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Original Research Article (Clinical)

A pilot clinical study of an add-on Ayurvedic formulation containing *Tinospora cordifolia* and *Piper longum* in mild to moderate COVID-19

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ABSTRACT

Background: After declaration of COVID- 19 as pandemic by WHO, countries adopted several measures to contain the spread as well as test and treat the patients. Further, as no effective management protocols to address this pandemic were available, a need was felt to explore the integration of modern and traditional medicines to treat COVID- 19 cases.
Objective: To undertake a study with Ayurveda formulation as add on to existing standard of care (SOC) and to compare the outcomes in terms of patient acceptability, the time to clinical recovery, hospital stay as well as any signs of drug-herb interaction between the Ayurveda formulation and the SOC.
Material and methods: An exploratory nonrandomized prospective study has been undertaken for comparing the outcomes of traditional Ayurvedic classical formulation of *Tinospora cordifolia (Guduchi)* and *Piper longum (Pippali)* as an add on to standard of care (SOC) using modern medicine with SOC alone. This has been done in mild and moderate COVID- 19 cases, at a tertiary care integrative Medicine hospital in the National Capital Region, Gurgaon, India. The outcomes have been evaluated in terms of the duration of hospital stay, the time to clinical recovery, safety and non- interference/interaction of Ayurvedic and Further, long term impact of COVID- 19 treatment has been evaluated using quality of life questionnaire after 3 months of discharge.
Results: Findings of present study reveals that the Ayurveda add-on formulation of *T. cordifolia (Guduchi)* and *P. longum (Pippali)* has reduced the length of hospital stay and improve the recovery time. General feeling of wellbeing and activity levels were better in the 3 month follow-up post discharge in the Ayurveda add-on group.
Conclusion: Addition of Ayurveda formulation has reduced the time of recovery and duration of hospital stay. However, this formulation needs further investigated to provide more information on effective and safe herbal add-on to SOC for better outcomes to treatment of COVID-19 disease.

1. Introduction

Alarming levels of spread and severity of disease forced the WHO to declare COVID-19 a pandemic on March 11, 2020 and no country has since been safe from its wrath. Countries have adopted several measures to detect, test, treat, isolate, and trace in order to stop the disease transmission and contain the spread among its populations. As there is no current standard best practice to treat the disease, countries are working with all resources in the arsenal [1].

There are claims from various quarters, especially from Traditional Chinese Medicine (TCM) and Korean oriental medicine for COVID-19 treatment. [2,3]. Announcement was made of the first version of Oriental Medicine Clinical Practice Guideline by the National University Network of Traditional Medicine Department of Internal Medicine [4] and Indian Systems of Medicine, collectively known as AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) [5]. Ayurveda is an experiential, intuitive, and

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holistic, whereas that of the modern medicine is based more on experimental, analytical, and reductive reasoning [6].

Ministry of Health and Family Welfare (MoHFW), Govt of India has published several clinical management protocols to standardize COVID care over the months of March, April, May, and June and have modified them in line with the international current best practices [7]. Ministry of AYUSH, Govt of India has also released several guidelines to each of its practitioners that suggest preventive and precautionary strategies [8]. Ayurveda has potential and possibilities to be employed both for prevention and treatment of COVID-19.

Ayurvedic texts have proposed models to predict outbreaks and propagation of epidemics as well as general guidelines for prevention and management of epidemics. The Susruta Samhita, one of the classical text books of Ayurveda has described the possibility of epidemic outbreaks of severe respiratory illnesses exhibiting a spectrum of symptoms like cough, breathing difficulties, fever, headache, running nose, and even anosmia (which is a symptom that has been reported in a subset of COVID-19 patients) [9].

An Ayurvedic assessment of the disease can help to classify the clinical presentations of COVID-19 on the basis of the *Tridosa* (three *dosa* which are *Vata*, *Pitta*, and *Kapha*) which forms the framework and logic around which Ayurveda understands disease and health. The standard methodology of deciphering the *dosa* base of the pathology through signs and symptoms using the algorithm of Ayurveda logic is equally applicable in understanding the disease spectrum of COVID-19 infection [10]. At present, based on the available data, we have some preliminary understanding of the stages and the sub-stages of the pathogenesis of the disease. Our preliminary analysis of the clinical and laboratory data of 17 patients (14 Italian + 3 Indian) has helped us profile this disease as '*Aganthuja Vatha Kapha Pradhana Sannipathika Jwara*'.

According to Ayurveda [11], the specific medication prescribed for the above pattern of *dosa* presentation and diagnosis is a combination of *Tinospora cordifolia* (*Guduchi*) and ***Piper longum*** (*Pippali*). Both the herbs are very well studied and documented and are abundantly available in the Indian sub-continent.

2. Materials and methods

2.1. Study design

COVID-19 *Guduchi* and *Pippali* (COVIDGAP) was undertaken at an integrated tertiary care facility in National Capital Region to evaluate the impact of a classical formulation (*Guduchi* and *Pippali*) as an add-on to Standard-of-Care (SOC) modern medicine in an integrative mode of management compared to SOC alone in mild and moderate, RT-PCR-confirmed COVID-19 positive patients. The study was conducted in two phases. In Phase I, 30 participants were enrolled in SOC + Ayurveda group by June 2020 and thereafter, 30 participants were recruited in the SOC group (Fig. 1). The study was conducted between 27th May 2020 and 3rd July 2020.

Study participants: Participants aged ≥18 years were eligible, based on their RT-PCR tested-positive or a mild and moderate COVID-19 disease according to MoHFW guidelines. All participants were admitted to the hospital, based on the severity of disease as per investigator's discretion.

Participants who had no severe or critical stages of the disease, and were willing to consume Ayurveda medicine, and signed the informed consent for the same, and had no known allergies to the various drug components were considered eligible.

Participants were excluded if they had severe COVID-19 disease and other immunosuppressant disease as per investigator's discretion.

Participants provided written consent prior to participate in study specific activates, and the protocol was approved by Institutional Ethics Committee. Considering the study design, safety of participants was also monitored by an Ayurvedic physician along with Allopathic team. The study was registered with the CTRI number: 2020/04/024882. All participants were discharged from facility in compliance with discharge policy of the MoHFW. The study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki, and local regulatory requirements. After and additional ethics committee review in November 2020, an extended follow-up by telephonic visit was scheduled for all participants to identify sequalae, or prolongation of symptoms if any.

2.2. Inclusion and exclusion criteria

Participants who had no severe or critical stages of the disease, and were willing to consume Ayurveda medicine, and signed the informed consent for the same, and had no known allergies to the various drug components were considered eligible.

Participants were excluded if they had severe COVID- 19 disease and other immunosuppressant disease as per investigator's discretion.

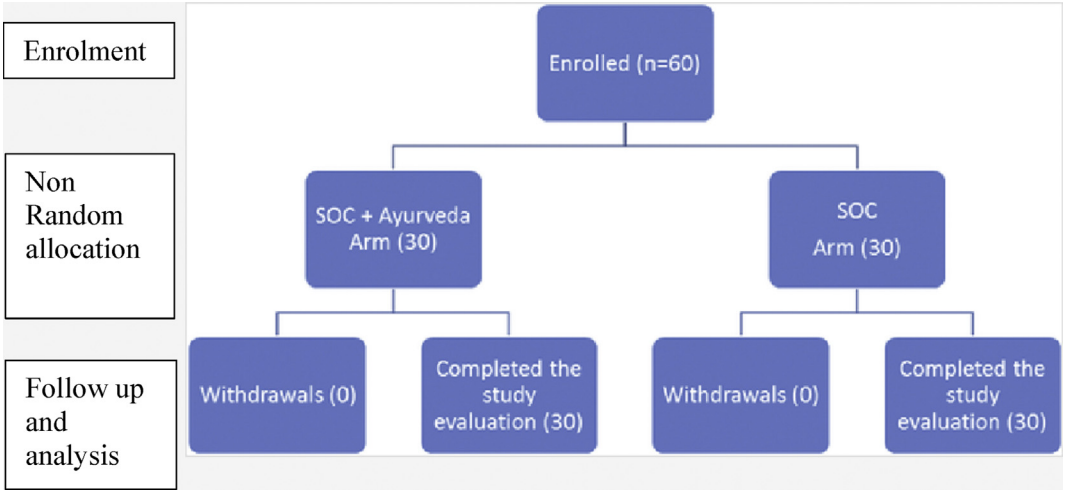

Fig. 1. CONSORT flow diagram.

2.3. Preparation and administration of medicine

The drug dosage form called *Kashaya* (decoction) was given as a daily dose of 180–200 ml, made up of two equal doses of 90–100 ml each, once in the morning before breakfast and once in the evening, before dinner to all participants enrolled in Phase I of the study. CCRAS sourced the study formulation from the market from licensed Ayurvedic manufacturers; *T. cordifolia* stem powder was manufactured by M.P. State Co-operative undertaking unit and *Pippali* choorna was produced by IMPCL. The *Kashaya* were freshly prepared for each dose as follows: 25 g of dry *T. cordifolia* stem powder shall be boiled in 400 ml water till only 100 ml water remains. This *Kashaya* is strained and filtered to discard the solid part and mixed with two 2 g ($^1/_3$ teaspoon) of finely powdered dried *P. longum* fruit [12]. This is one dose of the medicine.

The drug was administered by the duty nurses at the patient bed-side. The treating modern medicine physician reserved the full authority to withhold the drug temporarily or withdraw the drug altogether at their discretion. All participants in Phase I were administered the *T. cordifolia* and *P. longum* combination, until discharge. In Phase II (comparator arm) participants on SOC medicines were considered.

2.4. Safety

Safety evaluation included physical examination, assessment of vital signs, clinical assessment, laboratory investigations, RT-PCR negativity and reporting of adverse events. The patients discharged were followed after three months to inquire about their health telephonically. The subjects were asked for their feedback on the following though a validated questionnaire, conducted by trained personnel.

i. General Health
ii. Limitations on Activities
iii. Emotional and Psychological Health Problems
iv. Specific Health Problem (Cardiac and Dermatological)

Ayurveda physician evaluated the patient and progression of the disease and its different stages based on the COVID19 Objective Clinical Severity Score (COCSS) data.

Clinical research coordinators having Master's degree in clinical research were responsible for obtaining feedback from COVID-19 discharged patients.

2.5. Study endpoints

The endpoint of the study was of hospital stay, the time to clinical recovery as well as patients whose condition worsened (severity of disease) as an exploratory outcome. We also evaluated for patient acceptability and any signs of drug-herb interaction between the study formulation and the SOC.

2.6. Statistical methods

The analysis included profiling of patients on different demographic, clinical, length of hospital stay, concomitant medications as well as quality of life in terms of general health, limitations on activities, emotional and psychological health problems and specific health problem (cardiac and dermatological) at 3 months. A detailed analysis was undertaken on both SOC and SOC + Ayurveda groups. Descriptive analysis of quantitative parameters were expressed as means and standard deviation. Categorical data were expressed as absolute number and percentage. Independent Student t-test was used for testing of mean difference between study groups. Cross-tables were generated and Chi-square test or normal variate Z test were used for testing of associations. p-value <0.05 is considered statistically significant. All analysis were done using SPSS software, version 24.0. IBM Bangalore India.

3. Results

3.1. Profile of subjects

Table 1 presents the distribution of subjects in SOC + Ayurveda and SOC groups according to gravity category of COVID-19 illness.

It was observed that 29 participants in each of the two groups were either asymptomatic or mildly symptomatic. Only 1 participant in each arm was moderately symptomatic. Thus, the participants covered in two groups were comparable (Table 1).

The reason for the smaller number of asymptomatic patients in the SOC group is that we started recruitment for the SOC group late in June, 2020, by which time the MoFHW regulation permitted home-care for asymptomatic cases and most people opted for the same. It should also be noted that the Ayurveda add-on group had been recruited and cared for in the initial period of the pandemic and therefore, had mandatorily spent more time in the hospital in comparison to the SOC group, who were recruited later in the study, owing to the revised provisions in the COVID-19 care protocol published by the government.

The groups were comparable by gender ($p = 0.796$) (Table 2).

The patients in SOC group were relatively of younger age (29.7 ± 7.3 years) as compared to SOC + Ayurveda group (38.7 ± 15.4 years) ($p = 0.005$) (Table 3).

3.2. Duration of treatment/hospital stay

One of the important outcome parameters is the duration of hospital stay. Table 4 provides the results on duration of hospital stay for subjects in two arms and the statistical significance of difference.

It is seen that the average hospital stay was lower (5.5 ± 2.4 days) for SOC + Ayurveda group as compared to SOC group (6.9 ± 3.1 days). The difference was 1.4 days, which was statistically significant ($p = 0.027$, one-tailed) (Table 4).

3.3. Sub-group analysis with COVID-19 medications (SOC)

The patients of both the SOC + Ayurveda and SOC groups have been categorized into five sub-groups based on the SOC given to them:

Table 1
The category of illness in accordance with MoHFW guidelines at baseline.

Category of patients	Gravity of clinical presentation	
	SOC + Ayurveda group (n = 30)	SOC group (n = 30)
Asymptomatic	13 (43.3%)	6 (20.0%)
Mild	16 (53.4%)	23 (76.7%)
Moderate	1 (3.3%)	1 (3.3%)

Chi square value = 3.835; p-value = 0.147.

Table 2
Distribution of patients by gender.

Gender	SOC + Ayurveda group (n = 30)	SOC group (n = 30)
Male	15 (50.0%)	16 (53.3%)
Female	15 (50.0%)	14 (46.7%)

Chi square value = 0.067; p-value = 0.796.

Table 3
Distribution of patients by age (years).

Age (years)	SOC + Ayurveda group (n = 30)	SOC group (n = 30)	Chi square/t-value	p-value
≤30	12 (40.0%)	18 (60.0%)	6.021	0.049[a]
31–40	7 (23.3%)	9 (30.0%)		
>40	11 (36.7%)	3 (10.0%)		
Mean ± SD	38.7 ± 15.4	29.7 ± 7.3	−2.892	0.005[a]

[a] p-value < 0.05, statistically significant.

Table 4
Length of hospital stay (days).

Length of hospital stay (days)	SOC + Ayurveda group (n = 30)	SOC (n = 30)	Difference	p-value
Mean ± SD	5.5 ± 2.4	6.9 ± 3.1	1.4	0.027[a] (one tailed)

[a] p-value < 0.05, statistically significant.

Table 5
Duration of hospital stay in the two groups according to concomitant medications used as SOC for COVID management.

SOC	SOC + Ayurveda group		SOC group	
	n = 30	Mean duration of hospital stay (in days)	n = 30	Mean duration of hospital stay (in days)
HCQ alone	14	5.8	12	6.2
HCQ + antibiotic/HCQ + antibiotic + antipyretic	5	4.8	2	7.5
HCQ + antipyretic	6	5.8	3	7.3
Antibiotic + antipyretic	2	4.0	1	15.0
No COVID related medicine was given	3	6.3	12	6.7

i. HCQ alone;
ii. HCQ + antibiotic/HCQ + antibiotic + antipyretic;
iii. HCQ + antipyretic;
iv. Antibiotic + antipyretic and,
v. No COVID related medicine given.

Table 5 provides the details on duration of hospital stay according to concomitant medication used together with number of patients in each group.

It may be noted that irrespective of the sub-categorization based on the allopathic medicine prescribed for COVID-19, across all sub-groups the Ayurveda add-on (SOC + Ayurveda) group had shorter duration of stay (mean number of days) in the hospital compared to the SOC (SOC + Ayurveda) group. Table 6 clearly shows this advantage in the Ayurveda add-on group and is reflecting even in the sub-group where no allopathic medication was given. It should be noted that the higher number of 'No medications given' (n = 12) in the SOC group in comparison to the add-on group (n = 3) is reflective of the change in prevalent COVID management protocol at the time the respective patients were admitted in the hospital. Nevertheless, it was interesting to note that, despite the mandatory extensive hospitalization requirements during the months of April and May (2020), the mean value of the number of days of hospitalization in patients who received no allopathic medication for COVID is shorter in the Ayurveda add-on sub-group.

3.4. Sub-group analysis with concomitant medications

Table 6 present the results according to HCQ used in concomitant medications used in the two groups. Considering the primacy given to the drug HCQ in the management of COVID-19 disease from the initial phase of the pandemic, we also did an analysis of the number of days of hospitalization of patients in both groups categorizing them based on the use of HCQ in their COVID-19 management. It is evident that in both the categories the patients in the Ayurveda add-on group had shorter duration of stay at the hospital in terms of mean number of days. Further, among these two sub-categories of patients, those who received HCQ seemed to have spent lesser number of days in the hospital.

3.5. Recovery time

Fig. 2 provides information on time to recovery for both the groups.

It is observed from the Fig. 2, that the patients in the Ayurveda group started getting discharged from day 3 of admission and all were discharged by the 11th day. On the contrary in the SOC group, the patients started discharging on day 4 and continued till day 14 for getting discharged. The average time of discharge for SOC + Ayurveda group (6.6 ± 2.4 days) was less than 1 day as compared to SOC group (7.6 ± 2.7 days).

Table 6
Duration of hospital stay in the two groups according to HCQ and no HCQ given.

Medicines prescribed	SOC + Ayurveda group		SOC group		t-value	p-value
	n	Mean ± SD	n	Mean ± SD		
HCQ given alone or with other antibiotic and antipyretic	25	5.6 ± 2.3	17	6.5 ± 2.4	1.207	0.235
HCQ not given	5	5.4 ± 3.1	13	7.3 ± 3.8	0.989	0.337

*p-value < 0.05, statistically significant.

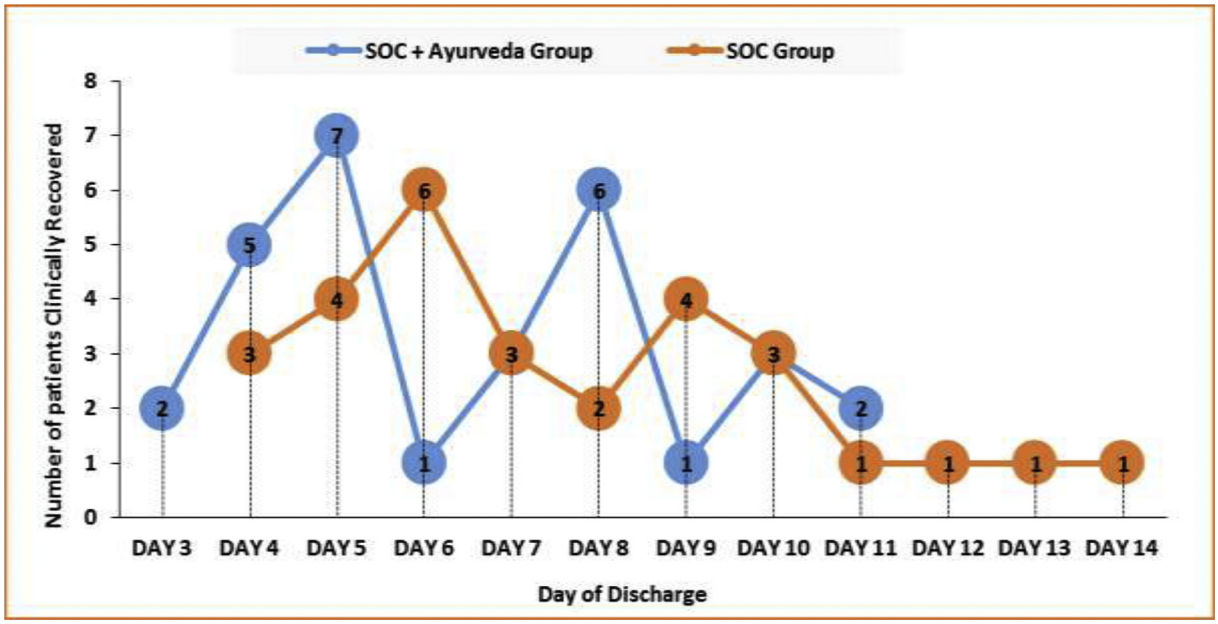

Fig. 2. Time to absence of clinical symptoms of COVID-19 and discharge from hospital.

3.6. Drug interactions and safety

Data regarding movement of patients to upward severity categories, adverse drug reactions, drug-herb interactions and mortality were analyzed for each of the two groups. The salient findings are as under:

- No patients in either of the groups moved upwards in the classification of severity and all were discharged, alive and well from the hospital.
- There was no mortality reported.
- There were no adverse drug reactions observed and reported in this study.
- No case of drug–herb interaction causing deterioration of clinical condition or quality of life of the patient was reported in the Ayurveda add-on group.
- 28 patients in the Ayurveda add-on group reported the Ayurvedic drug as acceptable and 2 reported it as being very bitter.

3.7. Quality of life after discharge

The patients discharged were followed after three months to inquire about their health telephonically. The details of those who responded are given in Table 7.

It is noted that 28 in the SOC + Ayurveda group and 29 in SOC group responded to phone calls. The overall non-response was 5% which is within acceptable limits (Table 7).

The subjects were asked for their feedback on the following though a validated questionnaire, conducted by trained personnel.

i. General health
ii. Limitations on activities
iii. Emotional and psychological health problems
iv. Specific health problem (cardiac and dermatological)

The results are summarized in Table 8. The salient findings are as under:

- As to general health, relatively higher proportion in the SOC + Ayurveda group reported their health as 'Very Good' and 'Much better now since discharge' as compared to SOC group.
- As to the limitations on activities, higher percentage in the SOC group reported tiredness as compared to SOC + Ayurveda group. Relatively higher proportion in SOC group reported that work efficiency has been affected as compared to SOC + Ayurveda group.
- The problems of frequent headaches, sleep disorder, felt nervous and stressed, irritations and angered were reported 10–15% in both the groups. The problem of lack of confidence and coping were reported by none in both the groups.
- Respiratory, cardiac, dermatological (skin), burning feet related problems were reported less in SOC + Ayurveda group as compared to SOC group. The need for oxygen support at home after discharge from hospital was reported by none in both the groups.

Cardiac sequelae was not statistically significant between the SOC + Ayurveda and SOC groups ($p > 0.05$) (Table 9).

4. Discussion

The proportions of the pandemic require that all measures in a clinical arsenal be utilized to identify a solution. The utilization of

Table 7
Response to the 3-month exploratory follow up phone call.

	SOC + Ayurveda group (n = 30)	SOC group (n = 30)	Total (n = 60)
Responded	28 (93.3%)	29 (96.7%)	47 (95.0%)
Not responded	2 (6.7%)	1 (3.3%)	3 (5.0%)

Table 8
Summary statistics for the 3-month exploratory QOL questionnaire.

QOL questions	SOC + Ayurveda group (n = 20)	SOC group (n = 23)	Total (n = 43)
General health			
As for today, would you say your health is			
Excellent	8 (28.6%)	4 (13.8%)	12 (21.1%)
Very good	6 (21.4%)	4 (13.8%)	10 (17.5%)
Good	13 (46.4%)	19 (65.5%)	32 (56.1%)
Fair	1 (3.6%)	2 (6.9%)	3 (5.3%)
Compared to health status since discharge, how would you rate your health in general now?			
Much better now since discharge	18 (64.3%)	15 (51.7%)	33 (57.9%)
Somewhat better now since discharge	8 (28.6%)	10 (34.5%)	18 (31.6%)
About the same since discharge	0 (0%)	4 (13.8%)	4 (7%)
Somewhat worse now since discharge	2 (7.1%)	0 (0%)	2 (3.5%)
Much worse since discharge	0 (0%)	0 (0%)	0 (0%)
Limitations of activities			
During physical activities – walking for 10 min, climbing stairs, bending, kneeling, lifting weight do you experience any of the following since discharge			
Tiredness	6 (21.4%)	9 (31%)	15 (26.3%)
Breathlessness	6 (21.4%)	3 (10.3%)	9 (15.8%)
Weakness	7 (25%)	11 (37.9%)	18 (31.6%)
Muscular pain	1 (3.6%)	5 (17.2%)	6 (10.5%)
Other	1 (3.6%)	3 (10.3%)	4 (7%)
No limitations experienced	10 (35.7%)	13 (44.8%)	23 (40.4%)
Do you feel your work efficiency has been affected due to health issue since discharge?			
Yes, limited a lot	0 (0%)	0 (0%)	0 (0%)
Yes, limited a little	3 (10.7%)	5 (17.2%)	8 (14%)
No, not limited at all	25 (89.3%)	24 (82.8%)	49 (86%)
Emotional and psychological health problems			
Never experienced frequent headaches since discharge	25 (89.3%)	26 (89.7%)	51 (89.5%)
Never faced problems in sleep since discharge	25 (89.3%)	28 (96.6%)	53 (93%)
Never been upset because of something that happened unexpectedly since discharge	26 (92.9%)	28 (96.6%)	54 (94.7%)
Never felt nervous and "stressed" since discharge	18 (64.3%)	26 (89.7%)	44 (77.2%)
How often have you felt confident about your ability to handle your personal problems since discharge? Fairly often	20 (71.4%)	29 (100%)	49 (86%)
Never found that you could not cope with all the things that you had to do since discharge?	28 (100%)	29 (100%)	57 (100%)
How often have you been able to control irritations in your life since discharge? – Very often	26 (92.9%)	26 (89.7%)	52 (91.2%)
Never been angered because of things that were outside of your since discharge	26 (92.9%)	27 (93.1%)	53 (93%)
Health problems/sequelae			
No respiratory related issue/s since discharge	25 (89.3%)	23 (79.3%)	48 (84.2%)
No need for oxygen support at home since discharge	28 (100%)	29 (100%)	57 (100%)
No cardiac related issue/s experienced since discharge	24 (85.7%)	22 (75.9%)	46 (80.7%)
No dermatological issue/s experienced since discharge	25 (89.3%)	24 (82.8%)	49 (86%)
Never felt burning feet or hands since discharge	28 (100%)	28 (96.6%)	56 (98.2%)

Table 9
Cardiac sequelae.

Cardiac sequelae	SOC + Ayurveda group (n = 20)	SOC group (n = 23)	Total (n = 43)	p-value
Chest pain	1 (5%)	4 (17.4%)	5 (11.6%)	0.211
Fatigue	1 (5%)	6 (26.1%)	7 (16.3%)	0.065
Weakness	2 (10%)	2 (8.7%)	4 (9.3%)	0.885
Excess sweating	2 (10%)	1 (4.3%)	3 (7%)	0.469

the Traditional Chinese Medicine system have set an example that traditional and modern systems may be integrated in facing this challenge with increased efficacy. Sanjeev Rastogi et al proposed a pragmatic graded strategy for integration of Ayurvedic medicine to facilitate learning and evidence generation ***Tinospora cordifolia***, and ***Curcuma longa*** were identified by them for exposed, asymptomatic quarantined patients [13].

Our initial review of clinical symptomatology of the disease and its classification in accordance with Ayurvedic principles [14] identified Covid 19 disease as a *vātakapha* dominant *sannipātajvara* of *āgantu* origin with *pittānubandha*.

Both groups felt that with careful monitoring and data management many research directions are likely to emerge on the management of Covid disease.

Pankaj Wanjarkhedkar et al [15] in their study of tablets of *Dasamoolkaduthrayam Kashaya* and *Guluchyadi Kwatham* in patients with mild to moderate symptoms, compare to SOC appeared to accelerate recovery of patients hospitalized for COVID 19 infection, in terms of both reduction of symptoms and duration of hospital stay. These findings are similar to the current study where the addition of Ayurvedic Formulation of ***Tinospora cordifolia***, and ***Curcuma longa*** in mild –moderate covid disease resulted in shortened time of recovery, and showed safety and no interference with allopathic prescriptions.

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Conflict of interest

None.

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