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【 ORIGINAL ARTICLE 】

Conventional and Kampo Medicine Treatment for Mild-to-moderate COVID-19: A Multicenter, Retrospective, Observational Study by the Integrative Management in Japan for Epidemic Disease (IMJEDI Study-observation)

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Abstract:

Objective Patients in whom coronavirus disease 2019 (COVID-19) was suspected or confirmed between January 1, 2020, and October 31, 2021, were enrolled from Japanese hospitals in this multicenter, retrospective, observational study.

Methods Data on the treatment administered (including conventional and Kampo medicine) and changes in common cold-like symptoms (such as fever, cough, sputum, dyspnea, fatigue, and diarrhea) were collected from their medical records. The primary outcome was the number of days without a fever (with a body temperature <37°C). The secondary outcomes were symptomatic relief and the worsening of illness, defined as the presence of a condition requiring oxygen inhalation. The outcomes of patients treated with and without Kampo medicine were compared.

Patients We enrolled 962 patients, among whom 528 received conventional and Kampo treatment (Kampo group) and 434 received conventional treatment (non-Kampo group).

Results Overall, after adjusting for the staging of COVID-19 and risk factors, there were no significant between-group differences in the symptoms or number of days being afebrile. After performing propensity score matching and restricting the included cases to those with confirmed COVID-19 who did not receive steroid administration and initiated treatment within 4 days from the onset, the risk of illness worsening was significantly lower in the Kampo group than in the non-Kampo group (odds ratio=0.113, 95% confidence interval: 0.014-0.928, p=0.0424).

Conclusion Early Kampo treatment may suppress illness worsening risk in COVID-19 cases without steroid use. Further randomized controlled studies are needed to confirm the clinical benefit of Kampo medicine for COVID-19.

Key words: COVID-19, symptom, conventional treatment, Kampo medicines, illness worsening, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in Wuhan, Hubei, China, in late 2019 (1). As of December 2021, more than 285 million cases of COVID-19 have been identified worldwide, with more than 5.42 million deaths recorded (2). The COVID-19 pandemic remains the world's largest public health problem, and a variety of infection control measures, such as vaccination, SARS-CoV-2 infection detection, patient isolation, and the development of treatment strategies, has continued (3).

The Centers for Disease Control and Prevention have reported the following clinical manifestations of COVID-19 that appear 2-14 days after exposure to the virus: a fever, chills, cough, dyspnea, fatigue, body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea (4). Approximately 80% of patients in the mild-to-moderate stage recover; however, the condition worsens in 20% of patients, who require hospitalization and oxygen administration (5).

One of the key points of treatment is to alleviate the symptoms and reduce the severity of COVID-19. Drug discovery and drug repositioning efforts have been undertaken. Anti-SARS-CoV-2 monoclonal antibodies and ribonucleoside analogs can be used in COVID-19 patients with mild-to-moderate disease, but these clinical applications are of limited applicability in patients with risk factors for severe disease (6). COVID-19 treatment is still under development; however, severe disease due to cytokine overreaction and drug resistance due to mutant strains remains a challenge.

Traditional Japanese (Kampo) medicine was widely used in Japan for the Spanish flu pandemic caused by the H1N1 influenza subtype virus from 1918 to 1920. Maoto granules, a Kampo medicine formulated from four plants [Japanese Pharmacopeia (JP) Ephedra Herb, JP Apricot Kernel, JP Cinnamon Bark, and JP Glycyrrhiza Root], was shown to relieve a fever faster than oseltamivir in a randomized controlled trial (RCT) (7). Kampo medicine is now used to treat common cold symptoms, bronchitis, and pneumonia under the national health insurance system in Japan. We previously reported that Kampo medicines, which are used for infections, have symptom-relieving, antiviral, anti-inflammatory, immunomodulatory, and antioxidant activities (8, 9) and may help alleviate the symptoms and suppress the worsening of COVID-19. Some case reports or case series of COVID-19 successfully treated with Kampo medicine have been reported (10, 11).

We therefore surveyed the actual treatment of patients with mild-to-moderate COVID-19 in Japan and investigated the clinical course, safety, and illness worsening after treat-

ment with conventional and Kampo medicine via a multicenter retrospective observational trial.

Materials and Methods

The study protocol was published in *Traditional and Kampo Medicine* on December 22, 2020, with the title, "Conventional and Kampo medicine in the treatment of mild-to-moderate COVID-19: A multicenter, retrospective observational study protocol by the Integrative Management in Japan for Epidemic Disease (IMJEDI study-observation)" (12).

Trial status

Protocol version 1.2 as of March 1, 2021
Recruitment start: January 1, 2020
Recruitment finish: October 31, 2021

Trial registration

The trial was registered with the University Hospital Medical Information Network (UMIN) (Reservation No. UMIN000041301) on August 4, 2020 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000047163).

Ethical approval

The protocol was approved by the Certified Clinical Research Review Board of Tohoku University (Sendai, Japan) on July 20, 2020 (Certification No. 19728). The authors certify that this study received ethical approval from an appropriate ethics committee. All procedures were conducted in conformance with the current version of the Declaration of Helsinki, revised in 2013.

This research did not use samples or other materials obtained from human subjects and consisted of purely academic research. Informed consent was obtained in an opt-out manner. However, information about the research, including its purpose, was made available to the public, and the participants were allowed to refuse participation. Disclosure of research-related matters was made by posting disclosure materials on the website or hospital bulletin board of each institution. The principal investigator or researcher responded to any inquiries.

Trial design

The Japanese Association for Infectious Diseases, Japanese Respiratory Society, Japan Primary Care Association, Japanese Society of Hospital Medicine, and the Japan Society for Oriental Medicine cooperated by posting the research collaboration on their websites. The study was designed as a multicenter, retrospective observational study. It was performed in collaboration with 23 medical facilities, including 7 university hospitals, 9 regional core hospitals, and 7 clinics.

Participants

Outpatients and inpatients were recruited from Japanese academic and non-academic hospitals. Patients were included if they: had confirmed or suspected mild-to-moderate COVID-19, were symptomatic, were ≥20 years old, were able to communicate in Japanese, and were treated using conventional and/or Kampo medicine and if the treatment was administered according to the patient's symptoms, clinical stage of COVID-19, and the patient's wishes.

The following criteria for symptomatic COVID-19 were used to determine staging in Japan: mild stage, oxygen saturation (SpO_2) ≥96% with cough without dyspnea; moderate stage I, SpO_2 93-96% with dyspnea and pneumonia findings; moderate stage II, SpO_2 ≤93%, and requiring oxygen administration and treatment; and severe stage, requiring intensive care or mechanical ventilation. The number of real-time reverse transcription-polymerase chain reaction (RT-PCR) tests that could be performed was limited from January to August 2020 in Japan, so suspected cases of COVID-19 based on the physicians' judgment of a fever, prolonged symptoms, and exclusion following other tests were also enrolled in this study.

The exclusion criteria were as follows: patients with dementia, psychosis, psychiatric symptoms, moderate stage II or severe COVID-19, or those who were deemed unsuitable for this study by a physician.

Treatments

The physicians in each collaborating institute treated patients and prescribed western and/or Kampo medicines based on the patients' symptoms and concerns. There was no guidance for prescription. Kampo medicines are prescribed based not simply on patients' complaints, signs, and symptoms but also on physical examinations, including abdominal examination, tongue inspection, pulse examinations, etc. However, as the extent of physical examinations in patients with COVID-19 was necessarily limited, prescription of Kampo medicines was provided according to symptoms in most cases.

Outcomes

The main outcome was the number of days without a fever (days with a body temperature <37°C). The secondary outcome was the number of days without common cold-like symptoms other than a fever (cough, dyspnea, fatigue, and diarrhea). The incidence of illness worsening, defined as requiring oxygen inhalation within 14 days of first visit, was also evaluated as a secondary outcome.

Sample size

A target sample size of 1,000 patients was planned based on the feasibility of the study. Since there are currently no drugs available that have demonstrated efficacy for mild or moderate COVID-19, and the efficacy of the symptomatic drugs used in this study is unknown, the sample size was set to the number of patients that could be treated in the outpatient clinic of the collaborating medical institutions during the study period.

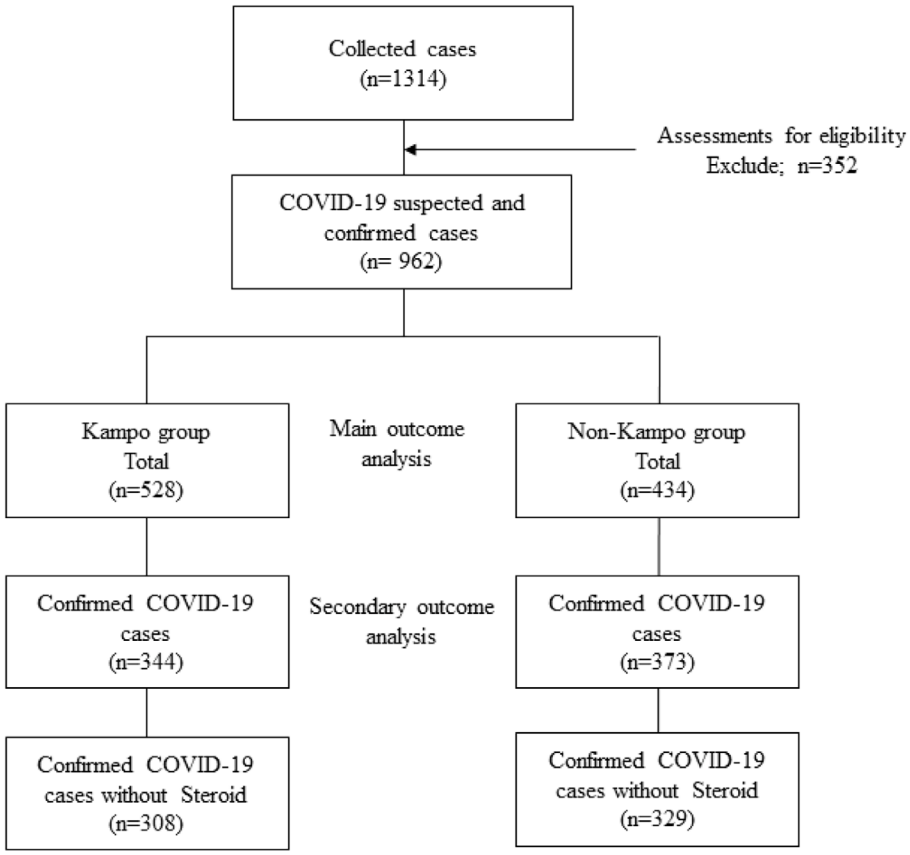

Figure 1. **Trial flowchart. COVID-19: coronavirus disease 2019**

Statistical analyses

For patient background factors, descriptive statistics were calculated for continuous variables, and comparisons between the groups were performed using *t*-tests. For categorical variables, the number of cases and proportions was calculated, and between-group comparisons were performed using the χ^2 test. For the primary endpoint, for each group, we estimated the Kaplan-Meier survival curves of days to symptomatic relief (fever), calculated the point estimates of the median survival and 95% confidence interval (CI), and compared the results between the groups using the log-rank test.

The secondary endpoint, i.e. common cold-like symptoms other than a fever (cough, dyspnea, fatigue, and diarrhea), was analyzed in the same way as the primary endpoint. Point estimates of the proportion of severe disease requiring oxygen administration during hospitalization up to Day 14 from the date of consultation and the difference between the groups were estimated as secondary endpoints. The χ^2 test was used for group comparisons. Since the severity of the disease reportedly varies with age and comorbidities (4), a complementary analysis was also considered. We used a Cox proportional hazard model to adjust for the age, body mass index (BMI), days from the COVID-19 onset to hospital visit, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, respiratory disease, renal dysfunction, cancer, smoking habit, COVID-19 stage at the first visit, white blood cell (WBC) count, lymphocyte count, C-reactive protein (CRP) level, and lactate dehydrogenase (LDH) level for group comparisons of days to symptomatic relief. In addition, we used a logistic regression model to adjust for the COVID-19 stage at the first visit for group comparisons of the proportion of cases with severe disease requiring oxygen administration.

We also performed propensity score matching to adjust possible confounders. Propensity scores were calculated as the probability of treatment using Kampo medicines based on the age, BMI, days from the COVID-19 onset to hospital visit, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, respiratory disease, renal dysfunction, cancer, smoking habit, COVID-19 stage at the first visit, WBC count, lymphocyte count, and CRP and LDH level. One-to-one greedy nearest neighbor matching method was used.

Statistical analyses were performed using SAS software (ver. 9.4; SAS Institute, Cary, USA).

Results

Patient characteristics

A flowchart of the trial is presented in Fig. 1. A total of 962 patients with COVID-19 (717 confirmed and 245 suspected) were included. Among the 962 total patients, 528 received Kampo medicine (Kampo group; Kampo medicine treatment with or without conventional treatment), and 434 received conventional treatment (non-Kampo group; conven-

Table 1. Demographic and Clinical Characteristics of the Participants at the Baseline.

Characteristics	Overall (n=962)	Kampo group (n=528)	Non-Kampo group (n=434)	p value
Gender				0.0140
Male; n (%)	533 (55.46)	274 (51.89)	259 (59.82)	
Female; n (%)	428 (44.54)	254 (48.11)	174 (40.18)	
Age; mean (SD), years	48.83 (17.08)	46.43 (16.05)	51.74 (17.84)	<.0001
Height; mean (SD), cm	164.61 (9.32)	164.56 (9.12)	164.67 (9.56)	0.8630
Body weight; mean (SD), kg	65.9 (15.6)	66.15 (15.58)	65.62 (15.63)	0.6208
Body mass index; mean (SD)	24.15 (4.61)	24.31 (4.75)	23.97 (4.45)	0.3010
Body mass index category				0.4197
<18.5; n (%)	67 (8.1)	35 (7.9)	32 (8.2)	
≥18.5 to <25; n (%)	463 (55.7)	236 (53.3)	227 (58.4)	
≥25 to <30; n (%)	217 (26.1)	122 (27.5)	95 (24.4)	
≥30; n (%)	85 (10.2)	50 (11.3)	35 (9.0)	
Risk factors				
Diabetes mellitus; n (%)	101 (10.5)	55 (10.42)	46 (10.6)	0.9268
Hypertension; n (%)	179 (18.61)	88 (16.67)	91 (20.97)	0.0881
Dyslipidemia; n (%)	120 (12.47)	66 (12.5)	54 (12.44)	0.9785
Cardiovascular disease; n (%)	60 (6.24)	32 (6.06)	28 (6.45)	0.8029
Respiratory disease; n (%)	82 (8.52)	40 (7.58)	42 (9.68)	0.2454
Renal dysfunction; n (%)	21 (2.18)	6 (1.14)	15 (3.46)	0.0143
Cancer; n (%)	35 (3.64)	14 (2.65)	21 (4.84)	0.0714
Smoking habit; n (%)	311 (32.33)	153 (28.98)	158 (36.41)	0.0142
Days from onset to visit; mean (SD), days	5.87 (4.07)	6.03 (4.47)	5.67 (3.51)	0.1716
Days from onset to visit				0.3875
within 7 days; n (%)	683 (72.0)	374 (71.5)	309 (72.5)	
from 8 to 14 days; n (%)	238 (25.1)	130 (24.9)	108 (25.4)	
over 15 days; n (%)	28 (3.0)	19 (3.6)	9 (21)	
Symptoms				
Fever; n (%)	688 (71.52)	339 (64.2)	349 (80.41)	<.0001
Chill; n (%)	61(6.34)	47 (8.9)	14 (3.23)	0.0003
Sweating; n (%)	29 (3.01)	27 (5.11)	2 (0.46)	<.0001
Fatigue; n (%)	385 (40.02)	195 (36.93)	190 (43.78)	0.0310
Headache; n (%)	243 (25.26)	143 (27.08)	100 (23.04)	0.1511
Joint pain; n (%)	94 (9.77)	64 (12.12)	30 (6.91)	0.0068
Runny nose; n (%)	149 (15.49)	88 (16.67)	61 (14.06)	0.2653
Nasal obstruction; n (%)	127 (13.2)	102 (19.32)	25 (5.76)	<.0001
Pharyngeal pain; n (%)	261 (27.13)	163 (30.87)	98 (22.58)	0.0040
Thirst; n (%)	26 (2.7)	23 (4.36)	3 (0.69)	0.0005
Cough; n (%)	564 (58.63)	298 (56.44)	266 (61.29)	0.1285
Sputum; n (%)	190 (19.75)	109 (20.64)	81 (18.66)	0.4427
Dyspnea; n (%)	163 (16.94)	93 (17.61)	70 (16.13)	0.5413
Chest pain; n (%)	58 (6.03)	52 (9.85)	6 (1.38)	<.0001
Nausea and/or vomiting; n (%)	53 (5.51)	36 (6.82)	17 (3.92)	0.0497
Diarrhea; n (%)	117 (12.16)	74 (14.02)	43 (9.91)	0.0524
Taste disorder; n (%)	231 (24.01)	139 (26.33)	92 (21.2)	0.0639
Smell disorder; n (%)	244 (25.36)	158 (29.92)	86 (19.82)	0.0003
Physical findings				
Body temperature; mean (SD), °C	37.2 (0.84)	37.04 (0.78)	37.41 (0.87)	<.0001
Pulse rate; mean (SD), beats/min	85.82 (15.09)	84.69 (14.86)	87.03 (15.25)	0.0225
Respiratory rate; mean (SD), beats/min	17.51 (3.06)	17.13 (2.76)	17.73 (3.21)	0.0587
Systolic blood pressure; mean (SD), mmHg	128.97 (19.4)	128.62 (20.19)	129.27 (18.7)	0.6602
Diastolic blood pressure; mean (SD), mmHg	81.47 (13.59)	80.77 (13.53)	82.08 (13.62)	0.2009
SpO_2; mean (SD), %	97.13 (1.4)	97.19 (1.34)	97.07 (1.47)	0.2294
Blood sampling test				
WBC count; mean (SD), /μL	5,203.97 (2,043.79)	5,193.47 (2,029.54)	5,213.97 (2,059.91)	0.8918
Lymphocyte count; mean (SD), /μL	1,303.44 (700.30)	1,396.25 (850.07)	1,200.78 (492.51)	0.0002
CRP; mean (SD), mg/dL	2.26 (3.34)	1.66 (2.42)	2.82 (3.94)	<.0001
LDH; mean (SD), U/L	220.46 (110.47)	208.46 (65.78)	231.38 (138.4)	0.0052
Chest X-ray or CT findings; positive (%)	460 (63.8)	192 (54.70)	268 (72.43)	<.0001
COVID-19 stage at the first visit				<.0001
Mild stage, n (%)	471 (49.84)	314 (61.33)	157 (36.26)	
Moderate stage I, n (%)	474 (50.16)	198 (38.67)	276 (63.74)	
Medication				
Antipyretics, general common cold medicines; n (%)	642 (66.7)	296 (56.1)	346 (79.72)	<.0001
Antitussive, expectorant; n (%)	294 (30.6)	147 (27.9)	147 (33.9)	0.0434
Antibiotics; n (%)	162 (16.8)	64 (12.1)	98 (22.6)	<.0001
Favipiravir; n (%)	102 (10.6)	19 (3.6)	83 (8.6)	<.0001
Remdesivir; n (%)	80 (8.3)	25 (4.7)	55 (12.7)	<.0001
Lopinavir and ritonavir; n (%)	13 (1.4)	12 (2.3)	1 (0.2)	0.0063
Ciclesonide; n (%)	29 (3.0)	4 (0.8)	25 (5.8)	<.0001
Nafamostat mesilate; n (%)	22 (2.3)	19 (3.6)	3 (0.7)	0.0027
Steroid; n (%)	86 (9.0)	42 (8.0)	44 (10.1)	0.2375
Others; n (%)	16 (1.7)	7 (1.3)	9 (2.1)	0.3667

COVID-19: coronavirus disease 2019, CRP: C-reactive protein, CT: computed tomography, LDH: lactate dehydrogenase, SpO_2: oxygen saturation, WBC: white blood cell

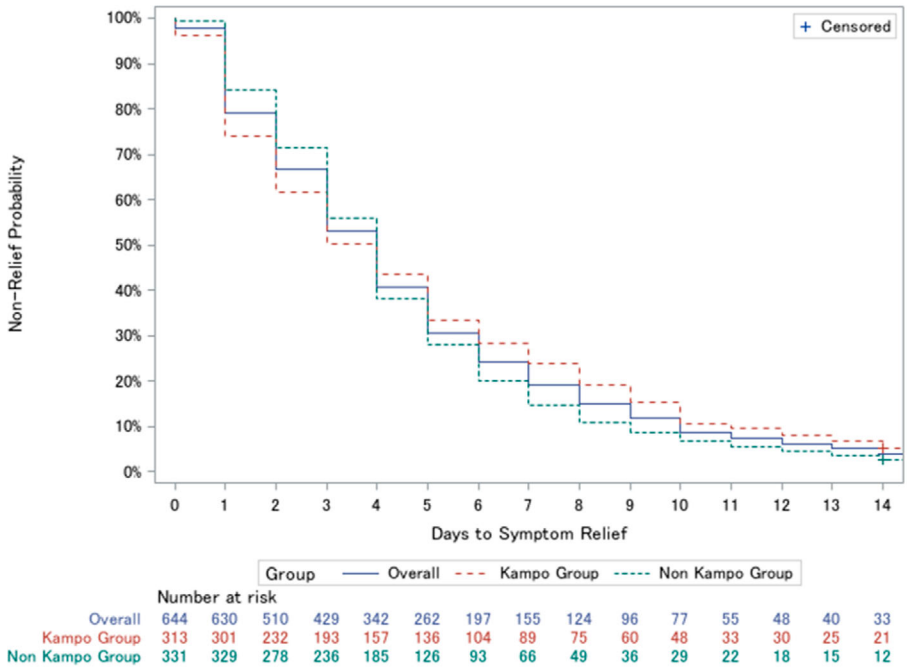

Figure 2. **Kaplan-Meier survival curves of days without a fever.**

tional treatment without Kampo medicine treatment). Among the 717 confirmed patients, 344 received Kampo medicine, and 373 received conventional treatment.

The patient characteristics are shown in Table 1. Patients in the Kampo group were younger than those in the non-Kampo group (46.4±16.1 vs. 51.7±17.8 years old, p< 0.0001). Regarding symptoms, there were significant differences between the Kampo and non-Kampo groups in the percentage of patients with a fever (64.20% vs. 80.41%, p< 0.0001), chills (8.90% vs. 3.23%, p=0.0003), sweating (5.11% vs. 0.46%, p<0.0001), fatigue (36.93% vs. 43.78%, p=0.0310), joint pain (12.12% vs. 6.91%, p=0.0068), nasal congestion (19.32% vs. 5.76%, p<0.0001), throat pain (30.87% vs. 22.58%, p=0.0040), thirst (4.36% vs. 0.69%, p= 0.0005), chest pain (9.85% vs. 1.38%, p<0.0001), nausea or vomiting (6.82% vs. 3.92%, p=0.0497), and smell disorder (29.92% vs. 19.82%, p=0.0003). Regarding comorbidities and lifestyle, there were significant differences between the Kampo and non-Kampo groups in the percentage of patients with renal dysfunction (1.14% vs. 3.46%, p=0.0143) and the percentage of smokers (28.98% vs. 36.41%, p=0.0142). Significant differences between the Kampo and non-Kampo groups were also observed in physical signs, such as the fever value (37.04±0.78 vs. 37.41±0.87°C, p<0.0001) and pulse rate (84.69±14.86 vs. 87.03±15.25 beats/minute, p= 0.0225).

The percentage of patients with pneumonia findings on X-ray imaging was significantly smaller in the Kampo group than in the non-Kampo group (54.70% vs. 72.43%, p< 0.0001). Furthermore, COVID-19 staging was also different between the groups (Kampo group: mild stage, 61.33% and moderate stage, 38.67%; non-Kampo group: mild stage, 36.26% and moderate stage, 63.74%, p<0.0001). Regarding laboratory findings, significant differences were noted between the Kampo and non-Kampo groups in lymphocyte counts (1,401.45±850.07 vs. 1,206.26±492.51, p=0.0002), CRP (1.66±2.42 vs. 2.82±3.94 mg/dL, p<0.0001), and LDH (209.22±65.22 vs. 223.57±71.58 U/L, p=0.0052). These results show differences in the background characteristics of the two groups.

Conventional treatments such as antipyretic and analgesic drugs, common cold drugs, antitussive and expectorant drugs, and antibiotics, were prescribed to 79.92% of patients in the Kampo group and 100.00% of those in the non-Kampo group. Patients for whom the COVID-19 diagnosis was confirmed received steroids both in the Kampo group (n =308, 89.5%) and the non-Kampo group (n=329, 88.2%).

Primary endpoint

The Kaplan-Meier survival curves of the days without a fever are shown in Fig. 2. The median number of days without a fever was 4.0 when considering all patients as well as when considering the patients in whom COVID-19 was confirmed.

In patients for whom COVID-19 was suspected or confirmed, the number of days without a fever was not significantly different between the groups (Kampo vs. non-Kampo: median days 4.0 vs. 4.0, p=0.1820). Among patients for whom COVID-19 was confirmed, there was no significant between-group difference in the number of days without a fever (Kampo vs. non-Kampo: median 4.0 vs. 4.0 days, p= 0.3236); in this group, the number of days without a fever was not significantly different between the groups for those who did not receive steroids (Kampo vs. non-Kampo: median 3.0 vs. 4.0 days, p=0.8909).

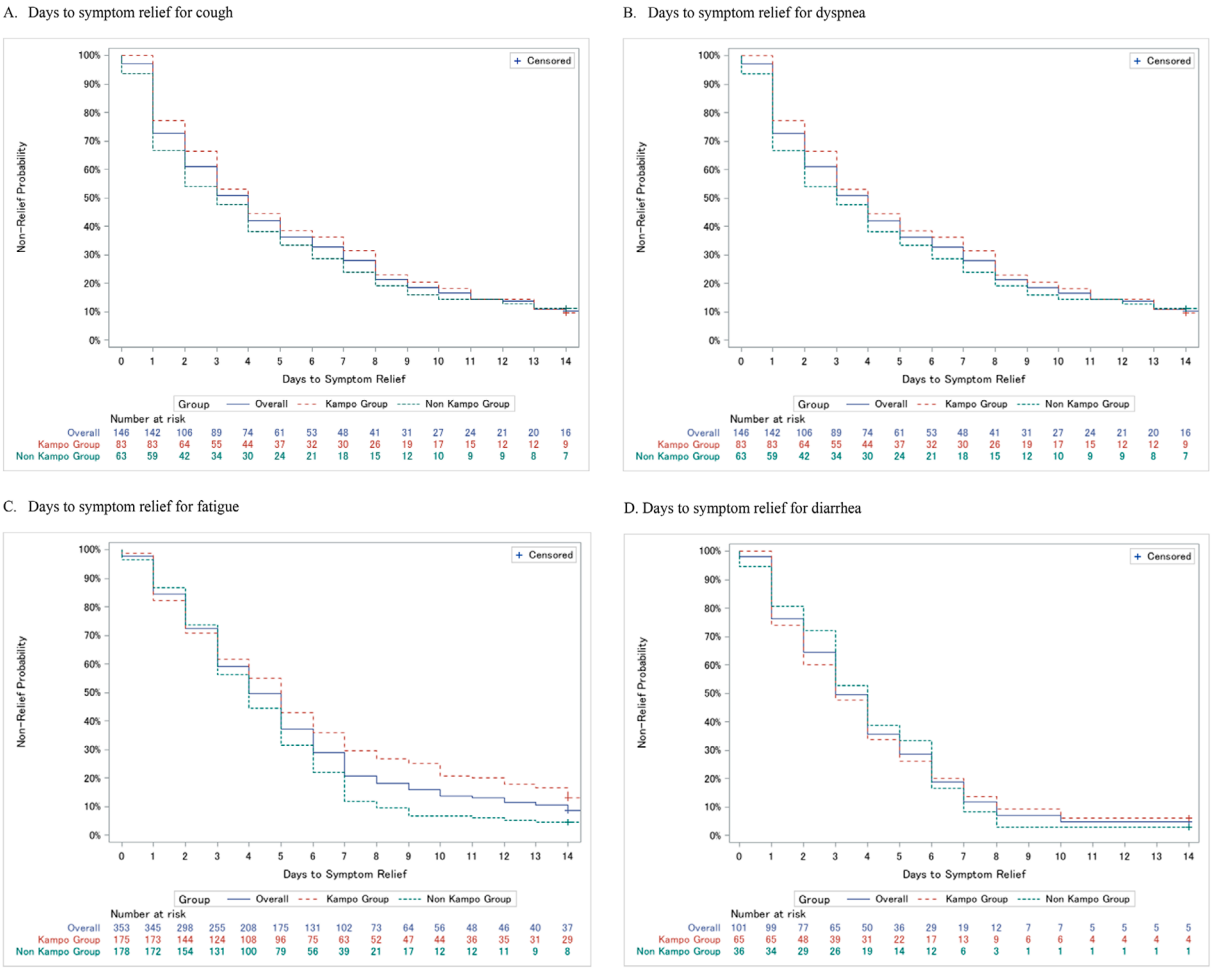

Figure 3. Kaplan-Meier survival curves of days until symptom relief. (A) Days to symptomatic relief for cough. (B) Days to symptomatic relief for dyspnea. (C) Days to symptomatic relief for fatigue. (D) Days to symptomatic relief for diarrhea.

Secondary endpoints

The Kaplan-Meier survival curves of days until recovery of cough, dyspnea, fatigue, and diarrhea are shown in Fig. 3 (A-D, respectively). Overall symptomatic relief and the comparison between the Kampo and non-Kampo groups are listed in Table 2.

Cough

In patients for whom COVID-19 was suspected or confirmed, the number of days until symptomatic relief of cough was 6.0, with no significant between-group difference noted (Kampo: median: 6.0 days, 95% CI: 5.0-7.0 days; non-Kampo: median: 6.0 days, 95% CI: 5.0-6.0 days; p=0.6236). Among those in whom COVID-19 was confirmed, the number of days until symptomatic relief of cough was 6.0, with no significant difference between the groups noted (Kampo: median: 6.0 days, 95% CI: 5.0-7.0 days; non-Kampo: median: 6.0 days, 95% CI: 5.0-7.0 days; p=0.5074). Among COVID-19 patients who did not receive steroids, the number of days until symptomatic relief of cough was 6.0, with no significant between-group difference noted (Kampo: median: 5.0 days, 95% CI: 5.0-6.0 days; non-Kampo: median: 6.0 days, 95% CI: 5.0-7.0 days; p=0.2370).

Dyspnea

In patients for whom COVID-19 was suspected or confirmed, the number of days until symptomatic relief of dyspnea was 4.0, with no significant between-group difference noted (Kampo: median: 4.0 days, 95% CI: 3.0-5.0 days; non-Kampo: median: 3.0 days, 95% CI: 2.0-4.0 days; p=0.4427). The number of days until symptomatic relief of dyspnea was 4.0 even when considering COVID-19 patients alone, with no significant between-group difference noted (Kampo: median: 4.0 days, 95% CI: 2.0-6.0 days; non-Kampo: median: 3.5 days, 95% CI: 2.0-5.0 days; p=0.7761). Among COVID-19 patients who did not receive steroids, the number of days until symptomatic relief of dyspnea was 4.0, with no significant between-group difference noted (Kampo: median: 4.0 days, 95% CI: 2.0-6.0 days; non-Kampo: median: 3.0 days, 95% CI: 1.0-4.0 days; p=0.0930).

Fatigue

In patients for whom COVID-19 suspected or confirmed, the number of days until symptomatic relief of fatigue was 4.0. This duration was significantly longer in the Kampo group than in the non-Kampo group (Kampo: median: 5.0 days, 95% CI: 4.0-6.0 days vs. non-Kampo: median: 4.0 days, 95% CI: 3.0-5.0 days, p=0.0008); however, after ad-

Table 2. Overall Symptom Relief and the Comparison between the Kampo and Non-Kampo Groups.

Symptom								
Target population	Overall	Kampo group	Non-Kampo group	Adjusted for risk factors**				
	Number of recovered patients/number of patients			p value*	Hazard ratio	Lower 95% CI	Upper 95% CI	p value
	Number of days until recovery (95% CI)							
Fever								
Total cases	619/644	297/313	322/331	0.1820	0.867	0.703	1.068	0.1794
	4.0 (3.0-4.0)	4.0 (3.0-4.0)	4.0(---)					
Confirmed COVID-19 cases	514/535	224/236	290/299	0.3236	0.948	0.763	1.178	0.6280
	4.0(---)	4.0 (3.0-5.0)	4.0(---)					
Confirmed COVID-19 cases without steroid	444/460	194/203	250/257	0.8909	1.011	0.798	1.280	0.9297
	4.0 (3.0-4.0)	3.0 (3.0-4.0)	4.0(---)					
Cough								
Total cases	471/525	250/278	221/247	0.6236	0.885	0.693	1.130	0.3265
	6.0 (5.0-6.0)	6.0 (5.0-7.0)	6.0 (5.0-6.0)					
Confirmed COVID-19 cases	361/402	166/181	195/221	0.5074	0.968	0.741	1.264	0.8105
	6.0 (5.0-6.0)	6.0 (5.0-7.0)	6.0 (5.0-7.0)					
Confirmed COVID-19 cases without steroid	309/340	142/152	167/188	0.2370	1.113	0.835	1.486	0.4651
	6.0 (5.0-6.0)	5.0 (5.0-6.0)	6.0 (5.0-7.0)					
Dyspnea								
Total cases	131/146	75/83	56/63	0.4427	0.756	0.460	1.243	0.2703
	4.0 (3.0-4.0)	4.0 (3.0-5.0)	3.0 (2.0-4.0)					
Confirmed COVID-19 cases	104/116	55/60	49/56	0.7761	0.791	0.459	1.362	0.3973
	4.0 (3.0-5.0)	4.0 (2.0-6.0)	3.5 (2.0-5.0)					
Confirmed COVID-19 cases without steroid	83/89	44/48	39/41	0.0930	0.594	0.324	1.089	0.0920
	4.0 (2.0-5.0)	4.0 (2.0-6.0)	3.0 (1.0-4.0)					
Fatigue								
Total cases	322/353	152/175	170/178	0.0008	0.750	0.561	1.002	0.0513
	4.0 (4.0-5.0)	5.0 (4.0-6.0)	4.0 (3.0-5.0)					
Confirmed COVID-19 cases	269/294	112/129	157/165	0.0059	0.803	0.592	1.091	0.1604
	5.0 (4.0-5.0)	5.0 (4.0-6.0)	4.0 (4.0-5.0)					
Confirmed COVID-19 cases without steroid	234/253	135/140	99/113	0.0021	0.783	0.562	1.090	0.1474
	4.0 (4.0-5.0)	5.0 (4.0-6.0)	4.0 (3.0-5.0)					
Diarrhea								
Total cases	96/101	61/65	35/36	0.9445	1.382	0.662	2.887	0.3894
	3.0 (3.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-5.0)					
Confirmed COVID-19 cases	78/81	46/48	32/33	0.5849	1.312	0.603	2.859	0.4937
	3.0 (3.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-6.0)					
Confirmed COVID-19 cases without steroid	71/72	41/42	30/30	0.7930	1.658	0.709	3.881	0.2436
	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.5 (3.0-6.0)					

COVID-19: coronavirus disease 2019

* Log-rank test between the Kampo and non-Kampo groups

**Risk Factors: age, BMI: body mass index, days from onset to visit, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, respiratory disease, renal dysfunction, cancer, smoking habit, COVID-19 stage at the first visit, WBC count, lymphocyte count, CRP, LDH

justing for age, staging of COVID-19, and risk factors, the difference was no longer significant (adjusted hazard ratio=0.750, 95% CI: 0.561-1.002, p=0.0513). In those for whom COVID-19 was confirmed, the number of days until symptomatic relief of fatigue was 5.0. The recovery time was significantly longer in the Kampo group than in the non-Kampo group (Kampo: median: 5.0 days, 95% CI: 4.0-6.0 days vs. non-Kampo: median: 4.0 days, 95% CI: 4.0-5.0 days, p=0.0059); however, after adjusting for age, staging of COVID-19, and risk factors, the difference was no longer significant (adjusted hazard ratio=0.803, 95% CI: 0.592-1.091, p=0.1604). Among COVID-19 patients who were not administered steroids, the number of days until symptomatic relief of fatigue was 4.0. The recovery time was significantly higher in the Kampo group than in the non-Kampo group (Kampo: median: 5.0 days, 95% CI: 4.0-6.0 days vs. non-Kampo: median: 4.0 days, 95% CI: 3.0-5.0 days, p=0.0021); however, after adjusting for age, staging of COVID-19, and risk factors, the difference was no longer significant (adjusted hazard ratio=0.783, 95% CI: 0.562-1.090, p=0.1474).

Table 3. The Results of Illness Worsening to Respiratory Failure Compared between the Groups after Adjusting for Stage, Treatment Initiation within 4 Days from the Onset, and Propensity Score Matching.

Subgroup	Target population					
	Kampo group	Non-Kampo group	Odds ratio	Lower 95% CI	Upper 95% CI	p value
	Number of illness worsened patients/ number of patients					
	Total cases					
Overall	36/502	65/423	0.425	0.277	0.654	<.0001
Adjusted for stage	35/488	65/422	0.566	0.361	0.887	0.0129
Adjusted for stage/started treatment within 4 days from the onset	13/194	34/168	0.377	0.187	0.760	0.0064
PS matching*/started treatment within 4 days from the onset	5/82	15/82	0.290	0.100	0.840	0.0226
	Confirmed COVID-19 cases					
Overall	29/325	63/364	0.468	0.293	0.748	0.0015
Adjusted for stage	29/321	63/363	0.642	0.395	1.046	0.0751
Adjusted for stage/started treatment within 4 days from the onset	11/133	33/154	0.428	0.201	0.913	0.0280
PS matching*/started treatment within 4 days from the onset	5/78	11/78	0.417	0.138	1.263	0.1220
	Confirmed COVID-19 cases without steroid					
Overall	15/289	41/320	0.373	0.202	0.689	0.0016
Adjusted for stage	15/285	41/319	0.543	0.288	1.026	0.0600
Adjusted for stage/started treatment within 4 days from the onset	3/112	22/136	0.193	0.055	0.680	0.0105
PS matching*/started treatment within 4 days from the onset	1/74	8/74	0.113	0.014	0.928	0.0424

*Propensity scores were calculated based on age, BMI, days from onset to visit, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, respiratory disease, renal dysfunction, cancer, smoking habit, COVID-19 stage at the first visiting, WBC count, lymphocyte count, CRP, LDH

Diarrhea

In patients for whom COVID-19 was suspected or confirmed, the number of days until symptomatic relief of diarrhea was not significantly different between the groups (Kampo: median: 3.0 days, 95% CI: 2.0-4.0 days; non-Kampo: median: 4.0 days, 95% CI: 3.0-5.0 days; p=0.9445). When considering cases wherein COVID-19 was confirmed, the number of days until symptomatic relief of diarrhea was also not significantly different between the groups (Kampo: median: 3.0 days, 95% CI: 2.0-4.0 days; non-Kampo: median: 4.0 days, 95% CI: 3.0-6.0 days; p=0.5849). Among the COVID-19 patients who did not receive steroids, the number of days until symptomatic relief of diarrhea was 4.0, with no significant between-group difference noted (Kampo: median: 3.0 days, 95% CI: 2.0-4.0 days; non-Kampo: median: 3.5 days, 95% CI: 3.0-6.0 days; p=0.7930).

Illness worsening

The comparison of the rates of illness worsening to respiratory failure between the groups after adjusting for stage, treatment initiation within four days from the onset, and propensity score matching is shown in Table 3.

Among patients for whom COVID-19 was suspected or confirmed, the proportion of patients experiencing illness worsening to the point that they required oxygen administration was 10.9% overall, 7.2% in the Kampo group, and 15.4% in the non-Kampo group. The difference between the groups was not statistically significant; however, after adjusting for the COVID-19 stage at the first visit, the risk of illness worsening was found to be lower in the Kampo group than in the non-Kampo group (adjusted odds ratio=0.566, 95% CI 0.361-0.887, p=0.0129). Among those for whom COVID-19 was confirmed, the proportion of patients experiencing illness worsening to the point that they required oxygen administration was 13.4% (overall), 8.9% (Kampo group), and 17.3% (non-Kampo group). The difference between the groups was statistically significant (p=0.0012); however, after adjusting for the COVID-19 stage at the first visit, the risk of illness worsening was found to be lower in the Kampo group than in the non-Kampo group (adjusted odds ratio=0.642, 95% CI: 0.395-1.046, p=0.0751). Furthermore, in patients who started treatment within 4 days of the onset, the risk of illness worsening was significantly lower in the Kampo group than in the non-Kampo group (adjusted odds ratio=0.428, 95%: confidence interval: 0.201-0.913, p=0.028). After performing propensity score matching and restricting the included cases to those with confirmed COVID-19 who did not receive steroid administration and who initiated treatment within 4 days from

Table 4. Kampo Medicines Prescribed in the Kampo Group (n=528).

Name of the Kampo medicine	n (%)
Shosaikotokakikyosekko	246 (46.59)
Kakkonto	225 (42.61)
Makyokansekito	74 (14.02)
Goreisan	44 (8.33)
Gokoto	41 (7.77)
Hochuekkito	40 (7.58)
Bakumondoto	25 (4.73)
Shosaikoto	22 (4.17)
Maoto	21 (3.98)
Kikyosekko	19 (3.6)
Saireito	17 (3.22)
Saibokuto	15 (2.84)
Jinsoin	9 (1.7)
Shoseiryuto	8 (1.52)
Kososan	4 (0.76)
Maobushisaishinto	4 (0.76)
Others	183 (34.66)

the onset, the risk of illness worsening was also significantly lower in the Kampo group than in the non-Kampo group (odds ratio=0.113, 95% confidence interval: 0.014-0.928, p=0.0424).

Kampo medicines

The list of Kampo medicines prescribed to the patients is shown in Table 4. The top five prescriptions were for shosaikotokakikyosekko (SSKKS), kakkonto (KT), makyokansekito, goreisan, and gokoto. SSKKS and KT are frequently used in combination.

Safety

No adverse events related to treatments for COVID-19 were reported.

Discussion

The present study showed the clinical treatment course of conventional and Kampo medicines in patients with mild- to moderate-stage COVID-19. The cases were collected from 23 medical facilities in Japan, thus well demonstrating the situation in the clinical setting of COVID-19.

The median time until fever improvement was 4.0 days, and the total rate of illness worsening was 10.92% in patients with mild- and moderate-stage COVID-19. In Japan, COVID-19 vaccination in elderly individuals started in April 2021 and was then gradually expanded to middle-aged to young adults. Most patients included in this study were therefore not vaccinated. Placebo data in prior RCTs have shown a median time until symptom improvement of 12 to 14 days (13, 14) and a rate of illness worsening of 5.0% to 8.3% (13, 15). However, the inclusion criteria of each study were different. Furthermore, the prevalent SARS-CoV-2 variant and vaccination status in other countries can influence the clinical course of the illness. These data therefore cannot be simply compared.

In our study, there was no significant difference in symptomatic relief with or without the administration of Kampo medicine, implying that subjective symptoms can be controlled with Kampo or conventional treatments. In patients with a confirmed COVID-19 diagnosis, the rate of illness worsening to the point that a patient required oxygen administration was lower in the Kampo group than in the non Kampo group. However, there were marked differences in staging between the groups. Additional analyses performed during the early treatment period (within four days of the onset) showed that the risk of illness worsening was significantly lower in the Kampo group than in the non-Kampo group. After performing propensity score matching and restricting the included cases to those of patients with confirmed COVID-19 who did not receive steroid administration and initiated treatment within four days from the onset, the risk of illness worsening was also found to be significantly lower in the Kampo group than in the non-Kampo group. These results suggest that, in addition to aiding symptomatic relief, early treatment with Kampo medicine may help prevent the progression of the disease in patients with mild-to-moderate COVID-19 without steroids.

In Japan, the use of several drugs is permitted to treat COVID-19 (6), including casirivimab plus imdevimab to treat mild-to-moderate disease in high-risk patients (16, 17) and remdesivir (18), baricitinib (19), and dexamethasone (20) to treat moderate-to-severe disease. The use of dexamethasone was shown to result in lower mortality rates among those who received either mechanical ventilation or oxygen administration but not among those who did not receive respiratory support (21). The Guide to Medical Treatment for COVID-19 in Japan recommends steroid use for hospitalized patients who require oxygen therapy (6). Despite these treatments, no reduction in illness worsening and mortality rate has been achieved because of the spread of mutant SARS-CoV-2 variants. Stage progression to severe COVID-19 is influenced by factors such as aging, cancer, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, dyslipidemia, body mass index >30, and smoking (22). Consequently, we adjusted the illness worsening rate for risk factors, excluding patients who received steroids. This additional analysis showed that the rate of illness worsening in the Kampo group was lower than that in the non-Kampo group, implying that Kampo medicine may suppress illness worsening.

In 2022, molnupiravir and nirmatrelvir-ritonavir were permitted for use as oral medicines for COVID-19 with some risk factors. Molnupiravir is a ribonucleoside analogue with antiviral activity against RNA viruses (23). In a double-blind, randomized, placebo-controlled trial performed with non-hospitalized adults diagnosed with COVID-19, rates of COVID-19-related hospitalization or death were lower among the patients who received molnupiravir than among those who received a placebo (6.8% vs. 9.7%); however,

molnupiravir is contraindicated in pregnant women, or else contraception is needed in such women (24). Nirmatrelvir has antiviral efficacy against SARS-CoV-2 with inhibiting 3CL protease. In non-hospitalized adult patients with COVID-19 who had at least 1 characteristic or coexisting condition associated with a high risk of progression to severe disease, treatment with nirmatrelvir-ritonavir was observed to have an efficacy of 88.9% in relative risk reduction of COVID-19-related hospitalization or death from any cause at 28 days; however, it should be used with caution due to the numerous drug interactions (25).

The combination of casirivimab and imdevimab (REGEN-COV) and sotrovimab neutralize antibodies against SARS-CoV-2. REGEN-COV is a co-package of two recombinant anti-SARS-Cov-2 spike protein monoclonal antibodies derived from human IgG1 (26). Intravenous REGEN-COV at a dose of 1,200 mg reduced the risk of COVID-19-related hospitalization or death (relative risk reduction of 71.7%) and shorted the median time to resolution of COVID-19 symptoms (10 vs. 14 days) (27). *In vitr*o, this antibody combination was shown to minimize the likelihood of rapid viral escape (28). However, it was suggested that the Omicron variant is resistant to REGEN-COV (29). Sotrovimab is a neutralizing antibody derived from S309 that recognizes a glycan epitope conserved in the Sarbecovirus subgenus; therefore, it is thought to be less likely to develop resistance to mutations (30, 31). Sotrovimab was found to be effective in reducing the risk of hospitalization or death in patients with mild to moderate COVID-19 with high risk in a multicenter, double-blind trial (relative risk reduction 85%) (32).

Cases of COVID-19 treated with Kampo medicines have already been reported. A case series of COVID-19-related olfactory disorder, in which recovery was promoted by Kampo medicine, was reported (33). The study showed that KT and SSKKS are the most frequently used Kampo medicines. Irie et al. also reported a case series of COVID-19 patients treated with KT combined with SSKKS (10, 11). In the present study, the most frequently used Kampo medicines were also KT and SSKKS, which were also used in combination. KT is used to treat the common cold, fever, headache, neck stiffness, and diarrhea. KT extract granules for approved use in Japan contain a dried extract of seven crude drugs: JP Pueraria Root, JP Jujube, JP Ephedra Herb, JP Glycyrrhiza, JP Cinnamon Bark, JP Peony Root, and JP Ginger. Conversely, SSKKS, which is composed of shosaikoto, platycodon root, and gypsum, is used for treating pharyngeal tonsillitis. SSKKS extract granules for ethical use contain a dried extract of nine crude drugs: JP Bupleurum Root, JP Scutellaria Root, JP Ginseng, JP Pinellia Tuber, JP Jujube, JP Ginger, JP Glycyrrhiza, JP Platycodon Root, and JP Gypsum. We previously reported that KT combined with SSKKS has pharmacological effects, including antiviral, anti-inflammatory, immunomodulatory, and antioxidant activities [8]. These prior studies and the additional analysis in the present study suggest that Kampo medicine may be effective against mild-to-moderate COVID-19 for symptom recovery and to suppress illness worsening.

Regarding traditional medicine, the clinical efficacy of the Chinese drug Qing Fei Pai Du Tang (QFPDT) has also been reported. In their observational study, Wang et al. reported that, among 98 patients treated with QFPDT for 9 days, 91.6% experienced relief from their major symptoms (34). Zhang et al. reported that QFPDT administration is associated with a substantially reduced risk of in-hospital mortality in patients with COVID-19 (35). However, the efficacy of QFPDT has been investigated only in observational studies; RCTs of QFPDT are therefore necessary. In the present study, makyokansekito and gokoto were also well-prescribed. The components of crude drugs used in these Kampo medicines are similar. Furthermore, similar compositions of makyokansekito and gokoto are also included in QFPDT. This can be considered to indicate a similarity between traditional Chinese and Kampo medicines in terms of the treatment strategy against COVID-19.

There are 148 types of Kampo products that can be prescribed under the national health insurance system in Japan. The incidence of adverse reactions to Kampo medicines was reported in the Japanese Adverse Drug Event Report database (36). Adverse drug events with KT, which was the most frequently used in the present study, included interstitial pneumonia with an incidence of 0.10, liver disorders with an incidence of 0.19, and pseudoaldosteronism with an incidence of 0.03 per 100,000 patients. In the present retrospective study, no remarkable adverse events associated with treatment for COVID-19 were reported. Since COVID-19-related symptoms varied and the symptoms changed in the spontaneous clinical course, the identification of symptoms associated with drugs or COVID-19 was difficult. Furthermore, almost all patients were followed up via remote consultation in the collaborating outpatient clinics, and although physicians confirmed that the symptoms changed, they did not follow up with blood sampling data.

Several limitations associated with the present study warrant mention. First, there was a limited number of RT-PCR tests that could be performed. From January 2020 to August 2020, the number of tests was insufficient to screen patients in Japan, so suspected COVID-19 cases were enrolled based on the physicians' judgment of a fever, prolonged symptoms, and exclusion by other tests. Second, this study was a multicenter retrospective observational trial; thus, the data were retrospectively registered. The background characteristics in the Kampo and non-Kampo groups varied. The relationship between the treatment and outcomes was able to be analyzed, but the level of proof of a cause-and-effect relationship elucidated via this design is considered to be poor. Third, the available drugs, including approved and unapproved drugs, changed over time; therefore, they were not uniform over the study period. Fourth, not all subtypes of SARS-CoV-2 could be identified, so the influence of subtypes could not be excluded. Fifth, as mentioned above, the safety assessment was insufficient. Since this was an observational study, the interpretation of the results was prelimi-

nary and limited, RCTs are warranted to address these limitations. The Japan Society for Oriental Medicine is an ongoing multicenter RCT to demonstrate the efficacy and safety of Kampo medicine for treating COVID-19 symptoms (37-39). In this RCT, KT and SSKKS have been selected as interventional medicines. This study will provide valuable information for COVID-19 treatment.

Importantly, Kampo medicine is inexpensive, which can help reduce medical expenses and provide economic medical benefits for flu patients (40). Furthermore, the product quality is highly controlled and is well-regarded internationally, with very low variability in products (41). In pandemic situations where medical treatment and distribution are restricted, Kampo medicine can be used inexpensively and widely to aid in infection control. The findings of our study also provide information that may guide drug repositioning of Kampo medicine to further combat the pandemic before the development of more vaccines and treatment drugs become available.

Conclusion

We demonstrated the clinical course of patients with mild- to moderate-stage COVID-19 who received treatment with conventional and Kampo medicines. The number of days of symptom relief was not significantly different between the Kampo and non-Kampo groups; however, in patients with confirmed COVID-19 who did not receive steroid treatment and initiated treatment within four days from the onset, the risk of illness worsening was significantly lower in the Kampo group than in the non-Kampo group. More RCTs are warranted to further evaluate the benefits of Kampo medicine against COVID-19.

Author's disclosure of potential Conflicts of Interest (COI).
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References

1. World Health Organization Novel Coronavirus (2019-nCOV) situation report-1 (2019) [Internet]. [cited 2021 Dec 31]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf
2. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. [cited 2021 Dec 31]. Available from: https://gisanddata.maps.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6
3. World Health Organization. Coronavirus disease (COVID-19) pandemic [Internet]. [cited 2021 Dec 31]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
4. US Centers for Disease Control and Prevention. Symptoms of COVID-19 [Internet]. [cited 2021 Dec 31]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
5. Wu J, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA **323**: 1239-1242, 2020.
6. Ministry of Health, Labour and Welfare. Guide to medical treatment for COVID-19 version 6.0 [Internet]. [cited 2021 Dec 31]. Available from: https://www.mhlw.go.jp/content/000851082.pdf
7. Nabeshima S, Kashiwagi K, Ajisaka K, et al. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. J Infect Chemother **18**: 534-543, 2012.
8. Arita R, Ono R, Saito N, et al. Kakkonto, shosaikoto, *Platycodon grandiflorum* root, and gypsum (a Japanese original combination drug known as saikatsugekito): pharmacological review of its activity against viral infections and respiratory inflammatory conditions and a discussion of its applications to COVID-19. Tradit Kampo Med **7**: 115-127, 2020.
9. Takayama S, Kikuchi A, Makino T, Kainuma M, Namiki T, Ito T. Basic pharmacological mechanisms and clinical evidence of the efficacy of hochuekkito against infectious diseases and its potential for use against COVID-19. Tradit Kampo Med **8**: 3-21, 2021.
10. Irie Y, Nakae H, Fukui S. Three mild cases of coronavirus disease 2019 treated with saikatsugekito, a Japanese herbal medicine. Tradit Kampo Med **8**: 111-114, 2021.
11. Irie Y, Nakae H, Fukui S. Treatment of coronavirus disease 2019 with saikatsugekito: a case series. Tradit Kampo Med **8**: 211-220, 2021.
12. Takayama S, Kashima M, Namiki T, et al. Conventional and Kampo medicine in the treatment of mild to moderate COVID-19: a multicenter, retrospective observational study protocol by the integrative management in Japan for epidemic disease (IMJEDI study-observation). Tradit Kampo Med **8**: 106-110, 2021.
13. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA **325**: 1426-1435, 2021.
14. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med **385**: e81, 2021.
15. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs. placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA **324**: 2292-2300, 2020.
16. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med **385**: e81, 2021.
17. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med **385**: 1941-1950, 2021.
18. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the

treatment of COVID-19 - final report. N Engl J Med **383**: 1813-1826, 2020.

19. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med **384**: 795-807, 2021.

20. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA **324**: 1307-1316, 2020.

21. Horby P, Lim WS, Emberson JR, et al.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. Trial N Engl J Med **384**: 693-704, 2021.

22. US Centers for Disease Control and Prevention. Science brief: evidence used to update the list of underlying medical conditions associated with higher risk for severe COVID-19 [Internet]. [cited 2021 Dec 31]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html

23. Toots M, Yoon JJ, Cox RM, et al. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. Sci Transl Med **11**: eaax5866, 2019.

24. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med **386**: 509-520, 2022.

25. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitialized adults with COVID-19. N Engl J Med **386**: 1397-1408, 2022.

26. Deeks ED. Casirivimab/imdevimab: first approval. Drugs **81**: 2047-2055, 2021.

27. Weinrech DM, Sivapalasingam S, Norton T, et al. REGEN-CoV antibody combination and outcome in outpatients with COVID-19. N Engl J Med **385**: e81, 2021.

28. Copin R, Baum A, Wloga E, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. Cell **184**: 3949-3961.e11, 2021.

29. Tatham L, Sharp J, Kijak E, et al. Lack of ronapreve (REGN-CoV; casirivimab and imdevimab) virological efficacy against the SARS-CoV-2 omicron variant (B.1.1.529) in K18-hACE2 mice. bioRxiv. Forthcoming.

30. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature **583**: 290-295, 2020.

31. Tuccori M, Ferraro S, Convertino I, et al. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. MAbs **12**: 1854149, 2020.

32. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med **385**: 1941-1950, 2021.

33. Takayama S, Arita R, Ono R, et al. Treatment of COVID-19-related olfactory disorder promoted by kakkontokasenkyushin'i: a case series. Tohoku J Exp Med **254**: 71-80, 2021.

34. Wang R, Yang S, Xie C, et al. Clinical efficacy of Qing Lung detoxification in the treatment of novel coronavirus pneumonia. Pharmacol Clin Chin Mater Med 36, 2020 (in Chinese).

35. Zhang L, Zheng X, Bai X, et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: a national retrospective registry study. Phytomedicine **85**: 153531, 2021.

36. Arai I, Harada Y, Koda H, Tsutani K, Motoo Y. Estimated incidence per population of adverse drug reactions to Kampo medicines from the Japanese adverse drug event report database (JADER). Tradit Kampo Med **7**: 1, 2019.

37. Takayama S, Namiki T, Odaguchi H, et al. Prevention and recovery of COVID-19 patients with Kampo medicine: review of case reports and ongoing clinical trials. Front Pharmacol **12**: 656246, 2021.

38. Namiki T, Takayama S, Arita R, et al. A structured summary of a study protocol for a multi-center, randomized controlled trial (RCT) of COVID-19 prevention with Kampo medicines (integrative management in Japan for epidemic disease by prophylactic study: IMJEDI P1 study). Trials **22**: 23, 2021.

39. Takayama S, Namiki T, Ito T, et al. A multi-center, randomized controlled trial by the integrative management in Japan for epidemic disease (IMJEDI study-RCT) on the use of Kampo medicine, kakkonto with shosaikotokakikyosekko, in mild-to-moderate COVID-19 patients for symptomatic relief and prevention of severe stage: a structured summary of a study protocol for a randomized controlled trial. Trials **21**: 827, 2020.

40. Arita R, Yoshino T, Hotta Y, et al. National cost estimation of maoto, a Kampo medicine, compared with oseltamivir for the treatment of influenza in Japan. Tradit Kampo Med **3**: 59-62, 2015.

41. Arai I, Kawahara N. Kampo pharmaceutical products in the Japanese health-care system: legal status and quality assurance. Tradit Kampo Med **6**: 3-11, 2018.