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Effect of Tibetan herbal formulas on symptom duration among ambulatory patients with native SARS-CoV-2 infection: A retrospective cohort study☆

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ABSTRACT

Background: Despite abundant data regarding factors that influence COVID-19 symptom severity and need for hospitalization, few studies examine time to resolution of symptoms and potential complementary and

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOCs, variants of concern; COVID-19, coronavirus disease of 2019; CAM, complementary and alternative medicine; PCR, polymerase chain reaction; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SAS, Statistical Analysis System; SD, standard deviation; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; HIV, human immunodeficiency virus infection; RA, rheumatoid arthritis; Hep B, hepatitis B; Hep C, hepatitis C; y, years; Q1, first quartile; Q3, third quartile; IQR, interquartile range; CI, confidence interval; WHO, World Health Organization; BMI;, body mass index; NF-κB, nuclear factor kappa B; MAPK3, mitogen-activated protein kinase 3; CCL2, chemokine (C-C motif) ligand 2; PTGS2, prostaglandin-endoperoxide synthase 2; IL-1β, interleukin-1β; IL-6, interleukin-6; CDC, Centers for Disease Control and Prevention; NCIRD, National Center for Immunization and Respiratory Diseases.

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alternative therapies that may expedite outpatient recovery. Uncertainty in expected symptom duration and potential missed opportunities to decrease this time persist. Likewise, studies tracking outpatient COVID-19 experiences among marginalized communities are lacking.

Objective: To describe the impact of complex Tibetan herbal formula regimens on symptom duration among ambulatory patients with native SARS-CoV-2 infection.

Methods: This multi-center, cohort study assessed deidentified data from patients with laboratory-confirmed SARS-CoV-2 infection. The study assessed cases from March 12, 2020 to May 5, 2021 for which vaccinations were not available, and thus reflect native infections.

Intervention: Diagnoses were made via telemedicine by a traditional Tibetan medical physician, and herbal formulas were prescribed based on specific symptom presentation of COVID-19 using the personalized medicine approach integral to traditional Tibetan medicine.

Results: Of 145 patient cases assessed for eligibility, 86 (59.3%) met inclusion criteria, and 67 (46.2%) had documented symptom resolution. Resolution of symptoms occurred within a median [interquartile range (IQR)] of 11.7 (10.1–13.5) days. The most common symptoms reported were cough and fever. Time to recovery did not significantly differ based on symptom presentation at baseline, except for a couple symptom groupings such as headache and joint pain where recovery time was shorter when those symptoms were present.

Conclusions and relevance: Ambulatory patients diagnosed with SARS-CoV-2 infection receiving Tibetan herbal formulas had recovery from symptoms at a median of 11.7 days, fewer than other published reports in patients following standard of care. The Tibetan approach of targeting treatment based on symptom groups, especially those within classical Tibetan medical nosology, appears to result in quick symptom resolution.

1. Introduction

In native infections with the initial Wuhan-Hu-1 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through Delta variants of concern (VOCs), data pooled from international sources suggest that 85% of unvaccinated people have mild illness and 14% develop severe disease requiring hospitalization (Cheng et al., 2021; Wu and McGoogan, 2020; Liguoro et al., 2020). These earliest COVID-19 infections demonstrated greater symptom severity than later VOCs, including higher rates of hospitalization, intensive care admissions, and death, especially among unvaccinated individuals (Lewnard et al., 2022). For severe and high risk cases, antivirals and steroids have been administered to facilitate rehabilitation and increase survival rates (Sanders et al., 2020). Yet for most mild- and medium-severity cases, at the time of our study, an effective treatment did not exist. Though current vaccination rates are high and antivirals are now widely administered for mild- and medium-severity ambulatory cases, only remdesivir has exhibited some evidence for reducing time to recovery, yet still with inconsistent results (Vegivinti et al., 2022). Likewise, symptom rebound has been reported for oral antivirals, particularly among the vaccinated (Ranard et al., 2023). Thus, the role of traditional therapeutics in reducing time to recovery for an emerging viral infection is timely and pertinent and may be instructive for future novel infectious agents.

Despite a paucity of biomedical treatments early in the COVID-19 pandemic, traditional medicine, largely vis-à-vis modalities of complementary and alternative medicine (CAM), provided therapeutic care beyond the recommended supportive management (Kumar et al., 2022) of rest, isolation and over-the-counter medications for symptom management. These treatments ameliorated impacts of inflammatory cytokines throughout disease course (Lim et al., 2021) and strengthened physical and mental resilience (Seifert et al., 2020). Numerous countries have implemented traditional medicine supplementation in biomedical protocols for COVID-19 cases (Kumar et al., 2022; Lyu et al., 2021; Wang et al., 2021; Panda et al., 2022; Zhang et al., 2023). A review assessing 32 randomized control trials, totaling 3177 COVID-19 patients treated with herbal intervention as adjuvant therapy, showed significantly greater improvement in clinical outcomes compared to conventional Euroamerican biomedicine alone (Kumar et al., 2022).

In the absence of treatment during the first year of the pandemic, Tibetan communities in North America, as well as those familiar with such resources, relied on Tibetan medicine for their healthcare support. As such, we had an opportunity to conduct an observational study of patients under Tibetan medicine standard of care administered by ambulatory clinics across North America. Patient cases observed in the study relied on Tibetan medicine exclusively.

Tibetan medicine approaches patient care through comprehensive paradigms that integrate dietary, behavioral, and mental health guidance; as well as herbal formulas and external therapies—massage, moxibustion, needle therapies, compresses, and medicinal bath (Hofer, 2014). Herbal formulas comprise botanical and mineral species from high altitude Himalayan regions and South Asian lowlands, developed over long exposure histories to epidemics.

Studies assessing mild cases of wild-type native infections, followed by standard of care (i.e., rest, isolation, and OTC medications) guidelines from Centers for Disease Control and Prevention (2022), World Health Organization (2022), and local health authorities (Brigham and Women's Hospital, 2020), varied in their estimates of symptom duration to recovery (Velavan et al., 2021; Sakurai et al., 2020; Zhen-Dong et al., 2020; Sun et al., 2021; Skipper et al., 2020), due in part to insufficient tracking systems and registries (Alwan, 2020) and a general emphasis on hospitalized cases (Guan et al., 2020; Dorjee et al., 2020; Huang et al., 2020). Several outpatient studies did track symptoms during native wild-type infections (Tenforde et al., 2020; Sun et al., 2021; Bergquist et al., 2020; Wei et al., 2020; Yan et al., 2020; Clemency et al., 2020; Lapostolle et al., 2020; Joffily et al., 2020; Zimmerman et al., 2021; Zayet et al., 2021; Huang et al., 2021; Logue et al., 2021; Mancuso et al., 2020; Makaronidis et al., 2021; Woodruff et al., 2020). However, only three studies followed participants to full symptom resolution (Blair et al., 2021a, 2021b; Lane et al., 2021; Pettrone et al., 2021), and only one study examined whether symptoms at disease onset predicted symptom duration (Lane et al., 2021). Of these studies, patients returned to their usual health in a median of 20 (Blair et al., 2021a, 2021b), 21 (Pettrone et al., 2021), and 15–21 days (Lane et al., 2021), respectively.

Our purpose is to describe symptom presence and recovery in a population that uses traditional Tibetan medicine. We conducted the study prior to vaccine availability and were able to collect detailed information about symptom presentation and time to recovery.

2. Methods

2.1. Study design and participants

The study team invited physicians of Tibetan medical clinics in North America, recognized by national medical licensing bodies in Tibet, China and India (Craig and Gerke, 2016; Pordié and Blaikie, 2014), to attend online meetings explaining the study. Twenty physicians attended recruitment meetings: fifteen enrolled. Reasons cited for study

non-participation included burden of time for documentation and patient record deidentification limitations.

Patients contacting the Tibetan outpatient clinic from March 12, 2020 to May 5, 2021 with suspected COVID-19 infection had data collected using a standard reporting template (Supplementary Table 1) (N = 145). Patients with incomplete symptom resolution information (N = 28), hospital admission (N = 3, including 1 incomplete data), and treatment start after the first two weeks of symptoms (N = 2) were excluded. Data on use of Western medications (over-the-counter drugs like acetaminophen) were collected, and participants using both Tibetan and over-the-counter medications simultaneously were also excluded (N = 3, including 2 of the 3 hospitalized patients). See Supplementary Figure 1 for a flow diagram of inclusion and exclusion criteria.

Confirmed presence of SARS-CoV-2 was desired but testing site limitations during this period led to a decision to accept suspected cases for potential later confirmation by antibody testing. However, time and resources required for antibody tests prohibited confirmations and none of our suspected cases were subsequently confirmed. Only cases confirmed using polymerase chain reaction (PCR) or equivalent laboratory test (e.g., rapid antigen test) were included. All patients were unvaccinated. Follow up on September 15, 2021 assessed recurrent or persistent symptom reports.

The study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) requirements.

2.2. Informed consent

Patients consented at the outpatient clinic to have their data deidentified and analyzed for research purposes. Physicians consented with study staff for data submission of confirmed cases. Institutional Review Boards of University of Wisconsin-Madison, University of Minnesota, and Dartmouth College approved the protocol. All procedures followed ethical standards of the Helsinki Declaration of the World Medical Association.

2.3. Treatments

Patients contacted clinics based on infection status. Attending physicians administered a telemedicine consultation to assess additional diagnostics from the Tibetan medical perspective, including psychophysiological constitutional characteristics (Cameron et al., 2012; Luo and Li, 2021). Physicians applied personalized medicine treatment approaches endemic to Tibetan medicine that: (1) specifies formulas to constitution, symptom presentation, and disease course; and (2) provides personalized guidance on diet, thermoregulation, nurturing social interactions (though remote), and methods of maintaining positive mental attitudes. Several patients applied physician-guided external therapies (medicinal bath, warm medicinal oil compresses, herbal vapor inhalations). See Supplementary Figure 2 for a schematic diagram detailing treatment by disease phase with Tibetan herbal formulas among participating study physicians.

Physicians prescribed three to five formulas individualized to patient, followed by altered regimens depending on recovery progress. Over the treatment course, a patient could take up to 10 different formulas with up to 140 ingredients. Most common Tibetan formulas administered include: Trültang, Agar-35, Khyung-nga, Pangyen-15, Dadüd, Pangtsi-12, Tsowo-8, Agar-15, Tazi Marpo, Norbu-7 Tang, Tsowo-25 and Gurgum-13, listed according to administration frequency for confirmed cases, where numbers constitute formula name. Key ingredients include: *Inula racemosa*, *Rubus ellipticus*, *Tinospora cordifolia*, *Pedicularis decorissima*, *Acorus calamus*, *Dolomiaea souliei*, *Terminalia chebula*, *Terminalia bellirica*, *Phyllanthus emblica*, *Gentiana algida*, *Pterocephalus hookeri*, *Pegaeophyton scapiflorum*, *Meconopsis horridula*, *Aconitum naviculare*, *Aconitum ludlowii*, *Adhatoda vasica*, and *Swertia chirayita*, though species vary across source regions. See Supplementary Table 2 for a list of the principal Tibetan herbal formulas used across included cases, along with their respective herbal ingredients, average duration of use, and number of patients in study that used each formula. Some formulations are simmered and decocted; others were crushed as spherical pellets taken with hot water; a few were imbibed as herbal syrups and pastes.

2.4. Statistical analysis

The primary outcome of interest was time to recovery, defined as number of days between reported symptom onset and symptom remission (last date all symptoms were no longer reported). Additional variables of interest included baseline participant characteristics, namely, age, race/ethnicity, presence of comorbidities, and presence of specific symptoms.

Comparison of characteristics between those eligible for analyses (confirmed COVID-19 infection) to unconfirmed and excluded cases was performed using Analysis of Covariance for continuous covariates (e.g., age) and Chi-Square test (Mantel-Haenszel test of trend (Mantel and Haenszel, 1959)) for categorical covariates (e.g., age group, gender, symptom presence). Time to recovery was log-transformed and geometric mean and 95% confidence intervals were computed. Analysis of Variance was used to compare time to recovery between levels of covariates, including specific symptom presence. SAS (v9.4, SAS Instituted, Cary, NC) was used for all analyses. We also conducted exploratory cluster and factor/principal components analyses to assess symptom groupings based on explained variation and similarity metrics, where symptom patterns in time to recovery were assessed (e.g., if someone reports cough, they often also report fever). Symptom clusters were defined to replicate symptom groups reported in prior work (Lane et al., 2021): upper respiratory (sore throat, rhinorrhea); lower respiratory (cough, shortness of breath); gastrointestinal (nausea, diarrhea); neurologic (myalgia, fatigue, headache).

3. Results

3.1. Demographic data and comorbidities

Of the 145 patient cases assessed, the included cohort comprised 67 patients. Table 1 presents the demographic data. For the included cohort, mean (SD) age was 44.7 (12.7) years and females comprised 49.3% of the sample. In terms of race and ethnicity, patients were predominantly Tibetan (80.6%), followed by White non-Hispanic (14.5%).

Most common comorbidities were liver disease (10.1%), diabetes (Type II) (9.0%), and hypertension (9.0%). The former two conditions reflect general high incidence within Tibetan communities (Namdul et al., 2001; Sangmo et al., 2007; Ba-Jia et al., 2020). At least one comorbidity was present for 12 patients (17.9%); two or more comorbidities for 6 patients (9.0%). There were no reported comorbidities in 49 patients (73.1%).

3.2. Clinical outcomes

We found cough and fever to be the most common presenting symptoms at disease onset among included cases (Table 1). Other common presenting symptoms included fatigue, headache, sore throat, and reduced appetite; and less commonly, insomnia, chest pain, digestive difficulties, sweats, rhinorrhea, and brain fog.

Exploratory cluster analysis identified headache and joint pain as symptoms often reported concurrently. Cough and fever grouped distinctly from the cluster of symptoms most highly associated with COVID-19, namely, shortness of breath and loss of smell and taste. The latter cluster also included reduced appetite and nausea.

3.3. Time to recovery

Patients contacted an outpatient clinic an average of 1.0 (IQR 0–5.0)

Table 1
Demographic characteristics, comorbidities, and initial symptoms.

	All Subjects (*N* = 145)		Confirmed (*N* = 67)		Unconfirmed (*N* = 45)			Excluded (*N* = 33)		
Characteristic	***N***	**Distribution**	***N***	**Distribution**	***N***	**Distribution**	***P*-value**	***N***	**Distribution**	***P*-value**
Sex										
Female	79	(54.5%)	33	(49.3%)	27	(61.4%)	0.21	19	(57.6%)	0.44
Age, mean (SD), y	44.3	(15.0)	44.7	(12.7)	44.8	(14.8)	0.18	37.0	(17.9)	**0.02**
<18	3	(2.1%)	0	(0.0%)	0	(0.0%)		3	(9.1%)	
18-34	31	(21.4%)	16	(23.9%)	7	(15.6%)	0.10	8	(24.2%)	0.09
35-49	49	(33.8%)	24	(35.8%)	16	(35.6%)		9	(27.3%)	
50-64	33	(22.8%)	19	(28.4%)	11	(24.4%)		3	(9.1%)	
≥65	14	(9.7%)	5	(7.5%)	6	(13.3%)		3	(9.1%)	
NA	15	(10.3%)	3	(4.5%)	5	(11.1%)		7	(21.2%)	
Race/Ethnicity										
Tibetan	111	(76.6%)	54	(80.6%)	32	(71.1%)	0.25	25	(75.8%)	0.58
Comorbidities										
Any comorbidities, None	111	(76.6%)	49	(73.1%)	38	(84.4%)	0.25	24	(72.7%)	0.65
One	20	(13.8%)	12	(17.9%)	4	(8.9%)		4	(12.1%)	
2+	14	(9.7%)	6	(9.0%)	3	(6.7%)		5	(15.2%)	
Diabetes (Type I/II)	7	(4.8%)	6	(9.0%)	0	(0.0%)	**0.04**	1	(3.0%)	0.28
Hypertension	10	(6.9%)	6	(9.0%)	2	(4.4%)	0.37	2	(6.1%)	0.62
Other cardiovascular disease (excluding hypertension)	5	(3.4%)	2	(3.0%)	1	(2.2%)	0.81	2	(6.1%)	0.46
Cancer (active solid, blood, lymphatic malignancy)	2	(1.4%)	0	(0.0%)	1	(2.2%)	0.22	1	(3.0%)	0.15
Asthma	6	(4.1%)	2	(3.0%)	3	(6.7%)	0.36	1	(3.0%)	0.99
Chronic respiratory disease (COPD, ILD, excluding asthma)	3	(2.1%)	1	(1.5%)	0	(0.0%)	0.41	2	(6.1%)	0.21
Smoker, current or former	4	(2.8%)	0	(0.0%)	2	(4.4%)	0.08	2	(6.1%)	0.20
Chronic neurological disease (dementia)	0	(0.0%)	0	(0.0%)	0	(0.0%)		0	0.0%	
Immunosuppression (HIV, RA, organ transplant)	1	(0.7%)	0	(0.0%)	1	(2.2%)	0.22	0	0.0%	
Chronic kidney disease (any stage)	1	(0.7%)	0	(0.0%)	1	(2.2%)	0.22	0	0.0%	
Liver disease (Cirrhosis, Hep B, C)	8	(5.5%)	7	(10.4%)	0	(0.0%)	0.08	1	(3.0%)	0.20
Metabolic disease (obesity)	3	(2.1%)	1	(1.5%)	1	(2.2%)	0.78	1	(3.0%)	0.61
Other	10	(6.9%)	4	(6.0%)	1	(2.2%)	0.35	5	(15.2%)	0.13
Symptoms at Illness Onset										
Symptoms Count			6	4 9	5	3 6	**0.01**	5	0 7	**0.04**
Symptoms Count (by group) 0-2			7	(10.4%)	8	(17.8%)	0.09	12	(36.4%)	**0.02**
3-5			31	(46.3%)	24	(53.3%)		10	(30.3%)	
6+			7	(43.3%)	13	(28.9%)		11	(33.3%)	
Cough	97	66.9%	43	(64.2%)	35	(77.8%)	0.13	19	(57.6%)	0.52
Shortness of breath	39	26.9%	19	(28.4%)	11	(24.4%)	0.65	9	(27.3%)	0.91
Fever	90	62.1%	43	(64.2%)	31	(68.9%)	0.61	16	(48.5%)	0.14
Chills	38	26.2%	18	(26.9%)	10	(22.2%)	0.58	10	(30.3%)	0.72
Fatigue	67	46.2%	37	(55.2%)	19	(42.2%)	0.18	11	(33.3%)	**0.04**
Muscle cramps	26	17.9%	16	(23.9%)	3	(6.7%)	**0.02**	7	(21.2%)	0.77
Myalgia	42	29.0%	18	(26.9%)	14	(31.1%)	0.63	10	(30.3%)	0.72
Headache	59	40.7%	33	(49.3%)	12	(26.7%)	**0.02**	14	(42.4%)	0.52
Rhinorrhea	35	24.1%	24	(35.8%)	5	(11.1%)	**0.004**	6	(18.2%)	0.07
Sore throat	57	39.3%	30	(44.8%)	20	(44.4%)	0.97	7	(21.2%)	**0.02**
Joint pain	41	28.3%	24	(35.8%)	13	(28.9%)	0.45	4	(12.1%)	**0.01**
Anxiety	28	19.3%	15	(22.4%)	9	(20.0%)	0.76	4	(12.1%)	0.22
Fear, panic	34	23.4%	24	(35.8%)	7	(15.6%)	**0.02**	3	(9.1%)	**0.005**
Diarrhea	12	8.3%	3	(4.5%)	3	(6.7%)	0.62	6	(18.2%)	**0.03**
Reduced appetite	42	29.0%	29	(43.3%)	6	(13.3%)	**<0.001**	7	(21.2%)	**0.03**
Nausea	29	20.0%	12	(17.9%)	8	(17.8%)	0.99	9	(27.3%)	0.28
Anxious dreams	13	9.0%	8	(11.9%)	3	(6.7%)	0.36	2	(6.1%)	0.36
Anosmia	30	20.7%	21	(31.3%)	5	(11.1%)	**0.01**	4	(12.1%)	**0.04**
Ageusia	29	20.0%	20	(29.9%)	4	(8.9%)	**0.008**	5	(15.2%)	0.11

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; HIV, human immunodeficiency virus infection; RA, rheumatoid arthritis; Hep B, hepatitis B; Hep C, hepatitis C; y, years; SD, standard deviation (Mean). P-values reflect the comparison of that group to the primary analysis group (confirmed COVID-19 cases). Distribution is Mean (SD, standard deviation) or Median (Q1 Q3) or N (%) depending on the type of data. P-values reflect the comparison of that group to the primary analysis group (confirmed COVID-19 cases). **Blue** bolded values are P-value < 0.05. Other symptoms experienced by 44 (30.3%) of all subjects included insomnia, back pain, weight loss, digestive difficulty, bloating, burning eyes, unclear vision, night sweats, runny nose, dry mouth, blood in sputum, lung distress.

day after confirmed COVID-19 test, and 3.0 days (IQR 0–4.0) after symptom onset. Symptom resolution occurred a median of 11.7 (IQR 10.1–13.5) days from symptom onset, shown in Table 2A. Approximately 64.2% of patients recovered by the first or second weeks of their illness, and a cumulative 94.0% reached recovery by the third week. Out of the 4 patients that did not reach recovery by the third week, 2 had shortness of breath that took approximately 90 days to resolve; the other 2 expressed intermittent experiences of anxiety and fatigue at follow up. This may represent long COVID, defined as symptoms lasting 60 days or more (Nasserie et al., 2021).

Table 2
Recovery time and covariates by analysis group.

(A) Recovery time and distribution by analysis group and recovery week

Group	Total Time to Resolution (days)	(Q1, Q3)	*P*-value	Recovery Week 1	2	3	4	5	*N* (%)
Confirmed	11.7	(10.1, 13.5)		9	34	20	3	1	67
				13.43%	50.75%	29.85%	4.48%	1.49%	100%
Unconfirmed	17.7	(14.9, 21.1)	**<.001**	10	6	13	2	14	45
				22.22%	13.33%	28.89%	4.44%	31.11%	100%

P-values reflect comparison to the primary analysis group (confirmed COVID-19 cases). **Blue** bolded values are P-value < 0.05.
Week 1 is 1-7 days; week 2, 8-14 days, week 3, 15-21 days, week 4 22-28 days, week 5, 29+ days.

(B) Recovery time for covariates by analysis group

Factor	Confirmed (*N* = 67) *N*	Mean Time to Resolution	(95% CI)	*P*-value	Unconfirmed (*N* = 45) *N*	Mean Time to Resolution	(95% CI)	*P*-value
Sex								
Female	33	11.66	(10.0, 13.6)	0.99	27	17.28	(13.0, 22.9)	0.55
Male	34	11.69	(10.0, 13.6)		17	19.83	(13.9, 28.3)	
Age, mean (SD), y								
18-34	16	12.68	(10.2, 15.8)	0.58	7	21.51	(12.3, 37.6)	0.83
35-49	24	12.13	(10.2, 14.5)		16	18.83	(13.0, 27.3)	
50-64	19	10.22	(8.4, 12.5)		11	15.14	(9.7, 23.7)	
≥65	5	13.12	(8.9, 19.3)		6	19.10	(10.4, 35.0)	
NA	3	10.63	(6.4, 17.6)		5	14.27	(7.4, 27.7)	
Race/Ethnicity								
non-Tibetan	13	13.52	(10.6, 17.2)		13	21.22	(14.0, 32.1)	
Tibetan	54	11.27	(10.0, 12.7)	0.19	32	16.45	(12.6, 21.4)	0.31
Comorbidities								
Any comorbidities, None	49	11.24	(9.9, 12.7)	0.39	38	16.67	(13.1, 21.2)	0.39
One	12	12.24	(9.5, 15.8)		4	21.23	(10.2, 44.4)	
2+	6	14.50	(10.1, 20.7)		3	29.83	(12.7, 69.9)	
Diabetes	6	13.23	(9.2, 19.0)	0.48	0			
No diabetes	61	11.53	(10.3, 12.9)		45	17.71	(14.1, 22.2)	
Hypertension	6	14.73	(10.3, 21.1)	0.18	2	23.04	(8.0, 66.6)	0.62
No hypertension	61	11.41	(10.2, 12.8)		43	17.49	(13.9, 22.0)	
Other cardiovascular disease	2	10.58	(5.7, 19.8)	0.76	1	15.00	(3.3, 67.5)	0.83
No other cardiovascular disease	65	11.71	(10.5, 13.1)		44	17.77	(14.2, 22.3)	
Cancer	0				1	9.00	(2.0, 40.0)	0.37
No cancer	67	11.68	(10.5, 13.0)		44	17.98	(14.4, 22.5)	
Asthma	2	15.00	(8.0, 28.0)	0.43	3	35.37	(15.2, 82.2)	0.10
No asthma	65	11.59	(10.4, 12.9)		42	16.85	(13.5, 21.1)	
Chronic respiratory disease	1	9.00	(3.7, 21.8)	0.56	0			
No chronic respiratory disease	66	11.72	(10.5, 13.1)		45	17.71	(14.1, 22.2)	
Chronic neurological disease	0				0			
No chronic neurological disease	67	11.68	(10.5, 13.0)		45	17.71	(14.1, 22.2)	
Immunosuppression	0				1	50.00	(11.5,218.3)	0.17
No immunosuppression	67	11.68	(10.5, 13.0)		44	17.29	(13.8, 21.6)	
Chronic kidney disease	0				1	43.00	(9.8,189.3)	0.24
No chronic kidney disease	67	11.68	(10.5, 13.0)		44	17.35	(13.9, 21.7)	
Liver disease (Cirrhosis, Hep B, C)	7	0.56	(6.9, 13.3)	0.21				
No liver disease (Cirrhosis, Hep B, C)	60	11.95	(10.7, 13.3)					
Metabolic disease	1	8.00	(3.3, 19.3)	0.40	1	50.00	(11.5,218.3)	0.17
No metabolic disease	66	11.74	(10.5, 13.1)		44	17.29	(13.8, 21.6)	
Other comorbid condition	4	18.22	(11.9, 28.0)	**0.04**	1	21.00	(4.7, 94.5)	0.82
No other comorbid condition	63	11.35	(10.2, 12.7)		44	17.64	(14.1, 22.1)	
Symptoms								
Symptoms Count (by group) 0-2	7	13.07	(9.4, 18.3)	0.78	8	14.86	(8.8, 25.2)	0.75
3-5	31	11.62	(9.9, 13.6)		24	18.84	(13.9, 25.6)	
6+	29	11.42	(9.7, 13.5)		13	17.58	(11.6, 26.6)	
Cough	43	11.57	(10.1, 13.2)	0.82	35	19.13	(14.9, 24.6)	0.20
No cough	24	11.88	(9.9, 14.2)		10	13.51	(8.5, 21.6)	
Shortness of breath	19	11.04	(9.0, 13.5)	0.52	11	21.64	(13.8, 33.9)	0.32
No shortness of breath	48	11.94	(10.5, 13.6)		34	16.59	(12.9, 21.4)	
Fever	43	11.89	(10.4, 13.6)	0.66	31	16.89	(12.9, 22.1)	0.54
No fever	24	11.30	(9.4, 13.5)		14	19.67	(13.2, 29.4)	
Chills	18	12.55	(10.2, 15.5)	0.43	10	25.14	(15.8, 39.9)	0.10
No chills	49	11.37	(10.0, 12.9)		35	16.02	(12.5, 20.5)	
Fatigue	37	11.91	(10.3, 13.8)	0.70	19	18.08	(12.8, 25.5)	0.87
No fatigue	30	11.40	(9.7, 13.4)		26	17.44	(13.0, 23.4)	
Muscle cramps	16	9.67	(7.8, 12.0)	**0.05**	3	31.43	(13.4, 73.7)	0.18
No muscle cramps	51	12.39	(11.0, 14.0)		42	17.00	(13.5, 21.3)	
Myalgia	18	12.73	(10.3, 15.7)	0.34	14	16.41	(11.0, 24.5)	0.66
No myalgia	49	11.31	(10.0, 12.8)		31	18.32	(14.0, 24.0)	
Headache	33	10.71	(9.2, 12.5)	0.12	12	18.51	(12.0, 28.6)	0.81
No headache	34	12.70	(10.9, 14.7)		33	17.42	(13.4, 22.6)	
Rhinorrhea	24	12.18	(10.2, 14.6)	0.57	5	28.50	(14.8, 55.0)	0.14
No rhinorrhea	43	11.40	(10.0, 13.1)		40	16.68	(13.2, 21.0)	
Sore throat	30	10.17	(8.7, 11.9)	**0.02**	20	22.04	(15.9, 30.5)	0.08
No sore throat	37	13.06	(11.3, 15.0)		25	14.86	(11.1, 19.9)	
Joint pain	24	10.16	(8.5, 12.1)	0.06	13	19.97	(13.2, 30.3)	0.50
No joint pain	43	12.62	(11.1, 14.4)		32	16.86	(12.9, 22.0)	
Anxiety	15	13.83	(11.1, 17.3)	0.10	9	19.73	(12.0, 32.5)	0.64
No anxiety	52	11.12	(9.9, 12.5)		36	17.23	(13.4, 22.1)	
Fear, panic	24	12.22	(10.2, 14.6)	0.54	7	16.68	(9.4, 29.5)	0.82
No fear, panic	43	11.38	(9.9, 13.0)		38	17.90	(14.0, 22.9)	
Diarrhea	3	9.65	(5.8, 16.1)	0.46	3	13.69	(5.8, 32.5)	0.55
No diarrhea	64	11.78	(10.5, 13.2)		42	18.04	(14.3, 22.7)	
Reduced appetite	29	11.79	(10.0, 13.9)	0.88	6	17.12	(9.3, 31.6)	0.91
No reduced appetite	38	11.59	(10.0, 13.4)		39	17.80	(14.0, 22.7)	
Nausea	12	11.43	(8.8, 14.8)	0.86	8	20.47	(12.0, 34.8)	0.55
No nausea	55	11.73	(10.4, 13.2)		37	17.16	(13.4, 22.0)	
Anxious dreams	8	10.75	(7.9, 14.7)	0.58	3	10.98	(4.7, 25.9)	0.26
No anxious dreams	59	11.81	(10.5, 13.3)		42	18.32	(14.6, 23.0)	
Anosmia	21	12.82	(10.6, 15.5)	0.25	5	22.21	(11.4, 43.4)	0.48
No anosmia	46	11.19	(9.8, 12.7)		40	17.21	(13.6, 21.8)	
Ageusia	20	11.27	(9.2, 13.7)	0.67	4	17.91	(8.4, 38.0)	0.98
No ageusia	47	11.85	(10.4, 13.5)		41	17.69	(14.0, 22.4)	

Mean is the geometric mean. Separate analysis in confirmed and unconfirmed groups. **Blue** bolded values are P-value < 0.05.

3.4. Time to recovery by covariates

The distribution of time to recovery by covariates does not show distinct differences between males or females, nor by age. The only individual symptoms to show significant relationships with time to recovery are sore throat and muscle cramps, which, when present at baseline, predict faster recovery times (Table 2B). See Supplementary Figure 3 for summarized diagram of recovery time by baseline symptom versus no symptom for confirmed cases. Some symptom clusters were associated with faster time to recovery. Headache and joint pain as a symptom pair, identified from cluster analysis, had a median 10.5 days to recovery with a 95% CI [9.2, 11.9, $p = 0.010$]. The fever cluster (as Lane et al., 2021 defined, comprising one or more symptoms of fever, joint pain, chills and/or cramps) also demonstrated significant ($p = 0.04$) reduction in time to recovery of 11.1 days with a 95% CI [9.9, 12.4].

4. Discussion

We found the median time to resolution of symptoms for COVID-19 in the outpatient setting, under care management by Tibetan medicine practitioners administering Tibetan herbal formulas, was 11.7 (IQR 10.1–13.5) days. Time to recovery following public health recommendations for supportive management was previously reported as 15–21 days (Lane et al., 2021; Blair et al., 2021a, 2021b; Pettrone et al., 2021), during a similar span of time as reported here. Though a statistical comparison with these prior studies is not possible, they report a total time to recovery greater than the upper bound of the 95% confidence interval. This suggests that patients infected with similar COVID-19 variants (based on calendar periods) who used Tibetan medicine may have had faster symptom resolution than patients using other methods of supportive management.

Importantly, patient characteristics among our sample largely match those of prior studies, except the predominant Tibetan ethnicity among our participants. Only Lane et al. (2021) and Blair et al. (2021a, 2021b) provided similar details on patient characteristics, and so are employed as comparison samples. Our study had comparable distributions of age and sex, relative to those of the comparison studies, and all 3 studies had similar dominant comorbidities. However, our sample did have a high incidence of liver disease (10.1%), reflecting higher rates of hepatitis infection in the Tibetan community (Sangmo et al., 2007), which was not present in the comparison samples; whereas the comparison samples had over 40% and 27%, respectively, of participants with current or previous smoking history, of which our sample had few. Thus, we cannot exclude the possibility that ethnicity, in addition to the Tibetan herbal formulas, contributed to the recovery time reported in our sample. Indeed, we did find a slightly more rapid recovery (though not statistically significant) in Tibetan compared to non-Tibetan patients in our sample (Tables 2B) – 11.3 days to symptom resolution in Tibetan and 13.5 days in non-Tibetan patients (i.e., predominantly White non-Hispanic) ($p = 0.19$). Socioeconomic status was not reported in any of the 3 studies.

Cough and fever, our most commonly reported symptoms and with a distinct relationship in the cluster analysis, presented with similar frequency to that of other studies, which also identified cough and fever as the predominant symptoms among first ambulatory COVID-19 cases recorded in China, North America, and globally (WHO, 2020; Goyal et al., 2020; Guan et al., 2020). The relationships identified by cluster analysis that grouped symptoms most highly associated with COVID-19, namely shortness of breath and loss of smell and taste, with reduced appetite and nausea might identify symptoms underreported in a condition widely framed as a respiratory infection, though with known gastrointestinal presentation. It might also reflect physiological responses to taste/smell loss.

The Lane et al. (2021) study was the only study to report illness duration differences by specific symptoms. While this study found longer symptom durations when lower respiratory symptoms were present at disease onset, our study did not replicate this result. However, sore throat and muscle cramps at baseline did predict faster recovery times among our sample. This might be due to the lack of good standard of care treatment options for lower respiratory symptoms among conventional, over-the-counter options, whereas these symptoms are well-addressed by Tibetan herbal formulas. Likewise, sore throat and muscle cramps represent two different presentations of virulent infectious disease in Tibetan medical nosology—one presenting with symptoms more isolated to the upper body such as classic upper respiratory infection; and the other, more systemic in its presentation affecting various muscle groups, and impeding liver and kidney function.

The significant relationship present in the exploratory cluster analysis for the factor grouping of headache and joint pain illustrates a symptom pairing recognized in Tibetan medical nosology for virulent respiratory infections of this type (Gönpo, 2008). Though this symptom pair is often reported to present with more intense illness experiences, it also was found to be associated with swifter recovery times in our study, which may result from stronger antibody responses and/or more rapid symptom relief consequent to Tibetan formulas. The Tibetan medical understanding of such virulent infections links central nervous system inflammation to that in interstitial and synovial fluid spaces. Several formulas target these inflammatory pathways specifically and thus might account for swifter recovery times. Conversely, those who do not gain treatment access early with this symptom constellation would be predictably more susceptible to long COVID due to persistent central nervous system inflammation.

Grouping symptoms, either based on previously published groupings or on our cluster analysis, identified differences in time to recovery not present when considering symptoms individually, particularly swifter recovery among patients with both headache and joint pain, as well as those who had one or more fever cluster symptoms, including joint pain, chills and cramps in addition to fever. This may be because Tibetan medicine targets presentation of symptoms groups, rather than diagnosis, and thus will be highlighted in time to recovery analyses.

During the period in which our study occurred, development of severe symptoms requiring hospitalization was more likely among individuals with hypertension and/or high BMI. The prevalence of hypertension among our cases is consistent with that reported by other outpatient studies as the most common comorbidity among ambulatory cases (Lane et al., 2021; Ramasamy et al., 2021; Arons et al., 2020; Blair et al., 2021a, 2021b; Kirtana et al., 2020; Li et al., 2020). Although our study could not assess BMI, 65.2% of our included cases had one or more other risk factor known to predict more severe disease such as diabetes, chronic liver disease, dyspnea, male sex and older age (Cheng et al., 2021; Dinnes et al., 2021). Despite the high prevalence of risk for severe disease, very few patients in our sample experienced long COVID, which is more common among those with severe disease (Hedberg et al., 2023). This further emphasizes the value of the Tibetan medicine approach beyond rapid time to recovery.

4.1. Related work on administered Tibetan herbal formulas

Despite limited pharmacological analysis of Tibetan formulas due to their complex multi-ingredient formulations, which often include dozens to over a hundred botanicals and minerals, research on their therapeutic effects is emerging (Tidwell and Nettles, 2019). For example, Tibetan formulas have demonstrated wide ranging biological activities related to treating inflammatory conditions and infectious disease, including properties that are antimalarial (Wangchuk et al., 2012; Wangchuk et al., 2013a; Wangchuk et al., 2013b) anticancer (Jenny et al., 2005; Choedon et al., 2006; Choedon et al., 2011; Zhao et al., 2018), antimicrobial (Wangchuk et al., 2014), antiviral (Sangmo et al., 2007), vascular- and neuroprotective (Korwin-Piotrowska et al., 1992; Exner et al., 2006; Melzer et al., 2006), and immune- and inflammation-modulatory (Vennos et al., 2013; Radomska-Lesniewska

et al., 2013; Wangchuk et al., 2015, 2018; Ginsburg et al., 2011), through multi-compound, multi-target pleiotropic signatures (Schwabl et al., 2013; Schwabl and Valk, 2019). A recent review (Zhang et al., 2023) discusses common treatment strategies used in Tibetan regions of China for COVID-19. The review describes ten formulas, also used in patients in the current study, detailing ingredients, target pathways, and therapeutic functions. Among targeted pathways are those regulating tumor necrosis factor-α, NF-κB, glyceralddhyde-3-phosphate dehydrogenase, MAPK3, epidermal growth factor receptor, pulmonary redox imbalance, ACE2 receptor binding, proteolytic processes, endothelial cell signaling, viral replication, and cytokine activity (CCL2, PTGS2, IL-1β, IL-6). Formulas alleviating symptoms from upper respiratory tract infections demonstrate shortened time to resolution for cough, airway protection, and spontaneous bactericidal activity of blood serum including for recurrent infections (Jankowski et al., 1991; Luo et al., 2022; Xioafeng et al., 2021). Several formulas have been shown as protective against cardiovascular and cerebrovascular disease, including myocardial ischemia injury (Long et al., 2020). Likewise, many of the formulas ameliorate neuroinflammation, which is gaining greater attention for its role in COVID-19 pathophysiology (Spudich and Nath, 2022; Sriwastava et al., 2021). Swift recovery times among our study population might be attributed to the above-described therapeutic effects.

4.2. Limitations

Although physicians in the current observational study gave patients guidance on adaptive mindsets to cultivate, and maladaptive stress responses to avoid, herbal formulas comprised the primary therapy, targeting the virulent infectious disease phases recognized by Tibetan medicine (Tidwell and Gyamtso, 2021). See Supplementary Figure 2 for a schematic diagram detailing treatment by disease phase with Tibetan herbal formulas. Nevertheless, we recognize the potential therapeutic significance of the patient-physician relationship. Additional limitations of our study are multifold. To address a few, the naturalistic study design prohibits the ability to make causal claims. Reliance on patient self-reports has high susceptibility to recall bias and potential cultural differences in reporting certain symptom types. In addition, our sample does not have a comparator control population for the same study period following standard of care and it represents limited diversity and thus limits generalizability. Finally, testing site limitations for confirming cases led to a relatively small study population.

4.3. Conclusion

Despite the limitations, this is the first study to characterize the duration of COVID-19 symptoms in an outpatient setting for patients using Tibetan medicinal formulas. With median time to symptom resolution for COVID-19 under Tibetan medicine care management in the outpatient setting as 11.7 days and time to recovery following public health recommendations for supportive management previously reported as 15–21 days (Lane et al., 2021; Blair et al., 2021a, 2021b; Pettrone et al., 2021), our results suggest patients with similar COVID-19 variants may have had faster symptom resolution under Tibetan medicine care than patients using other supportive management methods. An increasing number of SARS-CoV-2 infections in those first evaluated as outpatients has increased and variants of concern demonstrating differential transmission dynamics and disease course progressions continue to emerge (CDC and NCIRD, 2022). A better understanding of symptom duration among outpatients with COVID-19, particularly those treated by traditional, complementary and alternative medicine such as Tibetan medicine, can help direct care, inform transmission reduction, tailor public health messaging, and boost recognition of CAM modalities that may ameliorate disease severity and reduce recovery time. Furthermore, this study attempts to address concerns of populations susceptible to epidemiological invisibility (Gurung et al., 2021) by contributing one of the few assessments of outpatient experiences among such marginalized communities, particularly those drawing upon cultural resources for therapeutic care in one of the greatest global health crises of the current era.

CRediT authorship contribution statement

Cheme Jetsun: Conceptualization, Investigation, Writing – review & editing. **Blake Kristin:** Data curation, Project administration, Resources, Writing – review & editing. **Jungney Jetsun:** Data curation, Project administration, Writing – review & editing. **Palkyi Tenzin:** Data curation, Project administration, Writing – review & editing. **Skopicki Natalie:** Data curation, Writing – review & editing. **Riordan Kevin M.:** Data curation, Formal analysis, Writing – review & editing. **Rosenkranz Melissa:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. **Lee Kristine E.:** Data curation, Formal analysis, Methodology, Software, Validation, Writing – review & editing. **Craig Sienna:** Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Namdul Tenzin:** Conceptualization, Methodology, Project administration, Software, Supervision, Writing – review & editing. **Weirich Erica:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Tidwell Tawni:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Dhondrup Rinchen:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Wangmo Phuntsog:** Conceptualization, Funding acquisition, Investigation, Resources, Writing – review & editing. **Kalzang Yangdron:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Weil Anasuya:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Youdon Tsering:** Investigation, Writing – review & editing. **Nyinda Nashalla Gwyn:** Conceptualization, Investigation, Writing – review & editing. **Nyinda Tsundu Sengye:** Conceptualization, Investigation, Writing – review & editing. **Dakpa Tenzing:** Investigation, Writing – review & editing. **Gyal Yangbum:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Ridak Dawa:** Investigation, Writing – review & editing. **Tsomo Tsering:** Conceptualization, Investigation, Writing – review & editing. **Yangzom Dickyi:** Conceptualization, Investigation, Writing – review & editing. **Youdon Namseling Nyima:** Conceptualization, Investigation, Writing – review & editing.

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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbii.2024.100051.

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