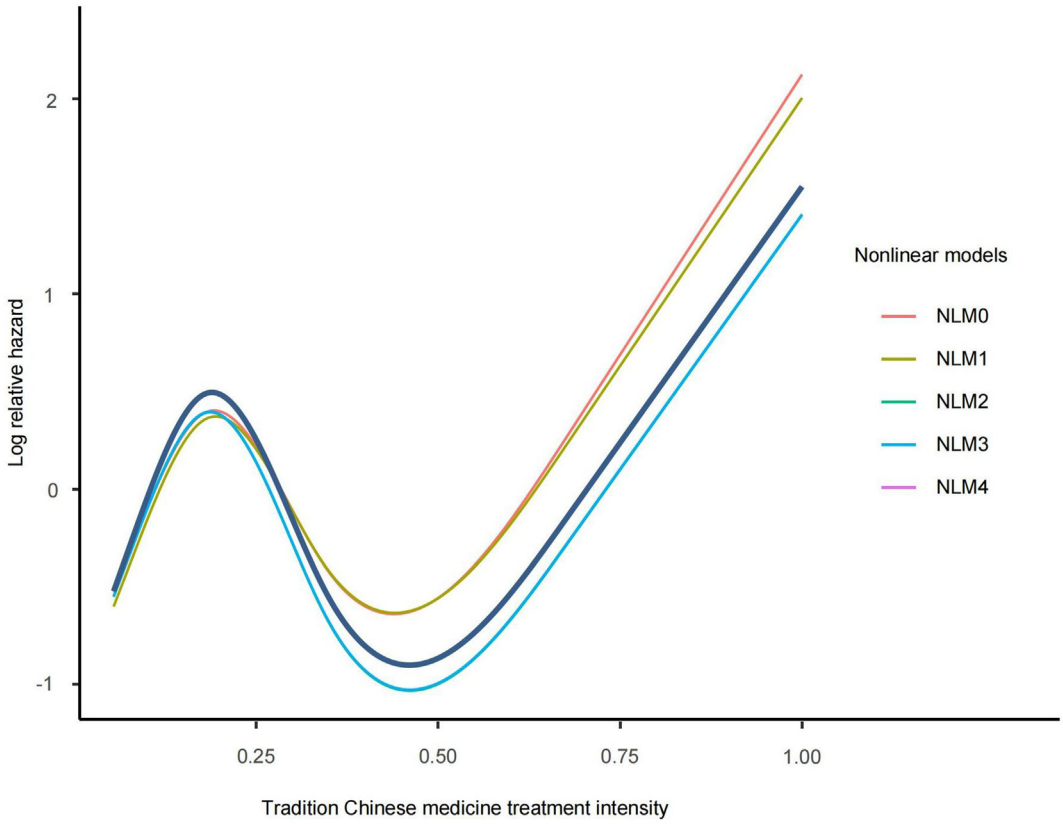

Fig. 2. The sharp between the log relative hazard of negative conversion time of SARS-CoV-2 RNA before day 7 and TCMTI following adjustments in RSC cox multiple models. Model 0 only included TCMTI, whereas Model 1 was adjusted for sex and age. Model 2 was further adjusted for marital status, patient recruitment time, volunteering, and wards. Moreover, Model 3 was adjusted for various comorbidities (including hypertension, diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease, pulmonary infection) and food allergy. Model 4 further adjusted for all post-line covariates, including respiratory drug, circulatory drug, antibiotic, digestive system drug, NSAIDs, and other drug treatment intensities (TIs). Abbreviations: *CIs*: confidence intervals. NLM: nonlinear model. NSAIDs: non-steroidal anti-inflammatory drugs. RCS: Restricted cubic spline. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity. TI: treatment intensity.

illustrated by the crossing of the Kaplan–Meier survival curves (Fig. 3). Thus, a time-dependent Cox model with time-split functions was constructed using a splitting time of 11.5 days. The product of splitting time and TCMTI (high vs. low TCMTI) was then considered a time-dependent covariate in proportional hazards Cox regression models.

A low TCMTI was a significant risk factor for prolonging the time to SARS-CoV-2 RNA negativity in all five models (Table 3. all $P < 0.001$). The *HRs* for the effect of TCMTI on the time to SARS-CoV-2 RNA negativity slightly varied between 1.578 and 1.857 across the five models (Table 3). Moreover, a considerable positive association was observed between a low TCMTI and the length of time to SARS-CoV-2 RNA negativity (Fig. 4). This indicates that a high TCMTI may reduce the time to SARS-CoV-2 RNA negativity in patients with COVID-19.

The lasso Cox regression model revealed seven independent variables as significant predictors of the time to SARS-CoV-2 RNA negativity in patients with mild COVID-19 within the first seven days of hospital admission. These variables included TCMTI, age, ward, patient recruitment time, respiratory system drug TI, digestive system drug TI, and NSAIDs TI (all $P < 0.01$) (Table S5).

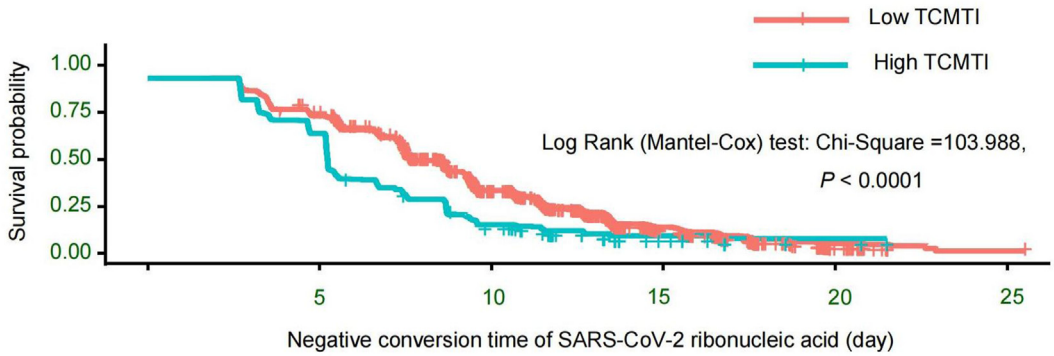

Fig. 3. Kaplan–Meier survival analysis showing that median days of the negative conversion time of SARS-CoV-2 RNA have significant differences between the high and low TCMTI groups. Abbreviations: RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity.

Table 3
The association between TCMTI (high TCMTI group vs. low TCMTI group) and the negative conversion time of SARS-CoV-2 RNA was explored with time-dependent cox regression models adjusted by different covariates.

Models	*HR* (95 % *CIs*)
Model 0	1.578 (1.400, 1.779)
Model 1	1.857 (1.661, 1.076)
Model 2	1.701 (1.516, 1.908)
Model 3	1.703 (1.517, 1.911)
Model 4	1.769 (1.575, 1.986)

Notes: 1) TCMTI group includes high TCMTI group and low TCMTI, and the low TCMTI group is reference. 2) Model 0 only included TCMTI. Model 1 was adjusted for gender and age. Model 2 was further adjusted for marital status, patient recruitment time, volunteer and wards. Model 3 was further adjusted for various comorbidities (hypertension, diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease, pulmonary infection, and so on) and food allergy. The fully model 4 further adjusted for all post-line covariants, it included respiratory drug TI, circulatory drug TI, antibiotic TI, digest drug TI, NSAIDs drug TI and others drug TI. Abbreviations: *CIs*: confidence intervals. HR: hazard ratios. NSAIDs: non-steroidal anti-inflammatory drugs. RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity. TI: treatment intensity.

Table 4
RMST model were conducted to explore the association between TCMTI (high TCMTI group vs. low TCMTI) and the negative conversion time of SARS-CoV-2 RNA.

Models	Estimate (95 % *CIs*)
Model 0	−2.081 (−2.616, −1.545)
Model 1	−1.851 (−2.084, −1.617)
Model 2	−1.942 (−2.177, −1.707)
Model 3	−1.947 (−2.182, −1.712)
Model 4	−1.909 (−2.144, −1.675)

Notes: 1) TCMTI group includes high TCMTI group and low TCMTI, and the low TCMTI group is reference. 2) Model 0 only included TCMTI. Model 1 was adjusted for gender and age. Model 2 was further adjusted for marital status, patient recruitment time, volunteer and wards. Model 3 was further adjusted for various comorbidities (hypertension, diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease, pulmonary infection, and so on) and food allergy. The fully model 4 further adjusted for all post-line covariants, it included respiratory drug TI, circulatory drug TI, antibiotic TI, digest drug TI, NSAIDs drug TI and others drug TI. Abbreviations: *CIs*: confidence intervals. NSAIDs: non-steroidal anti-inflammatory drugs. RMST: restricted mean survival time. RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity. TI: treatment intensity.

3.2.4. RMST model demonstrated the association between TCMTI (high vs low TCMTI) and the negative conversion time of SARS-CoV-2 RNA

Adjusted RMST analysis truncated on the 21st day revealed a substantial benefit in the high TCMTI group. Compared to the low TCMTI group, participants in the high TCMTI group exhibited a reduction of 2.081 days in the negative conversion time of SARS-CoV-2 RNA during univariate analysis (Model 0, $P < 0.001$. Table 4). Similar results were observed in multiple models adjusted for various potential confounding factors (Models 1–4. Table 4). The estimated difference in the negative conversion time of SARS-CoV-2 RNA between participants receiving treatment in the high TCMTI group and those in the low TCMTI group was consistently close to 1.9 days in multiple models (Models 1–4, all $P < 0.001$. Table 4).

3.3. The association between TCMTI and log-transformation of hospitalization days

Univariate LRM analysis revealed a statistically significant correlation between log-transformed hospitalization days and variables such as age,

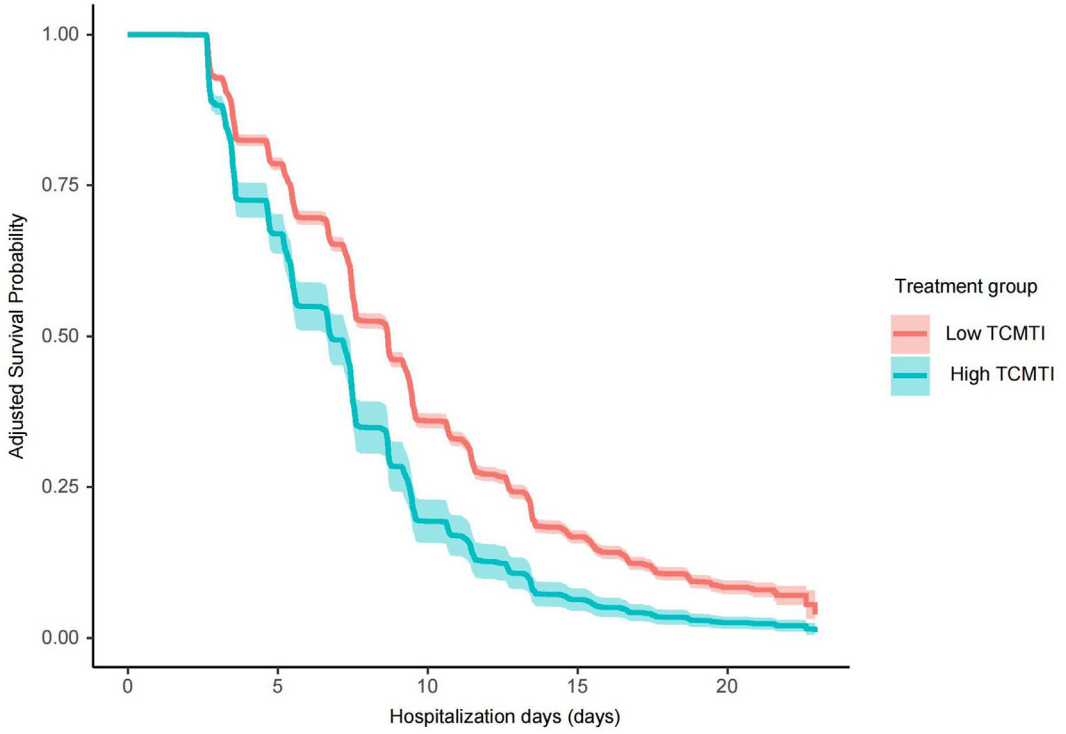

Fig. 4. High TCMTI can reduce the negative conversion time of SARS-CoV-2 RNA in patients with mild COVID-19. The calculation is based the Mode 4 (complete model), which was adjusted for all covariates. It included sex, age, marital status, patient recruitment time, volunteering, wards, various comorbidities (including hypertension, diabetes, cardiovascular and cerebrovascular diseases, chronic obstructive pulmonary disease, and pulmonary infection), food allergy, respiratory drug TI, circulatory drug TI, antibiotic TI, digestion drug TI, NSAIDs TI, and other drug TIs. Abbreviations: COVID-19: coronavirus disease 2019. NSAIDs: non-steroidal anti-inflammatory drugs. RNA: ribonucleic acid. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. TCMTI: traditional Chinese medicine treatment intensity. TI: treatment intensity.

patient recruitment time, temporary hospital ward, marital status, as well as respiratory, circulatory system, antibiotic, gastrointestinal, NSAIDs, and other drug treatment intensities (all $P < 0.001$. Table S6). Furthermore, the log-transformation of hospitalization days was 2.007 ± 0.02 and 2.378 ± 0.02 in the high and low TCMTI groups, respectively. This demonstrates that the log-transformation of hospitalization days was lower in the high-TCMTI group than in the low-TCMTI group (Model 0, coefficient = −0.162, 95 % *CI*: −0.160, 0.164. $P < 0.002$, Table S6). Additionally, the LRM models with increasing numbers of covariates (Models 1–4) consistently displayed a negative association between high TCMTI and log-transformed hospitalization days ($P < 0.001$, Table S7). In other words, patients with mild COVID-19 who received high TCMTI treatment experienced shorter hospitalization durations.

The application of LRM with RCS featuring four knots revealed a significant nonlinear relationship between TCMTI and the log transformation of hospitalization days (Fig. S2, Table S8). Additionally, the LRM model fitted with the RCS and four knots to explore the association between TCMTI and log-transformed hospitalization days outperformed the conventional LRM model (root sum square value: 751.964 vs. 921.645, $F = 169.681$, $P < 0.001$).

Multiple RCS models that were fitted with the LRM exhibited nonlinear associations. Moreover, all models were adjusted for various confounding factors (Fig. S3). These results indicate that a higher TCMTI value (approaching 1.0) corresponded to a smaller log transformation of hospitalization days (Table S9, Fig. S3).

3.4. Sensitivity analyses

Sensitivity analyses were conducted using the IPTW in the fully adjusted model (Model 4) to evaluate the impact of known confounding variables. A high TCMTI had a positive and statistically significant effect on the probability of SARS-CoV-2 RNA negativity at day 7 (*HR* = 1.481, 95% *CI:* 1.302, 1.683. $P < 0.001$), which was consistent with the initial findings. Additionally, unmeasured confounding factors, represented by two hypothetical variables, gamma and delta, may have influenced the association between TCMTI and the time to SARS-CoV-2 RNA negativity. The adjusted *HR*s in Model 4 ranged from 0.651 (95% *CI*: 0.580, 0.938) to 1.769 (95% *CI*: 1.575, 1.986) (Fig. S4-S5, Tables S10-S11). Among the 25 *HR*s and their corresponding 95 % *CI*s, 19 (95 % *CI*s) obtained similar results to those of the study, four HRs (95% *CI*s) showed no significant difference as their *CI*s included zero (Table S11) and two *HR*s (95% *CI*s) presented conflicting conclusions as their *HR*s ranged from 0.0 to 1.0 (Table S10).

4. Discussion

The cohort study showed that high TCMTI can shorten the time to SARS-CoV-2 RNA negativity and the length of hospitalization in patients with mild COVID-19. These findings demonstrate a nonlinear association between TCMTI and efficacy in patients with mild COVID-19. The encouraging findings provide clinical evidence to support the guidelines recommending TCM for patients with mild COVID-19.

Various association patterns have been observed between interventions and effect, including positive linear, S-shaped-, U-shaped-, and reverse L-shaped (or reverse J-shaped) curves. Nonlinear correlations are common in various medical contexts, such as in the U-shaped relationships between total cholesterol and mortality [36] or dietary copper intake and obesity risk [37]. They are equally common in L-shaped associations between linoleic acid in the adipose tissue and all-cause mortality [38] or variability in the association between TI and mortality by stage and cause-specific mortality [39]. The study also revealed a distinct nonlinear relationship between TI and disease outcome. Accurate investigation of the association between intervention measures and clinical outcomes can enable the precise selection of treatment regimens or clinical TIs to expedite patient recovery.

The mechanisms underlying TCM action against viral infections are complex. Viral respiratory infections, such as those caused by SARS-CoV, SARS-CoV-2, and H1N1, can elicit robust immune responses and cytokine storms. TCM possesses multi-component, multi-target, and multi-pathway characteristics [40], with broad-spectrum antiviral, anti-inflammatory, immunomodulatory, and organ–protective properties [40]. The efficacy of TCM against COVID-19 is primarily based on the synergistic interactions between various components from different herbs in a single formula [40]. The study further demonstrates that numerous chemical constituents of the herbs may achieve specific thresholds to accelerate pathogen clearance through immunomodulation and other mechanisms when TCMTI reaches a certain critical value in the blood. These findings showed that TCMTI could shorten the time to SARS-CoV-2 RNA negativity and length of hospitalization, with other study also demonstrating TCM potential against COVID-19 [22]. In contrast, another study reported no statistically significant difference in the time to SARS-CoV-2 RNA negativity, regardless of whether they received TCM treatment [41]. These inconsistent findings underscore the lack of consensus regarding TCM effects on the therapeutic outcomes of patients with COVID-19 in observational studies. Hence, there is a need for further randomized controlled trials investigating the clinical efficacy of TCM against COVID-19.

Although this study provided valuable insights into the potential therapeutic role of TCM against COVID-19, it had several limitations. First, a causal relationship between the TCM interventions and clinical outcomes could not be established because this was a retrospective observational study. Secondly, this study was confined to mild COVID-19 cases in Shanghai, China, which restricts their generalizability and may have resulted in a lower level of evidentiary support. Third, crucial pre-admission information for patients, such as the precise timing of viral infection and the interval between SARS-CoV-2 infection onset and temporary hospitalization, was not captured, potentially affecting the clinical treatment outcomes. Fourth, some electronic medical records rely primarily on the recollections of patients with COVID-19, introducing the possibility of memory bias. Therefore, rigorous large-scale multi-center randomized controlled trials are required to confirm the TCM efficacy.

5. Conclusions

The study revealed that TCM can reduce the time for SARS-CoV-2 RNA to turn negative and hospitalization duration in patients with mild COVID-19. Given its proven efficacy and safety, TCM can be considered a valuable approach for treating mild COVID-19. Future studies should design large-scale, multi-center, randomized controlled trials to comprehensively assess the effects of TCM on COVID-19.

Ethics approval and consent to participate

The trial was registered in the Chinese Clinical Trial Registry on Aug 31, 2022 (ChiCTR2200063151, http://www.chictr.org.cn/). This study was approved by the Ethical Review Committee of Longhua Hospital (2022LCSY065). All experimental procedures adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants after explaining the purpose, potential risks, and benefits of the study.

Availability of data and materials

Data supporting the findings of this study are available from the corresponding author, with permission from Shun-Xian Zhang (Email: zhangshunxian110@163.com).

Consent for publication

Not applicable.

Funding

This study was supported by the Project on Prevention and Treatment of COVID-19 with Traditional Chinese Medicine [grant number XGYJKY2022-09]; the Intervention Effect on COVID-19 in High-Risk Groups [grant number 2022ZYLCYJ05-10]; the Three-Year Action Plan for Promoting Clinical Skills and Innovation Ability of Municipal Hospitals [grant number SHDC2022CRS039]; Shanghai Natural Science Foundation [grant numbers 22ZR1462100, 23ZR1464000, 23ZR1463900]; and the talent fund of Longhua Hospital [grant number LH001.007].

Author contributions

Yue-Lai Chen and **Yu Tian**: Conceptualization and Data curation. **Wei Lu, Xiao-Xu Chen, Hua-Feng Wei, Xiao Wang, Jiao Li,** and **Dong Zhu**: Investigation. **Ming Yang**: Formal analysis. **Ming Yang** and **Shun-Xian Zhang:** Writing - original draft, Writing - review & editing. **Yue-Lai Chen**, **Ming Yang** and **Yu Tian** contributed equally to this work, and **Shun-Xian Zhang** is the corresponding author. All the authors have read and approved the final version 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 the paper.

Acknowledgements

Acknowledgment is forwarded to the study participants for their valuable information, and to data collectors, doctors, nurses, and supervisors for their commitment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.soh.2023.100049.

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