

Coronavirus Pandemic

Impact of traditional Chinese medicine on the prognosis of COVID-19 in cancer patients: a questionnaire-based survey

Man Yao^{1,2#}, Shuhui Tang^{3#}, Xiaowan Xu^{1#}, Guo Chen¹, Min Liu¹, Yannan Xu⁴, Shuang Xiang⁴, Xuan Zhang⁵, Xiaofeng Zhai¹, Hetong Zhao^{1,5}

¹ Department of Integrative Oncology, The First Affiliated Hospital of Naval Medical University, Shanghai, China

² Shanghai University of Traditional Chinese Medicine, Shanghai, China

³ Department of Oncology, The First Affiliated Hospital of Naval Medical University, Shanghai, China

⁴ School of Traditional Chinese Medicine, Naval Medical University, Shanghai, China

⁵ Department of Traditional Chinese Medicine, Navy NO.905 Hospital, Naval Medical University, Shanghai, China

Authors contributed equally to this work.

Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic, exacerbated by the emergence of new variants such as Omicron, has posed significant challenges to healthcare systems worldwide. This study aimed to explore the potential effectiveness of long-term traditional Chinese medicine (TCM) use on COVID-19 infection and post-infection symptoms in cancer patients.

Methodology: An anonymous online questionnaire was used to interview cancer patients who had used TCM (TCM group) and those who had never used TCM (non-TCM group) from March 31 to April 30, 2023. A self-reported questionnaire was developed to investigate and analyze the patients' demography, underlying cancer types, treatment (TCM or non-TCM), clinical symptoms, and post-acute COVID-19 related symptoms.

Results: A total of 996 cancer patients participated (607 TCM, 389 non-TCM). The non-TCM group had a higher infection rate (84.1% vs. 75.8%, $p = 0.002$). The TCM group reported significantly lower levels of post-COVID-19 symptoms at 3 months post-infection. Specifically, 98.0% of the TCM group reported no fatigue (91.7% in the non-TCM group, $p < 0.001$), and 98.7% reported no sleep difficulties (88.7% in the non-TCM group, $p < 0.001$). The median infection duration was 7 days in both groups, median body temperature was 38.2 °C in TCM and 38.3 °C in non-TCM group, and the fever duration was 2 days in both groups.

Conclusions: There was a potential association between long-term TCM use and improved COVID-19 outcomes among cancer patients. Further research is essential to validate these findings and decipher the underlying mechanisms.

Key words: COVID-19; Omicron; TCM; non-TCM; cancer patients.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of people globally [1]. Since the outbreak of SARS-CoV-2, adaptive mutations have occurred continuously, resulting in 5 variants of concern; namely, Alpha, Beta, Gamma, Delta, and Omicron. These variants have shown significant changes in transmission characteristics and virulence, posing a substantial threat to global public and human health [2]. Although the development and distribution of vaccines have provided hope for controlling the pandemic, effective therapeutic strategies remain a significant area of research.

Post-acute COVID-19 related conditions, commonly termed as "long COVID" or "post-acute sequelae of SARS-CoV-2 infection (PASC)," refer to a range of symptoms that persist for weeks or months after the acute phase of a COVID-19 infection [3,4]. These conditions encompass a wide array of clinical manifestations; including, but not limited to fatigue, cognitive disturbances, sleep difficulties, and respiratory complaints. The intersection of these conditions with underlying diseases like cancer is gaining research attention due to its implications for long-term patient care and quality of life.

Given the backdrop of their cancer conditions, patients with malignancies often exhibit compromised immunity, either due to the immunosuppressive nature of their oncological treatments or the inherent

immunosuppressive characteristics of the tumors themselves. Furthermore, many of these patients with malignant tumors have not completed their vaccine regimens for various reasons, placing them at a significant risk, especially in the face of the widespread prevalence of the Omicron variant [5]. A considerable proportion of cancer patients resort to traditional Chinese medicine (TCM) as part of their therapeutic regimen, reflecting a cultural preference and the potential benefits that such treatments provide [6]. The distinctive advantages of TCM have been fully demonstrated in coping with the long-term impacts of COVID-19 on health and life [7,8]. Over time, long-term consumption of these herbs may have a multitude of effects on these individuals' physiological and immune responses, potentially altering their vulnerability or resilience to various infections, including those of novel pathogens such as the SARS-CoV-2 virus. This has become a highlight of the "China solution" for epidemic prevention and control.

Given the widespread use of TCM among cancer patients, and the unique challenges posed by the COVID-19 pandemic, we aimed to explore the potential effectiveness of TCM in managing COVID-19 infection among cancer patients. Specifically, we hypothesized that TCM use may be associated with better COVID-19 outcomes.

Methodology

Table 1. Demographic characteristics of participants.

Variables	All	TCM (N = 607)	Non-TCM (N = 389)	p value
Age (years)				0.253
< 40	63 (6.3)	40 (6.6)	23 (5.9)	
40–70	778 (78.1)	479 (78.9)	299 (76.9)	
> 70	155 (15.6)	88 (14.5)	67 (17.2)	
Gender				0.837
Male	658 (66.1)	399 (65.7)	259 (66.6)	
Female	338 (33.9)	208 (34.3)	130 (33.4)	
BMI				0.478
< 18.5	69 (6.9)	45 (7.4)	24 (6.2)	
≥ 18.5, < 24	603 (60.5)	353 (58.2)	250 (64.3)	
≥ 24, < 28	268 (26.9)	176 (29.0)	92 (23.7)	
≥ 28	56 (5.6)	33 (5.4)	23 (5.9)	
Region				0.152
Northeast China	36 (3.6)	27 (4.4)	9 (2.3)	
North China	6 (0.6)	3 (0.5)	3 (0.8)	
East China	894 (89.8)	530 (87.3)	364 (93.6)	
South China	5 (0.5)	5 (0.8)	0 (0.0)	
Central China	25 (2.5)	19 (3.1)	6 (1.5)	
Northwest China	17 (1.7)	12 (2.0)	5 (1.3)	
Southwest China	13 (1.3)	11 (1.8)	2 (0.5)	
Type of cancer				
Head and neck cancer	73 (7.3)	27 (4.4)	46 (11.8)	< 0.001
Urological cancer	24 (2.4)	9 (1.5)	15 (3.9)	0.02
Gynecological cancer	63 (6.3)	48 (7.9)	15 (3.9)	0.011
Digestive tract cancer	708 (71.1)	421 (69.4)	287 (73.8)	0.152
Respiratory and thoracic cancer	187 (18.8)	131 (21.6)	56 (14.4)	0.005
Other type of cancer	12 (1.2)	5 (0.8)	7 (1.8)	0.233

TCM: traditional Chinese medicine; BMI: body mass index. Percentages are rounded to the nearest decimal and may not add to 100%.

Study design and participants

We conducted an anonymous online cross-sectional survey from 31 March to 30 April 2023 among a convenience sample of cancer patients diagnosed with COVID-19. The participants included those who had previously utilized TCM for oncological treatments (TCM group), and those who had primarily relied on western medical treatments and had never used TCM (non-TCM group). The TCM group included patients who were diagnosed with tumor, and had medical records indicating at least 1-month of TCM use. The study utilized the online survey tool "Questionnaire Star" to generate, distribute, and publish questionnaires. Electronic questionnaires were retrieved on mobile platforms. Ethical approval for this study was granted by the Institutional Review Board of Changhai Hospital, with the approval number of CHEC2022-056. All data were checked for completeness and consistency, and outliers were clarified or corrected through follow-up with the respondents.

Survey questionnaire

A self-reporting questionnaire was developed to assess the degree of infection, after reviewing similar studies previously published in the scientific literature, and according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version Nine)" [9]. The survey questionnaire was initially

drafted in Chinese and an English translation is provided in Supplementary Document 1.

The questionnaire consisted of three parts: (1) baseline characteristics (age, gender, body mass index (BMI), region); (2) cancer status (type of cancer, time of diagnosis, presence of cancer, duration of TCM use, treatment received 1 week prior to COVID-19, underlying health conditions); (3) symptoms related to COVID-19 infection (presence or absence of infection, whether the respondent is an asymptomatic carrier, time of infection, highest fever temperature, daytime cough severity, night time cough severity, sore throat severity, degree of nasal congestion or runny nose, headache severity, muscle/joint pain severity, level of shortness of breath, degree of nausea, level of chills or shivering, incidence of vomiting in the past 24 hours, incidence of diarrhea in the past 24 hours, whether hospitalization was required due to COVID-19 infection, whether TCM was used for COVID-19 treatment, and the number of COVID-19 vaccine doses received); (4) post-acute COVID-19 related conditions, including

fatigue, sleep difficulties, coughing, sore throat, etc. Each symptom was assessed on a severity scale ranging from "none" to "severe".

Data analysis

Data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). Sociodemographic characteristics and responses to the questionnaire were treated as categorical data and expressed as numbers and percentages. Differences between the TCM group and the non-TCM group were analyzed using Chi-square or Fisher's exact test for categorical variables. Continuous variables such as "median infection duration", "median body temperature", and "median duration of fever" were expressed as medians and interquartile ranges. Differences in these variables between the TCM and non-TCM groups were tested using the Mann-Whitney U test. Correlation analysis was conducted using the Pearson correlation test. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Table 2. Comparison of diagnosis duration, treatment modalities, and underlying diseases among patients in TCM and non-TCM groups.

Variables	All	TCM (N = 607)	Non-TCM (N = 389)	p value
Diagnosis time (years)				< 0.001
< 1	542 (54.4)	267 (44.0)	275 (70.7)	
≥ 1, < 3	250 (25.1)	165 (27.2)	85 (21.9)	
≥ 3, < 5	120 (12.0)	110 (18.1)	10 (2.6)	
≥ 5	84 (8.4)	65 (10.7)	19 (4.9)	
Duration of TCM treatment				< 0.001
Never used TCM	389 (39.1)	0 (0)	389 (100)	
< 3 months	91 (9.1)	91 (15.0)	0	
≥ 3 months, < 12 months	130 (13.1)	130 (21.4)	0	
≥ 1 year, < 3 years	206 (20.7)	206 (33.9)	0	
> 3 years, < 5 years	101 (10.1)	101 (16.6)	0	
≥ 5 years	79 (7.9)	79 (13.0)	0	
Currently carrying a tumor in the body				< 0.001
Yes	728 (73.1)	383 (63.1)	345 (88.7)	
No	124 (12.4)	97 (16.0)	27 (6.9)	
Don't know	144 (14.5)	127 (20.9)	17 (4.4)	
Treatment conducted one week before COVID-19				
Surgery	132 (13.3)	107 (17.6)	25 (6.4)	< 0.001
Chemotherapy	231 (23.2)	105 (17.3)	126 (32.4)	< 0.001
Radiotherapy	20 (2.0)	16 (2.6)	4 (1.0)	0.104
Targeted therapy	108 (10.8)	55 (9.1)	53 (13.6)	0.028
Immunotherapy	54 (5.4)	26 (4.3)	28 (7.2)	0.061
Immune modulator (eg. Thymosin)	24 (2.4)	21 (3.5)	3 (0.8)	0.006
TCM treatment	316 (31.7)	316 (52.1)	0 (0)	< 0.001
No treatment	395 (39.7)	166 (27.3)	229 (58.9)	< 0.001
Underlying diseases				
Coronary heart disease	42 (4.2)	27 (4.4)	15 (3.9)	0.747
Hypertension	361 (36.2)	246 (40.5)	115 (29.6)	< 0.001
Kidney disease	6 (0.6)	3 (0.5)	3 (0.8)	0.684
Respiratory disease	22 (2.2)	11 (1.8)	11 (2.8)	0.377
Cerebrovascular disease	14 (1.4)	10 (1.6)	4 (1)	0.583
Chronic liver disease	111 (11.1)	99 (16.3)	12 (3.1)	< 0.001
Hyperlipidemia	29 (2.9)	20 (3.3)	9 (2.3)	0.442
Diabetes	127 (12.8)	89 (14.7)	38 (9.8)	0.025
No underlying diseases	466 (46.8)	236 (38.9)	230 (59.1)	< 0.001
COVID-19 infection				0.002
Yes	787 (79)	460 (75.8)	327 (84.1)	
No	209 (21)	147 (24.2)	62 (15.9)	

TCM: traditional Chinese medicine; COVID-19: coronavirus disease 2019. Percentages are rounded to the nearest decimal and may not add to 100%.

Table 3. Comparison of symptoms at the time of COVID-19 infection in the TCM and non-TCM groups.

Variables	All	TCM (N = 460)	Non-TCM (N = 327)	p value
Asymptomatic infection				0.242
Yes	66 (8.4)	34 (7.4)	32 (9.8)	
No	721 (91.6)	426 (92.6)	295 (90.2)	
Daytime cough				0.256
No cough	268 (34.1)	144 (31.3)	124 (37.9)	
Occasional brief cough	411 (52.2)	253 (55.0)	158 (48.3)	
Frequent cough, slightly affects daily activities	92 (11.7)	55 (12.0)	37 (11.3)	
Frequent cough, severely affects daily activities	16 (2.0)	8 (1.7)	8 (2.4)	
Nighttime cough severity				0.825
No cough	376 (47.8)	224 (48.7)	152 (46.5)	
Brief cough during sleep or occasional nighttime cough	347 (44.1)	196 (42.6)	151 (46.2)	
Cough slightly affecting night sleep	53 (6.7)	34 (7.4)	19 (5.8)	
Cough severely affecting night sleep	11 (1.4)	6 (1.3)	5 (1.5)	
Throat pain				0.349
None	389 (49.4)	217 (47.2)	172 (52.6)	
Mild	292 (37.1)	177 (38.5)	115 (35.2)	
Moderate	80 (10.2)	55 (12)	25 (7.6)	
Severe	26 (3.3)	11 (2.4)	15 (4.6)	
Nasal congestion or rhinorrhea				0.932
None	481 (61.1)	276 (60.0)	205 (62.7)	
Mild	274 (34.8)	169 (36.7)	105 (32.1)	
Moderate	29 (3.7)	14 (3.0)	15 (4.6)	
Severe	3 (0.4)	1 (0.2)	2 (0.6)	
Headache				0.453
None	540 (68.6)	308 (67.0)	232 (70.9)	
Mild	214 (27.2)	134 (29.1)	80 (24.5)	
Moderate	29 (3.7)	16 (3.5)	13 (4.0)	
Severe	4 (0.5)	2 (0.4)	2 (0.6)	
Muscle or joint pain				0.896
None	554 (70.4)	320 (69.6)	234 (71.6)	
Mild	191 (24.3)	120 (26.1)	71 (21.7)	
Moderate	38 (4.8)	18 (3.9)	20 (6.1)	
Severe	4 (0.5)	2 (0.4)	2 (0.6)	
Shortness of breath (dyspnea)				0.116
None	633 (80.4)	361 (78.5)	272 (83.2)	
Mild	125 (15.9)	80 (17.4)	45 (13.8)	
Moderate	26 (3.3)	17 (3.7)	9 (2.8)	
Severe	3 (0.4)	2 (0.4)	1 (0.3)	
Nausea				0.378
None	710 (90.2)	418 (90.9)	292 (89.3)	
Mild	70 (8.9)	39 (8.5)	31 (9.5)	
Moderate	7 (0.9)	3 (0.7)	4 (1.2)	
Severe	0 (0)	0 (0)	0 (0)	
Chills or trembling				0.184
None	609 (77.4)	345 (75.0)	264 (80.7)	
Mild	141 (17.9)	94 (20.4)	47 (14.4)	
Moderate	32 (4.1)	18 (3.9)	14 (4.3)	
Severe	5 (0.6)	3 (0.7)	2 (0.6)	
Vomiting				0.805
None	751 (95.4)	440 (95.7)	311 (95.1)	
Mild	27 (3.4)	14 (3.0)	13 (4.0)	
Moderate	6 (0.8)	5 (1.1)	1 (0.3)	
Severe	3 (0.4)	1 (0.2)	2 (0.6)	
Diarrhea				0.202
None	716 (91.0)	414 (90.0)	302 (92.4)	
Mild	45 (5.7)	27 (5.9)	18 (5.5)	
Moderate	19 (2.4)	15 (3.3)	4 (1.2)	
Severe	7 (0.9)	4 (0.9)	3 (0.9)	
Were you hospitalized due to COVID-19 infection?				0.18
Yes	56 (7.1)	38 (8.3)	18 (5.5)	
No	731 (92.9)	422 (91.7)	309 (94.5)	
Did you receive traditional Chinese medicine treatment for COVID-19?				< 0.001
Yes	88 (11.2)	80 (17.4)	8 (2.4)	
No	699 (88.8)	380 (82.6)	319 (97.6)	
Number of COVID-19 vaccine doses received				< 0.001
0	381 (48.4)	300 (65.2)	81 (24.8)	
1	28 (3.6)	19 (4.1)	9 (2.8)	
2	153 (19.4)	75 (16.3)	78 (23.9)	
3	225 (28.6)	66 (14.3)	159 (48.6)	

COVID-19: coronavirus disease 2019; TCM: traditional Chinese medicine. Percentages are rounded to the nearest decimal and may not add to 100%.

Results

Participants’ characteristics

A total of 1,032 cancer patients were invited to participate in this online survey; among them, 36 participants returned incomplete questionnaires. Ultimately, 996 cancer patients completed the survey, resulting in an overall effective response rate of 96.5%. Among them, 607 (60.9%) were in the TCM group and 389 (39.1%) were in the non-TCM group (Table 1).

The demographic breakdown of the respondents revealed that the majority were from the East China region, accounting for 87.3% in the TCM group and 93.6% in the non-TCM group. The distribution of age, gender, BMI, and region showed no significant differences between the TCM and non-TCM groups ($p > 0.05$).

Among the 389 cancer patients with COVID-19 infection in the non-TCM group, 76.9% were aged between 40 and 70 years. The male to female ratio was 2:1. The predominant types of cancers in this group were digestive tract cancer (73.8%), respiratory and thoracic cancers (14.4%), and head and neck cancers (11.8%).

Similarly, among the 607 cancer patients with COVID-19 infection in the TCM group, 78.9% were aged between 40 and 70 years. The gender ratio in this group was slightly more balanced at 1.9:1. The primary cancer types were digestive tract cancer (69.4%), respiratory and thoracic cancers (21.6%), and gynecologic cancers (7.9%).

Diagnosis and treatment modalities

The non-TCM group had a significantly larger proportion of patients diagnosed within a year (70.7% vs. 44.0%; $p < 0.001$); and unsurprisingly, none had ever used TCM treatments (Table 2). The TCM group had a diverse duration of TCM treatments, with 13.0% having undergone treatment for > 5 years. Furthermore, a substantial number of the non-TCM cohort (88.7%) still had a tumor present in their bodies, in contrast to 63.1% in the TCM group ($p < 0.001$).

A higher percentage of the TCM group underwent surgery in the week leading up to the COVID-19 infection (17.6% vs. 6.4%, $p < 0.001$), whereas more non-TCM patients received chemotherapy (32.4% vs. 17.3%, $p < 0.001$). Expectedly, only the TCM group

received TCM treatments for their tumors, and 52.1% patients in this group had received TCM.

Concerning underlying diseases, the TCM group demonstrated a higher prevalence of hypertension (40.5% vs. 29.6%, $p < 0.001$), chronic liver disease (16.3% vs. 3.1%, $p < 0.001$), and diabetes (14.7% vs. 9.8%, $p = 0.025$). On the other hand, a significantly larger proportion of the non-TCM group had no underlying diseases (59.1% vs. 38.9%, $p < 0.001$).

COVID-19 infection and symptoms

In terms of COVID-19 infection rates, there was a noticeable discrepancy between the two groups. The non-TCM group exhibited a marginally increased susceptibility, with an infection rate of 84.1%, compared to 75.8% in the TCM group (Table 3). This difference was statistically significant ($p = 0.002$). However, both cohorts demonstrated similar patterns with regard to the symptomatic manifestations of the virus. A majority of patients across both groups exhibited symptoms, reflecting the typical clinical presentation of the disease. When delving deeper into the specific symptoms; such as cough severity, throat pain, nasal congestion, and others; no marked differences were discernible between the two groups ($p > 0.05$). Additionally, there was no difference between the two groups in terms of hospitalizations due to COVID-19 infection ($p > 0.05$).

A particularly intriguing facet of the findings pertained to the therapeutic interventions employed to combat the virus. A substantial 17.4% of the patients in the TCM group were administered TCM as a treatment modality for their COVID-19 infection, which was in contrast to a mere 2.4% in the non-TCM group ($p < 0.001$). This variation was statistically significant, emphasizing the potential protective role of TCM, not only in managing COVID-19 symptoms, but also in ensuring the continuity of crucial anti-tumor treatments amidst the pandemic.

Comparison of median infection duration, body temperature, and duration of fever between TCM and non-TCM groups

The clinical parameters in the TCM and non-TCM groups are summarized in Table 4. The median infection duration for the TCM group was 7 days (95%

Table 4. Comparison of median infection duration, body temperature, and duration of fever between TCM and non-TCM groups.

	TCM (N = 460)	Non-TCM (N = 327)	p value
Median infection duration (day) (95% CI)	7 (6–9)	7 (6–9)	0.178
Median body temperature (°C) (95% CI)	38.2 (37.6–38.6)	38.3 (36.8–38.6)	0.123
Median duration of fever (day) (95% CI)	2 (1–3)	2 (0–3)	0.003

TCM: traditional Chinese medicine; CI: confidence interval.

confidence interval (CI): 6–9); and this was the same in the non-TCM group (7 days; 95% CI: 6–9; $p = 0.178$). Interestingly, 48.6% of patients in the non-TCM group received 3 doses (2 doses and a booster shot) of the COVID-19 vaccine, while only 14.3% of those in the

TCM group had received all 3 doses. Moreover, a significant 65.2% of patients in the TCM group had never been vaccinated against COVID-19, compared to just 24% non-vaccinated patients in the non-TCM group. Both groups exhibited similar median body

Table 5. Comparative analysis of post-COVID-19 symptoms between TCM and non-TCM patients at 3 months post-infection.

Variables	All	TCM (N = 460)	Non-TCM (N = 327)	p value
Level of fatigue				< 0.001
None	751 (95.4)	451 (98.0)	300 (91.7)	
Mild	20 (2.5)	6 (1.3)	14 (4.3)	
Moderate	14 (1.8)	3 (0.7)	11 (3.4)	
Severe	2 (0.3)	0 (0)	2 (0.6)	
Level of sleep difficulty				< 0.001
None	744 (94.5)	454 (98.7)	290 (88.7)	
Mild	32 (4.1)	5 (1.1)	27 (8.3)	
Moderate	7 (0.9)	1 (0.2)	6 (1.8)	
Severe	4 (0.5)	0 (0)	4 (1.2)	
Level of coughing				0.198
None	776 (98.6)	456 (99.1)	320 (97.9)	
Mild	9 (1.1)	3 (0.7)	6 (1.8)	
Moderate	2 (0.3)	1 (0.2)	1 (0.3)	
Severe	0 (0)	0 (0)	0 (0)	
Level of sore throat				1
None	785 (99.7)	459 (99.8)	326 (99.7)	
Mild	2 (0.3)	1 (0.2)	1 (0.3)	
Moderate	0 (0)	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	0 (0)	
Level of chest discomfort/pain				0.325
None	781 (99.2)	457 (99.3)	324 (99.1)	
Mild	4 (0.5)	3 (0.7)	1 (0.3)	
Moderate	2 (0.3)	0 (0)	2 (0.6)	
Severe	0 (0)	0 (0)	0 (0)	
Level of muscle pain				0.27
None	779 (99.0)	457 (99.3)	322 (98.5)	
Mild	3 (0.4)	1 (0.2)	2 (0.6)	
Moderate	5 (0.6)	2 (0.4)	3 (0.9)	
Severe	0 (0)	0 (0)	0 (0)	
Level of palpitations				0.663
None	780 (99.1)	457 (99.3)	323 (98.8)	
Mild	6 (0.8)	2 (0.4)	4 (1.2)	
Moderate	1 (0.1)	1 (0.2)	0 (0)	
Severe	0 (0)	0 (0)	2 (0.6)	
Level of dizziness				0.378
None	756 (96.1)	444 (96.5)	312 (95.4)	
Mild	18 (2.3)	10 (2.2)	8 (2.4)	
Moderate	9 (1.1)	4 (0.9)	5 (1.5)	
Severe	4 (0.5)	2 (0.4)	2 (0.6)	
Level of joint pain				0.861
None	773 (98.2)	452 (98.3)	321 (98.2)	
Mild	5 (0.6)	3 (0.7)	2 (0.6)	
Moderate	7 (0.9)	4 (0.9)	3 (0.9)	
Severe	2 (0.3)	1 (0.2)	1 (0.3)	
Level of loss of appetite				0.140
None	769 (97.7)	453 (98.5)	316 (96.6)	
Mild	12 (1.5)	4 (0.9)	8 (2.4)	
Moderate	5 (0.6)	3 (0.7)	2 (0.6)	
Severe	1 (0.1)	0 (0)	1 (0.3)	
Level of smell disorder				0.172
None	785 (99.7)	460 (100)	325 (99.4)	
Mild	2 (0.3)	0 (0)	2 (0.6)	
Moderate	0 (0)	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	0 (0)	
Level of taste disorder				0.573
None	784 (99.6)	459 (99.8)	325 (99.4)	
Mild	3 (0.4)	1 (0.2)	2 (0.6)	
Moderate	0 (0)	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	0 (0)	

COVID-19: coronavirus disease 2019; TCM: traditional Chinese medicine. Percentages are rounded to the nearest decimal and may not add to 100%.

temperatures: 38.2 °C (95% CI: 37.6–38.6) for the TCM group and 38.3 °C (95% CI: 36.8–38.6) for the non-TCM group ($p = 0.123$). Notably, the median duration of fever was identical for both groups at 2 days; but the range varied slightly, ranging from 1–3 days in the TCM group and 0–3 days in the non-TCM group ($p = 0.003$).

Post-acute COVID-19 symptoms at 3 months post-infection

The analysis of post-infection symptoms, at 3 months after experiencing a COVID-19 infection, revealed significant differences between TCM and non-TCM patients (Table 5).

Fatigue is one of the most commonly reported long-term symptoms among COVID-19 survivors. Remarkably, patients in the TCM group fared notably better in this regard. A staggering 98.0% of TCM patients reported no fatigue, while 91.7% for those in the non-TCM group reported no fatigue ($p < 0.001$). Only a minimal percentage of the TCM group experienced mild (1.3%) or moderate (0.7%) fatigue, and none reported severe fatigue. In contrast, the non-TCM group had a higher proportion of individuals experiencing mild (4.3%), moderate (3.4%), and severe (0.6%) fatigue.

Sleep disturbances, another notable post-acute COVID-19 symptom, showed similar disparities between the groups. A significant 98.7% of the TCM cohort did not experience any sleep difficulties, underscoring the potential benefits of TCM in post-COVID care. In comparison, 88.7% of the non-TCM group reported no sleep disturbances. Mild sleep difficulties were more pronounced in the non-TCM group (8.3%) than in the TCM group (1.1%). Moderate sleep disturbances were rare in both groups, with 0.2% in the TCM group and 1.8% in the non-TCM group. Severe sleep difficulties, though rare, were only reported in the non-TCM group (1.2%).

Table 6. Correlation between duration of TCM use and COVID-19 symptoms.

COVID-19 symptoms	r	p value
Daytime cough	0.046	0.198
Nighttime cough severity	- 0.025	0.489
Throat pain	0.049	0.17
Nasal congestion or rhinorrhea	- 0.013	0.721
Headache	0.053	0.141
Muscle or joint pain	- 0.015	0.675
Shortness of breath (dyspnea)	0.066	0.065
Nausea	- 0.021	0.553
Chills or trembling	0.056	0.115
Diarrhea	- 0.017	0.64

r: Correlation coefficient; TCM: traditional Chinese medicine; COVID-19: coronavirus disease 2019.

When comparing other post-acute COVID-19 symptoms, 99.1% of TCM patients reported no coughing, compared to 97.9% in the non-TCM group. This trend continued across other symptoms: 99.8% in the TCM group did not experience a sore throat, compared to 99.7% in the non-TCM group; and muscle pain was absent in 99.3% of TCM patients versus 98.5% of non-TCM patients. Additionally, the proportion of TCM patients without symptoms such as chest tightness/pain, palpitations, dizziness, joint pain, loss of appetite, olfactory dysfunction, and taste disorders, was consistently higher compared to the non-TCM group.

Correlation of TCM duration with immediate and post-acute COVID-19 symptoms

Tables 6 and 7 summarize the relationship between the duration of TCM use and the immediate as well as long-term symptoms of COVID-19. Table 6 shows that immediate symptoms including daytime cough, throat pain, and headache displayed weak correlation coefficients with TCM use duration. However, none of the correlations were statistically significant. Table 7 summarizes the association between prolonged TCM use and the mitigation of post-acute COVID-19 symptoms. Notably, fatigue and sleep difficulty levels exhibited significant negative correlations with TCM use duration ($p < 0.01$). These findings suggest that extended TCM application potentially ameliorates the severity of post-acute COVID-19 symptoms, underscoring the therapeutic potential of TCM in managing the post-acute COVID-19.

Discussion

This study offers insights into the possible advantages of long-term TCM therapy for cancer patients infected with COVID-19. There was a significant difference in the rate of COVID-19 infection

Table 7. Correlation between duration of TCM use and post-acute COVID-19 symptoms.

Post-acute COVID-19 symptoms	r	p value
Level of fatigue	- 0.14	< 0.01
Level of sleep difficulty	- 0.184	< 0.01
Level of coughing	- 0.034	0.341
Level of sore throat	- 0.03	0.402
Level of chest discomfort/pain	0.011	0.765
Level of muscle pain	- 0.037	0.306
Level of palpitations	- 0.044	0.223
Level of dizziness	- 0.042	0.234
Level of joint pain	- 0.008	0.826
Level of loss of appetite	- 0.048	0.18
Level of smell disorder	- 0.053	0.135
Level of taste disorder	- 0.046	0.195

r: Correlation coefficient; TCM: traditional Chinese medicine; COVID-19: coronavirus disease 2019.

between the TCM and non-TCM groups, with an infection rate of 84.1% in the non-TCM group compared to 75.8% in the TCM group ($p = 0.002$). However, the symptomatic manifestation of the virus during infection was similar in both groups, although the TCM group experienced reduced fatigue and sleep difficulties compared to their non-TCM counterparts. This suggests a potential benefit in post-infection recovery for those receiving TCM treatment, which is of particular interest in regions where TCM has a significant presence. The significantly reduced rates of fatigue and sleep disturbances among TCM users underscore the potential benefits of this traditional approach (Table 5).

When comparing the differences in COVID-19 outcomes between the TCM and non-TCM groups, it is crucial to consider the psychological impact associated with the duration of cancer diagnosis. The non-TCM group, predominantly diagnosed within the past year, may have experienced heightened stress and anxiety, which may exacerbate COVID-19 symptoms. This factor may have contributed to the observed differences in symptom severity, such as increased fatigue and sleep difficulties in non-TCM patients, compared to the TCM group which generally consisted of patients with a more extended history of managing their condition. This consideration adds a layer of complexity to our findings and underscores the need for holistic patient management strategies that address physical and psychological health.

Post-acute COVID-19 is defined as persistent symptoms and/or late onset or long-term complications that last for more than 4 weeks after the initial onset of symptoms [3]. The lower rates of severe symptoms and better overall wellbeing among cancer patients treated with TCM can be attributed to the holistic approach that TCM takes, focusing on the whole body rather than just treating the disease. This can result in better symptom management and an enhanced quality of life.

The findings of this study can have significant implications for the treatment of COVID-19 in cancer patients. The potential benefits of combining TCM and non-TCM approaches should be explored. An integrated treatment plan that combines symptom management and quality of life improvement of the TCM approach, with the infection control efficiency of non-TCM can potentially provide a more comprehensive and effective treatment strategy for cancer patients with COVID-19.

In light of the ongoing search for effective COVID-19 treatments, particularly for vulnerable populations such as cancer patients, it is crucial to explore the use

of non-traditional medicines. Recent studies have highlighted a range of non-traditional treatments used for COVID-19 in cancer patients; including, but not limited to, the use of specific antivirals, monoclonal antibodies, and herbal supplements that are not typically categorized under TCM [10–13]. These treatments have been observed to offer varying degrees of symptomatic relief and impact on patient health [14,15]. For instance, some herbal supplements have been reported to significantly shorten the time to sustained clinical recovery in COVID-19 patients compared to nirmatrelvir–ritonavir [16]. Comparative studies suggest that while TCM has a well-established safety profile, particularly in long-term use in cancer patients, the non-traditional treatments require careful monitoring for potential adverse effects [17].

TCM, with its millennia-old history, has a unique theoretical system and boasts rich preventative and therapeutic methods for various ailments [18]. With the advancement of research in TCM, its clinical value is increasingly recognized globally. TCM approaches disease treatment by restoring the balance between the body's yin and yang — two opposing yet complementary forces that govern one's health. As a complementary and alternative medical approach, TCM has been utilized for a long time in China, especially among cancer patients. In fact, TCM is embraced as a mainstream therapeutic strategy due to its efficacy and favorable safety profile, which sets it apart from western medical treatments. Given the widespread application of TCM, its potential merits in reducing mortality among cancer patients warrant further exploration [19,20]. Our findings provide preliminary support for the notion that this holistic approach may offer some protective effects against severe COVID-19 infection.

Additionally, the benefits of TCM may also stem from its focus on individualized treatment. TCM practitioners prescribe treatment regimens based on the individual's unique pattern of symptoms and overall constitution [21]. This personalized approach may help optimize each patient's immune response, enhancing their resilience to infections such as COVID-19.

Our findings are consistent with previous research showing the potential benefits of TCM in managing infectious diseases [22,23]. TCM has been shown to aid in preventing COVID-19 infections, reducing the conversion rate of close contacts, and decreasing the viral load in infected patients. Furthermore, TCM assists in alleviating COVID-19 symptoms, mitigating inflammation, lowering the severity rate, and shortening the time to viral clearance. It also proves

beneficial in improving digestive and respiratory symptoms in long-term COVID-19 patients by enhancing lung functionality. An evidence-based evaluation study, grounded in historical TCM literature and nearly two decades of TCM experience in preventing severe acute respiratory syndrome (SARS) and H1N1, indirectly indicates that herbal medicine can help avoid COVID-19 infections among high-risk populations [24]. Concurrently, meta-analysis evaluations reveal that the adjunctive use of TCM significantly enhances clinical efficacy; relieves symptoms like fever, cough, and fatigue in COVID-19 patients; reduces the time to symptom resolution; improves the rate of abnormal computed tomography (CT) image resolution; and decreases the severity rate in patients [25]. However, in contrast to these studies, our research centered on cancer patients who had utilized TCM treatments and contracted COVID-19. To our knowledge, no prior research has ventured into this specific area, making our study the pioneering exploration into the long-term effects of TCM on the prognosis of cancer patients infected with COVID-19.

Furthermore, our findings emphasize the potential benefits of TCM in managing post-acute COVID-19 symptoms, particularly in reducing fatigue and sleep disturbances. The TCM group's reduced rates in these areas suggests an enhancement in overall post-infection quality of life, and indicates a promising avenue for future research and therapeutic interventions. The holistic approach of TCM may play a vital role in mitigating these prolonged symptoms, highlighting its potential significance in the wider medical community.

Another important aspect to consider is the potential mechanism through which TCM may improve outcomes in COVID-19 infection. One possibility is that the individualized treatment focus of TCM, tailored to the patient's unique symptom pattern and constitution, may facilitate a more comprehensive recovery process, addressing not only the acute viral infection but also the longer-term systemic imbalances that can result from it. For instance, TCM may modulate the immune response, reduce inflammatory reactions, or exert other effects that influence the disease process and outcomes [26–28]. While the specific mechanisms are yet to be fully elucidated, existing research suggests that TCM can have a wide range of effects on immune function and inflammation [29–31]. Therefore, understanding these mechanisms can provide valuable insights into the potential benefits of TCM in managing COVID-19 infection.

Evidence from various research studies indicates that TCM can ameliorate symptoms in post-acute

COVID-19 patients, particularly digestive and respiratory symptoms. TCM has also been shown to have an effect on the improvement of abnormal CT imaging and enhanced lung function [32]. COVID-19 infection, as a stress-inducing event, often triggers anxiety, worry, or fear in individuals, subsequently leading to insomnia [33,34]. TCM has demonstrated certain advantages in alleviating fatigue and anxiety [35,36].

While our study provides preliminary evidence supporting TCM's potential benefits, a comprehensive understanding of these therapeutic strategies necessitates more in-depth comparative research. It is worth noting that TCM needs to be used under the guidance of a clinician. It is important to note that while our findings provide intriguing insights, the study's design was observational and cannot establish direct causality between TCM use and improved post-COVID symptoms. Therefore, randomized controlled trials are warranted to confirm these associations. Moreover, considering the complexity and heterogeneity of TCM therapies, future research should aim to identify the specific components or combinations that are most effective for COVID-19.

Nonetheless, our study serves as a stepping stone towards understanding the potential role of long-term TCM therapy in managing COVID-19. It underscores the need to integrate TCM and non-TCM methods, and to conduct rigorous scientific research on TCM, which may open new avenues for tackling this global pandemic.

However, this study has inherent limitations that warrant consideration. Firstly, as a cross-sectional study, our research design inherently cannot establish causality between TCM use and observed outcomes. Secondly, our reliance on self-reported data introduces the potential for recall bias, which could affect the accuracy of symptom and treatment reporting. Thirdly, we did not control for variations in healthcare settings or the expertise of practitioners, both of which may influence patient outcomes. Fourth, most of the subjects included in this study were patients with mild and moderate COVID-19, and severe cases were not included in the study. Additionally, external factors such as differences in healthcare facilities, patient demographics, and the specific nature of underlying cancer conditions may have impacted our findings. While our study accounted for several variables, potential confounding factors like age, gender, disease severity, and the presence of other comorbidities may influence the outcomes of COVID-19 infection. A more extensive study design adjusting for these potential

confounders may provide a more comprehensive understanding of the relationship between TCM usage and COVID-19 outcomes among cancer patients. Future research should aim for a more rigorous study design to address these limitations and delve deeper into the potential benefits and mechanisms of TCM in managing COVID-19 among cancer patients.

Conclusions

Our study indicates that long-term TCM use may be associated with milder post-COVID-19 symptoms among cancer patients. Further research is needed to confirm these findings, explore potential mechanisms, and understand the full spectrum of outcomes associated with TCM.

Authors contributions

MY and HZ, study design; ST, GC, ML, YX, SX, XZ and XX, data collection; MY, preparation of all tables; HZ and XZ manuscript draft. All authors read and approved the final manuscript.

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Corresponding authors

Hetong Zhao, MD.
1328 Huashan Road, Changning District, Shanghai 200003, China.
Tel: 021-81818085
Fax: 021-81818092
Email: zhtzhao@126.com

Xiaofeng Zhai, MD.
168 Changhai Road, Yangpu District, Shanghai 200433, China.
Tel: 021-81867042
Fax: 021-31166666
Email: zhaixfch@163.com

Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Document 1. English version of survey questionnaire.

Survey on long-term traditional Chinese medicine (TCM) use on coronavirus disease 2019 (COVID-19) outcomes among cancer patients

Dear Participant,

Thank you for your attention. On behalf of Dr. Hetong Zhao, we invite you to partake in this survey designed to understand the implications of TCM in the management of COVID-19 symptoms. Your participation is sought as you are actively engaged in the clinical practice of TCM or have experienced its therapeutic benefits.

Our research survey encompasses 43 questions, capturing details about your demographic characteristics; and your experiences, perceptions, and outcomes related to TCM in the context of COVID-19. It is estimated that the questionnaire will take between 5–10 minutes of your time.

The survey will be conducted via a secure online platform. Assuring the utmost confidentiality, all responses will be stored securely, and access will be limited to the research team only. Your personal information remains protected, and you are free to pause or withdraw from the survey at any point if any questions cause discomfort.

While there might not be a direct benefit to you from participating in this survey, your valuable insights can influence TCM research directions, potentially aiding countless individuals affected by post-acute COVID-19. Furthermore, the findings will shape strategies for integrating traditional and contemporary medical approaches in the face of global health crises.

For any queries or concerns related to this survey or other related topics, please feel free to reach out to the study coordinator, Dr. Hetong Zhao (zhtzhao@126.com).

We genuinely appreciate your contribution and time.

Hetong Zhao, MD, PhD.

Department of Integrative Oncology, Changhai Hospital, Naval Medical University, Shanghai, China.

Survey on long-term traditional Chinese medicine (TCM) use on COVID-19 outcomes among cancer patients

1. Gender

- Male
- Female

2. Age: _____

3. Height (in centimeters): _____

4. Weight (in kilograms): _____

5. Current region

- Northeast China
- North China
- East China
- South China
- Central China
- Northwest China
- Southwest China

6. Type of tumor you have

- Head and neck cancer
- Urological cancer
- Gynecological cancer
- Digestive tract cancer
- Respiratory and thoracic cancer
- Other type of cancer

7. How many years has it been since you were diagnosed with the tumor? _____

8. Duration of using TCM for tumor treatment

- Never used
- Less than 3 months
- 3–12 months
- 1–3 years
- 3–5 years
- More than 5 years

9. Did you have a tumor in your body when you contracted COVID-19?

- Yes
- No
- Not sure

10. Which of the following tumor-related treatments did you undergo 1 week before your COVID-19 diagnosis? (You can select more than one)

- Surgery (resection, intervention, radiofrequency, microwave ablation, etc.)
- Radiation therapy
- Chemotherapy
- Targeted therapy
- Immunotherapy
- TCM treatment
- Immunomodulators (thymosin, thymopentin, etc.)
- None

11. Do you have any of the following underlying diseases?

- Hypertension
- Coronary heart disease
- Hyperlipidemia
- Diabetes
- Cerebrovascular disease (including cerebral infarction, cerebral thrombosis, cerebral hemorrhage, etc.)
- Chronic respiratory disease (including chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, tuberculosis, etc.)

- Chronic kidney disease
- Chronic liver disease (including viral hepatitis, cirrhosis, etc.)
- Organ transplantation
- None of the above

12. Did you contract COVID-19?

- Yes
- No

13. Start date of COVID-19 infection (confirmed by antigen or nucleic acid test) _____

14. End date of COVID-19 infection (confirmed by antigen or nucleic acid test) _____

15. Highest body temperature during COVID-19 infection: ____

16. How many days did you have a fever during your COVID-19 infection? ____

17. Daytime cough severity during COVID-19 infection

- No cough
- Occasional
- Mild
- Severe

18. Nighttime cough severity during COVID-19 infection

- No cough
- Occasional
- Mild
- Severe

19. Severity of throat pain during COVID-19 infection

- None
- Mild
- Moderate
- Severe

20. Severity of nasal congestion or runny nose during COVID-19 infection

- None
- Mild
- Moderate
- Severe

21. Severity of headache during COVID-19 infection

- None
- Mild
- Moderate
- Severe

22. Severity of muscle or joint pain during COVID-19 infection

- None
- Mild
- Moderate
- Severe

23. Severity of shortness of breath (dyspnea) during COVID-19 infection

- None
- Mild
- Moderate
- Severe

24. Severity of nausea during COVID-19 infection

- None
- Mild
- Moderate

- Severe
25. Severity of chills or shivering during COVID-19 infection
- None
 - Mild
 - Moderate
 - Severe
26. Number of vomiting episodes within 24 hours during COVID-19 infection
- None
 - 1–2 times
 - 3–4 times
 - 5 or more times
27. Number of diarrhea episodes (loose or watery stools) within 24 hours during COVID-19 infection
- None
 - 1–2 times
 - 3–4 times
 - 5 or more times
28. Were you hospitalized for COVID-19 treatment?
- Yes
 - No
29. Did you receive TCM treatment for COVID-19 related symptoms or post-COVID conditions?
- Yes
 - No
30. Was your antitumor treatment delayed due to COVID-19?
- Yes
 - No
31. How many doses of the COVID-19 vaccine did you receive? _____
32. Severity of fatigue 3 months after contracting COVID-19
- None
 - Mild
 - Moderate
 - Severe
33. Severity of sleep difficulty 3 months after contracting COVID-19
- None
 - Mild
 - Moderate
 - Severe
34. Severity of cough 3 months after contracting COVID-19
- None
 - Mild
 - Moderate
 - Severe
35. Severity of sore throat 3 months after contracting COVID-19
- None
 - Mild
 - Moderate
 - Severe
36. Severity of chest discomfort or pain 3 months after contracting COVID-19
- None
 - Mild
 - Moderate
 - Severe

37. Severity of muscle pain 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

38. Severity of palpitations 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

39. Severity of dizziness 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

40. Severity of joint pain 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

41. Severity of loss of appetite 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

42. Severity of smell disorder 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe

43. Severity of taste disorder 3 months after contracting COVID-19

- None
- Mild
- Moderate
- Severe