

Effect of Adjunct Tele-Yoga on Clinical Status at 14 Days in Hospitalized mild and Moderate COVID-19 Patients: a Randomized Controlled Trial

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Abstract

Background: We tested if tele-yoga intervention could aid in better clinical management for hospitalized patients with mild to moderate COVID-19 when complemented with the standard of care.

Methods: This was a randomized controlled trial conducted at the Narayana Hrudalaya, Bengaluru, India on hospitalized patients with mild to moderate COVID-19 infection, enrolled between May 31st and July 22, 2021. Patients (n=225) were randomized in 1:1 ratio [adjunct tele-yoga (n = 113), or standard of care (n = 112)]. Adjunct yoga group received intervention in tele-mode within 4 hours post-randomization until 14 days along with the standard of care. The primary outcome was clinical status at 14th-day post-randomization assessed with a 7-category ordinal scale. The trial included 11 secondary outcomes, including 28-day mortality.

Results: As compared with standard of care alone, the proportional odds of having a higher score on the seven-point ordinal scale at day 14 was ~1.9 for the adjunct tele-yoga group (95% CI, 1.18-3.18). CRP and LDH levels were comparatively reduced in the adjunct tele-yoga group 5th day post-randomization. CRP reduction was also observed as a potential mediator for the improvement of clinical outcomes in the adjunct tele-yoga group. There were no significant differences between the treatment groups concerning the duration of hospitalization, all-cause mortality at day 28; log-rank P = 0.144, and other outcomes.

Conclusion: The observed clinically relevant outcomes in COVID-19 patients at day 14 contest the use of tele-yoga as a complementary treatment in hospital settings.

Introduction

The rapid global spread of the Corona virus-related pneumonia outbreak, which was described first in December 2019, has led to the evolution of one of the most extensive pandemics in human history so far.¹⁻³ Though, the mainstay of treatment¹⁻³ for patients with COVID-19 pneumonia remains symptomatic and supportive care,⁴⁻⁶ the devastating impact of the pandemic led to a parallel unprecedented quest of identifying new and/or repurposed pharmacological treatments.⁵⁻¹⁰ Unfortunately, the initial indications from these studies were disappointing which further aggravated the search of strategies based on complementary and alternative medicine.⁵⁻¹¹ Amidst this uncertainty, several key clinicians and scientists identified and proposed the adjunct potential of yoga for enhancing the effectiveness of standard of care with respect to Covid management in acute settings.¹² Authors emphasized the relevance of certain practices of yoga and meditation in helping reduce the severity of COVID-19 disease, including its collateral effects and sequelae,¹² further underlined with the immunomodulatory, anti-inflammatory and stress modulatory potential of yoga.¹³⁻¹⁵ Hence, we conducted this clinical trial to address the necessity of testing the effectiveness of adjuvant tele-yoga to the standard of care in improving the clinical outcomes for adults hospitalized with COVID-19. This trial was supported under a special call announced by the Department of Science and Technology, Government of India under the scheme, Science and Technology of Yoga and Meditation (SATYAM).¹⁶

Design And Amendments

The protocol was approved by the institutional ethics committee from each site and conducted in compliance with the Declaration of Helsinki. The study protocol was approved for funding by Department of Science and Technology, Government of India (Appendices no. I and IV). Additionally the study was also approved in a high level committee meeting conducted by Government of Karnataka, India to ensure control and management of COVID-19 outbreak. All patients or legally authorized representatives provided the written informed consent. Given the uncertainty in the recruitment and random allocation of the study subjects in chaotic hospital settings amidst the pandemic, the trial was initially planned as a non-randomized one. and their presumed lack of was initially planned as a non-randomized clinical trial wherein an integrative yoga based supportive care was planned to be administered as an adjunct intervention for hospitalized COVID-19 patients. However, the protocol was amended on 14th May 2020, on the basis of emerging feasibility of conducting a randomized trial as emphasized by the clinicians and its superior design. The study was registered at clinical trial registry of India (CTRI/2020/09/027915).

Participants:

Given a significant proportion of requirement of timely hospitalization and management of Covid 19 patients, we recruited hospitalized COVID-19 patients in this trial. Those with moderate disease along with the presence of comorbidities, or those with initially mild disease but experiencing worsening of symptoms or depletion of oxygen saturation were referred and managed at the Mazumdar Shaw Medical Center, Narayana Hrudalaya, Bengaluru, India. Laboratory confirmed SARS-CoV-2 cases defined as mild or moderate according to FDA guidance were included with following eight symptoms:¹⁷ fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, and shortness of breath with exertion. Additionally we also included the moderate disease definition of respiratory rate $\geq 15 < 30$ and/or partial $90-94\%$.¹⁸ In line with prior reports, this trial enrolled patients with mild and moderate COVID-19 who were receiving no more than 4 liters per minute of supplemental oxygen.¹⁹ Notable exclusion criteria included a peripheral oxygen saturation of 93% or less while breathing ambient air, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 300, a respiratory rate of at least 30 breaths per minute, and a heart rate of 125 or more beats per minute. Full eligibility criteria are listed in eTable 2 in Supplement 3.

Outcomes:

We used the 7-category ordinal scale used that has been used in different COVID-19 therapeutic trials.^{7,20} The primary outcome was clinical status at day 14th post-randomization, assessed with a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization.²⁰ The scale consisted of 7 mutually exclusive categories: 1, death; 2, hospitalized, receiving extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; 3, hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy; 4, hospitalized, receiving supplemental oxygen without positive pressure or high flow; 5, hospitalized, not receiving supplemental oxygen; 6, not

hospitalized and unable to perform normal activities; and 7, not hospitalized and able to perform normal activities. To distinguish between categories 6 and 7, study personnel assessed the patient's performance of usual activities with questions consistent with validated health status measures.²¹

Patients who were discharged from the hospital were contacted by tele-phone for assessment of the COVID Outcome Scale at 7, 14, and 28 days after randomization. Complete information on the inclusion and exclusion criteria is provided in the Supplementary Appendix. All the patients provided written or electronic informed consent before randomization. The secondary outcome set included: scores on the COVID Outcomes Scale at days 7, and 28 post-randomization; all-cause all-location mortality at 28 days post-randomization, duration of days at hospital, 5th day changes postrandomization for viral load expressed as cyclic threshold (Ct), and inflammatory markers and perceived stress scores at day 14 postrandomization. Other auxillary markers were HbA1c, blood hemogram, kidney function markers, etc. All protocol amendments were authorized and approved by the institutional review board or independent ethics committee.

Clinical and Laboratory Monitoring:

Assessments:

Data were collected daily, from randomization until day 14, in the patient proformas. For patients who were discharged before day 14, a structured tele-phone call to the patient or the patient's family was conducted on or after day 14 by an interviewer who was unaware of the assigned trial group in order to assess vital status and return to routine activities.. All samples were processed by PCR for genes N and E of SARS-CoV-2. Demographic, clinical, laboratory, and radiology data from patients' medical records were collected by the research team. The data were evaluated by a trained team of physicians. The date of disease onset was defined as the day when the symptom was noticed. Data on symptoms, vital signs, laboratory values on biomarkers of disease progression, biomarkers [C-reactive protein (CRP), D-Dimer, Interleukin 6 (IL-6), ferritin, and Lactate dehydrogenase (LDH)], and treatment measures during the hospital stay were collected. Patient assessments included physical examination, respiratory status (respiratory rate, type of oxygen supplementation, blood oxygen saturation, and radiographic findings), adverse events, and concomitant medications. On study days 1, and 5, blood samples were obtained for measurement of blood cell counts, serum creatinine, glucose, total bilirubin, and liver transaminases, and inflammatory biomarkers. Perceived stress was assessed using Perceived Stress Scale 10 (PSS-10).²² Site investigators assessed clinical status daily from day 1 through day 14 or hospital discharge on a 7-point ordinal scale. In case of over a day change in the scores observed for the clinical status worse scores of the hospitalized patients were documented. A final assessments on clinical status were done on the day 28 personally for hospitalized patients or through tele-phonc interview for already discharged patients.

Intervention:

We built a yoga protocol adjusted to isolated patients and staff, including delivery through tele- (videos) as well as in person intervention. Clinical guidelines were followed up for treating patients via tele-yoga and hands on techniques in cooperation with the medical heads of departments. Instructional short videos were prepared in different languages constituting the intervention. At day 1 hands on intervention was carried out in the COVID wards through teams of certified yoga therapists in personal protective suites, within 4 hours of randomization. Those who were discharged before 14 days post-randomization, tele-yoga sessions were continued from their home settings. The practices of yoga were included based on the reported effects on strengthening of the respiratory muscles, and respiratory function [development of awareness of expansion and contraction of the airways, continuous and rhythmic breathing, reported to aid in thorough oxygenation of the lungs etc] and also known to reduce inflammation. (For details on the intervention see the appendices I and V). These exercises were followed by quick relaxation and subsequent 10 minutes of pranayama (breathing exercises), consisting of right nostril breathing/and alternate nostril breathing and Brahmari. The practice sessions ended with guided relaxation with a resolve. Patients received daily tele-yoga intervention with relaxation/meditative practices for twice for day.

Standard of Care:

Standard of care was based on the recommendations of the Indian Council of Medical Research, which was updated as per the evolving evidence generated in drug trials and international consensus guidelines.^{23,24} Overall, it included antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants at the discretion of the clinicians.

Randomization

Randomization was done in permuted blocks of 4 in sequences created by the unblinded research staff in Microsoft Excel version 19.0 who provided masked allotment to the yoga trainers. Owing to the nature of the intervention, blinding was not possible, but outcome measures were blinded for the randomisation groups. Eligible patients were randomly assigned in a 1:1 ratio to receive either standard of care or adjunct yoga. Allocation assignment was concealed from investigators and patients.

Statistical analysis:

Analysis was performed with SPSS version 23 [IBM Corp., (N.Y., USA)]. The total intent-to-treat (ITT) sample size of 230 patients with a 1:1 randomization of adjunct tele-yoga to standard of care provides approximately 80% power to detect a 15% difference between treatment groups in time cumulative hospital discharge (i.e.,with or without limiting abilities) rates of 80% in the adjunct tele-yoga group and 75% in standard of care group, at 14th day postrandomization, using a two-sided 5% alpha. The trial was analyzed by comparing patients randomized to adjunct tele- yoga vs those randomized to standard of care, with the placebo group serving as the referent. The primary outcome was analyzed with a multivariable proportional odds model with age, and sex. Further adjustments with baseline (prerandomization) COVID Outcomes Scale category, and duration of acute respiratory symptoms are reported as posthoc analysis. Results are presented with corresponding 95% confidence intervals For

patients who were discharged prior to 14 days after randomization, primary outcome ascertainment was completed by tele-phone calls. Patients who could not be reached by tele-phone for the primary outcome assessment at day 14 had the COVID Outcomes Scale score carried forward from a day 7 follow-up call if such a call was successfully completed or had a category 6 score (not hospitalized and unable to perform normal activities) imputed if no prior follow-up calls were successfully completed. For patients who remained hospitalized 14 days after randomization, primary outcome ascertainment was completed by medical record review.

Given the deviation from normality for the study variables, analysis of covariance was done using the rank transformation to study the influence of adjunct tele-yoga intervention on biomarker levels at day from postrandomization.

Heterogeneity of treatment effect by prespecified baseline characteristics was evaluated by adding an interaction term between randomized group assignment and the baseline characteristic of interest in the primary model. Baseline characteristics evaluated in heterogeneity of treatment effect analyses included baseline COVID Outcomes Scale category, and duration of symptoms prior to randomization, age, sex, and race/ethnicity.

All-cause mortality was estimated using the Kaplan-Meier product limit method. Adjunct tele-yoga group was compared with the standard of care group using the log-rank test, and the mean estimates and 95% CIs were provided.

We also used the `paramed` command in SPSS to perform mediation analysis by fitting a linear regression model to the outcomes with yoga treatment and the mediators included were the covariates and then fitting a regression model to the mediator (linear or logistic depending on the mediator) including treatment as a covariate.

Post Hoc Analyses

We also conducted sensitivity analyses of the primary end point (1) adjusting for day 1 clinical score; and (2) adjusting for duration of symptoms. Additionally we also performed a post-hoc analysis that was stratified by CRP and LDH levels. We also calculated and compared the proportions of patients with a 1-point or greater improvement, no change or worsening of clinical status at days 7, 14, and 28.

Table 1
Baseline Patient Characteristics

Variable	Overall (n = 225)	Tele- yoga (n = 113)	Control (n = 112)	P value
Age, median IQR	43 (35– 53)	42 (35- 53.5)	43 (36–52)	0.657
Gender				;
Female	102 (45.33)	51 (45.13)	51 (45.54)	1.00
Male	123 (54.67)	62 (54.87)	61 (54.46)	
Coexisting conditions				
Hypertension, n (%)	47 (20.89)	21 (18.58)	26 (23.21)	0.416
Diabetes, n (%)	85 (37.78)	42 (37.17)	43 (38.39)	0.891
Coronary artery disease, n (%)	15 (6.67)	5 (4.43)	10 (8.93)	0.193
Hypothyroidism, n (%)	25 (11.11)	14 (12.39)	11 (9.82)	0.672
COPD, n (%)	3 (1.33)	3 (2.65)	0 (0)	0.222
Asthma, n (%)	2 (0.89)	0 (1.73)	2 (1.80)	0.244
Symptoms				
Fever/chills, n (%)	158 (70.22)	73 (64.61)	85 (75.89)	0.080
Cough, n (%)	163 (72.44)	82 (72.57)	81 (72.32)	1.000
Sore throat, n (%)	28 (12.44)	16 (10.71)	12 (14.16)	0.545
Nausea/Vomiting, n (%)s	13 (5.78)	7 (6.19)	6 (5.36)	1.000
General weakness, n (%)	92 (40.89)	48 (42.48)	44 (39.28)	0.685
Breathlessness, n (%)	105 (50.72)	44 (41.90)	61 (59.80)	0.006**

Variable	Overall (n = 225)	Tele- yoga (n = 113)	Control (n = 112)	P value
Headache, n (%)	57 (25.33)	34 (30.09)	23 (20.54)	0.125
Diarrhea, n (%)	11 (5.31)	4 (3.81)	7 (6.86)	NS
Previous medication use – no. (%)				
Glucocorticoid	7 (3.03)	5 (4.35)	2 (1.67)	NS
ACE inhibitor	12 (5.19)	7 (6.19)	5 (4.46)	NS
Angiotensin II–receptor antagonist	8 (3.46)	3 (2.61)	5 (4.35)	NS
Baseline ordinal Covid outcome score – no. (%)				
3.Hospitalized, receiving non-invasive mechanical	92 (40.89)	54 (47.79)	38 (33.93)	0.60
4.Hospitalized, receiving supplemental oxygen without positive pressure or high flow; requiring low-flow supplemental oxygen;	125 (55.56)	57 (50.44)	68 (60.71)	
5. Hospitalized, not receiving supplemental oxygen	8 (3.56)	2 (1.77)	6 (5.36)	
Ct value	28.00 (22.5– 32.00)	27.00 (22.50– 30.00)	28.0 (22.50– 33.00)	0.125
Inflammatory markers				
C-reactive protein, mg/l	24.82 (8.09– 63.67)	28.16 (8.43– 65.46)	26.71 (8.47– 67.40)	0.854
Ferritin, mg/dl	196 (81.85– 421)	179 (82.30- 404.50)	203(77.40– 441)	0.616
D-dimer, ng/ml	167 (94.00- 242.00)	170 (94– 245)	179 (95– 250)	0.953
LDH, U/L	302 (241– 392)	296 (226.50– 355)	319 (248- 436.94	0.057
IL-6, mg/dL	37.65 (11.27– 80.02)	31.89 (11.93– 79.99)	39.76 (10.21– 76.15)	0.808

Variable	Overall (n = 225)	Tele- yoga (n = 113)	Control (n = 112)	P value
Haemogram				
Hb (g/dL)	13.50 (12.20– 14.60)	13.6 (12.10– 14.70)	13.2 (12.20– 14.45)	0.406
ALC ($\times 10^9$ /L) /L)a	1.27 (0.87– 1.92)	1.21 (0.84– 1.86)	1.34 (0.88– 1.95)	0.472
AMC ($\times 10^9$ /L)	0.46 (0.29– 0.74)	0.45 (0.28– 0.72)	0.50 (0.32– 0.77)	0.343
ANC ($\times 10^9$ /L)	4.23 (2.85– 6.71)	4.17 (2.91– 6.64)	4.39 (2.73– 6.83)	0.606
PSS	19 (15– 24)	20 (16– 25)	19 (13.25– 23)	0.023*

For continuous variables, median and IQR (Interquartile range) have been presented due to the non-normality of the data. Correspondingly, Mann-Whitney tests were used to assess if differences between the study groups were statistically significant. For categorical variables, Chi-square/Fisher's exact tests were used to check if there were any association between the groups. Ct, cyclic threshold value; ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; PSS, Perceived stress scale.

Results

During the 60-days of enrollment period, 326 patients were screened; 66 (20.24%) patients were excluded for being hospitalized for more than 48 hours at the time of screening, 24 (7.36%) had tested negative for RT-PCR at day 0 (baseline) for coronavirus disease 2019. Further, 11 eligible patients refused to participate (2.76%) (see Fig. 1, Trial Profile.). Hence, out of 236 eligible patients, 225 could be randomized, 113 were randomized to the adjunct tele-yoga and 112 were randomized to the standard of care group. The last outcome assessment was on July 31st 2021. Overall the median age of the participants was 43 years (IQR, 35–53 years), 54.67% were male, 32.43% had diabetes, 20.89% had hypertension, and 6.67% had coronary artery disease. Demographics and baseline disease characteristics of participants in both groups are presented in Table 2; there was an equal distribution of age, gender, days before onset of symptoms, comorbidities, and inflammatory markers between the study arms (Tables 2 and S2). Overall, 70.22% of the patients presented with perceived or objective fever, 72.44% presented with cough, 12.44% presented with sore throat, 25.33% presented with headache and 50.72% presented with breathlessness with no remarkable differences between groups. The median duration of symptoms prior to

randomization was 3 days (IQR, 2–4 days) in both the groups. There were no differences in vital signs, or full blood count also between the groups (Table S2). Of 113 patients in the adjunct yoga group, 29 (76%) were discharged before 7 days post-randomization, hence, were continued with tele-yoga sessions till 14th.

Primary Outcome:

The primary outcome (status on the seven-point ordinal scale at day 14) was assessed in all patients who were still hospitalized on day 14th or were tele-phonically interviewed if had been discharged earlier (see the Supplementary Appendix and Fig. S2). The distribution of patients' scores on the seven-level ordinal scale at 14 days is shown in Fig. 2. Patients randomized to the adjunct tele-yoga group had significantly higher odds of a better clinical status distribution on the 7-point ordinal scale compared with those randomized to standard care (odds ratio, 1.94, 95% CI = 1.18–3.18) (Fig. 2). Sensitivity analyses of the primary end point adjusting for day 1 clinical status score, and symptom duration using the intention-to-treat population produced no significant difference (Table S3). The results for the primary outcome were not different across the prespecified subgroups (Table S4).

Secondary Outcomes:

There were significant differences between the adjunct tele-yoga and standard care groups in terms of improvement in clinical status at 7th day (partially adjusted for age odds ratio, 3.61; 95% CI, 2.11–6.05; $P < 0.001$) but the outcome on 28th day was not significant (adjusted odds ratio, 95% CI = 1.03–3.44) (Table S5). At day 5, there was significant reductions in CRP ($p = 0.001$) and LDH levels ($P = 0.029$) in the adjunct yoga group compared to the standard of care alone (Fig. 3 and Table S6). There were no significant differences between the treatment groups in duration of hospitalization (Fig. 3). The Kaplan-Meier estimates of all-cause mortality at day 28 were 1.80% vs 5.40% for standard of care; log rank $P = 0.144$; adjusted hazard ratio [HR], 0.26; 95% CI, 0.05–1.30). (Figure S3)

Exploratory outcomes:

Since we could establish significant reductions in CRP and LDH at day 5 from post-randomization in the adjunct yoga group compared to the standard of care group alone, we further tested for their mediating effects on the intervention (Table 2). The analyses indicated CRP as potential mechanistic mediator of adjunct yoga on the improved clinical status at 14th day post intervention. There was also differences between proportions of subjects with atleast 1 unit change in outcomes at day 7 from baseline between adjunct tele-yoga as compared to the standard of care groups. However, the distributions were not different for days 14 and 28 (Figure S4).

Adverse Effects

None of the 8 deaths through day 28 (5 [1%] in the standard of care, and 3 [2%] in the adjunct tele-yoga group occurred in the Covid 19 patients could be attributed to the tele-yoga intervention (Table S7). In the

tele-yoga group, extension of hospitalization was 10.62%, whereas in the standard of care alone it was 21.875%. Single cases each of sinus tachycardia, and pulmonary embolism was observed in the yoga group as compared to no cases in the standard of care.

#Only hospitalized patients who were not receiving supplemental oxygen or who were receiving up to 4 liters per minute of supplemental oxygen were eligible for the trial. Patients who had scores on other levels of the seven-level ordinal scale were not eligible. Adjusted for baseline age, sex, comorbidities (diabetes, hypertension, hypothyroid,), the primary outcome (status on the seven-point ordinal scale at day 14) was assessed in all patients who were still in the hospital on day 15 exactly and in outpatients (by means of tele-phone interview) as close to day 14 as possible.

Primary outcome: Distribution n (%)	Total Subjects (n = 225)	Tele-yoga (n = 113)	Standard of care (n = 112)
7: Not hospitalized with no limitations on activities	96 (42.67)	52 (46.02)	44 (39.29)
6: Not hospitalized but with limitations on activities	87 (38.67)	51 (45.13)	36 (32.14)
5: Hospitalized, not receiving supplemental oxygen	27 (12.00)	7(6.19)	20 (17.86)
4: Hospitalized, receiving supplemental oxygen	6 (2.67)	1 (0.88)	5 (4.46)
3: Hospitalized, receiving noninvasive ventilation or high-flow nasal cannula	2 (0.89)	1 (0.88)	1 (0.89)
2: Hospitalized, receiving mechanical ventilation	3 (1.33)	1 (0.88)	2 (1.79)
1: Death	4 (1.78)	0 (0.00)	4 (3.57)
Proportional Odds Ratio (OR, 95%CI)	1.94 (1.18–3.18) P = 0.01		
Model is adjusted for age and gender			

Table 2

Indirect, direct and total effects of the mediation models on COVID-19 outcomes at 14 days post-randomization

	Effect size	Proportion mediated
Direct effect of the adjunct tele-yoga vs. standard of care Adjunct yoga	0.41(0.03–0.78)	-
Total effect of the model	0.54 (0.17–0.91)	-
Indirect (mediating) effects		
LDH	-0.01 (-0.10-0.04)	Not significant
CRP	0.06 (0.05–0.16)*	11.11%

Discussion

This study is a pioneer clinical trial that investigated the short-term acute interventional benefits of adjunct tele-yoga practice for clinical management of hospitalized COVID-19 patients. We could establish a ~ 1.9-fold improvement in the clinical status at 14th day post-randomisation, in mild and moderate hospitalized COVID-19 patients (Odds Ratio = 1.94, 95% CI = 1.18–3.18) as compared to those with only standard of care. The odds of improvement with yoga intervention were higher at the 7th day (Odds ratio = 3.61, 95% CI = 2.13–6.10. However, the effectiveness of the intervention was not found to be sustained at 28th day post-randomization (Odds Ratio 1.70, 95% CI = 0.97–2.99), P = 0.07). Since, patients had several coexisting diseases and were subjected to a diverse medication regimen, the complementary effects of tele-yoga could have been influenced by the heterogeneity of the sample and its treatment. However, when analyzed in the post hoc subgroup analysis, adjunct yoga was found to be effective across all the strata of covariates. Concerning influence of the intervention on mortality related outcomes, no benefit could be observed for the adjunct yoga intervention with respect to mortality (adj HR 0.26; 95% CI, 0.05–1.30).

We could establish support for the primary end points with the observed secondary improvement in crucial biomarkers in the tele-yoga group compared to the standard of care at 5th day post-randomization, CRP (P = 0.001) and LDH (P = 0.029). Both CRP and LDH have been reported as prognostic markers of deterioration in COVID 19 patients including mild/non severe cases as well.^{25,26} We could also establish a mediation effect of CRP modulation underlying effectiveness of tele-yoga intervention (~ 11% proportion mediation on the observed improved outcome of clinical status at day 14). This inflammation reducing effect of yoga well aligns with the physiological modulation of vagal tone, one of the widely reported effects of yoga and meditation.^{12,13} The anti-inflammatory potential of yoga could serve as a step forward in the fight against other serious forms of infectious diseases with a dominant inflammatory component, as proposed for malaria, HIV/ AIDS, and SARS, among others. COVID-19.

We could not observe a significant effect of adjunct tele-yoga on perceived stress scale in COVID 19 patients ($P = 0.69$). We speculate that the failure to obtain the desired effect on stress and several other variables could be due to the primarily virtual mode of the delivery of the intervention and the short duration of intervention. However, the beneficial clinical outcomes observed in the study hold special significance in the present era with re-emerging and recurring viral infections.^{27,28} Overall the findings of this study support the exploratory notions of several researchers and clinicians that certain meditation, yoga asana (postures), and pranayama (breathing) practices may be effective adjunctive means of treating SARS-CoV-2 infection.¹² The findings also pave the foundation for the clinical implementation of tele-yoga-based adjunct interventions in hospital settings for the management of infectious diseases. A previous study on yoga had also reported it to be effective as an adjunct to anti-tuberculosis treatment (ATT) in patients with pulmonary tuberculosis by reducing the symptom scores, sputum conversion on microscopy, and improvement in the lung capacity and radiographic pictures.²⁹

This clinical exploration is one of the earliest to be reported amongst several other concomitant attempts to establish the efficacy of additional systems of medicine, against the combat of COVID-19, well reflected by 67 such registered in the Clinical Trial Registry of India (CTRI).³⁰ Hence, given the lack of available findings from clinical trials on COVID 19 and Yoga based interventions, the findings of this trial could not be presented with comparisons.

The study has several strengths. One of the strengths of the study is the inclusion of WHO criteria for assessing the benefit on clinical status for patients hospitalized with mild and moderate coronavirus disease 2019 (COVID-19). This is the first report wherein yoga-based intervention was provided in a tele-mode to Covid 19 patients. This was done to prevent health care employees from being infected. Importantly, the trial included inflammatory markers as study outcomes, wherein an anti-inflammatory mediating influence of yoga intervention could be established improving the outcomes of hospitalized mild to moderate COVID patients. A key feature of the trial was the early implementation of treatment within 7 days of symptom onset (median duration of 3 days) which has been considered important for the treatment protocol, in particular antivirals like remdesivir.

The trial was limited to hospitalized Covid 19 patients which restricts the generalizability of the findings to other populations involving home-base care. The assessments were limited to 28 days post randomization, reporting long-term outcomes of trial participants should have been considered. Given the nature of intervention, the study used an open-label design, which could have led to biases in patient care and reporting of data. Though prespecified for days 14, and other than clinical status and subjective outcomes, other laboratory parameters could not be routinely collected due to logistic challenges.

Overall we could observe clinically relevant effects among hospitalized patients with mild to moderate COVID-19, contesting the use of tele-yoga as a complementary treatment for patients with this disease. However, the positive signal found in this small scale trial warrants the conduction of larger trials using tele-yoga for the treatment of COVID-19.

Declarations

Data availability:

The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Author Contributions:

Vijaya Majumdar and Manjunath N K take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Nagarathna R, Mannjunath NK, Vijaya Majumdar. Acquisition, analysis, or interpretation of data: Suryanarayan Panigrahi, Sarthak Sahoo, Adithi Giridharan, Mounika Reddy, Rakshitha Nayak and Vijaya Majumdar, Drafting of the manuscript: Vijaya Majumdar and Manjunath NK, Critical revision of the manuscript for important intellectual content: Manjunath NK, Nagarathna R, Muralidhar Kanchi, Hongasandra R Nagendra. Statistical analysis: Vijaya Majumdar, Obtained funding: Vijaya Majumdar, Manjunath NK, and Nagarathna R, Administrative, technical, or material support.

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Conflict of Interest Disclosures:

Authors declare no conflict of interest

Additional Contributions:

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Figures

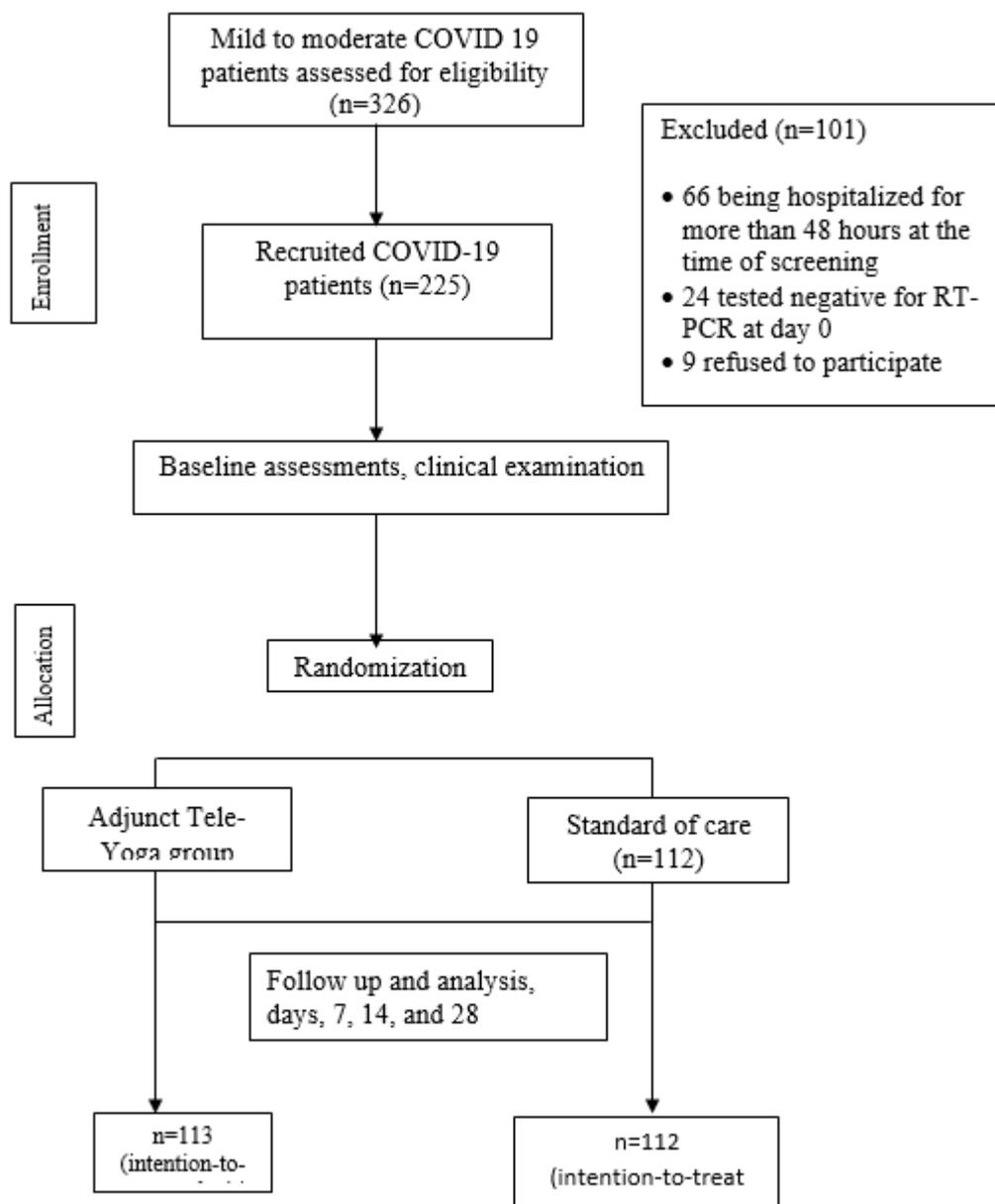


Figure 1

Trial Profile

DAY14

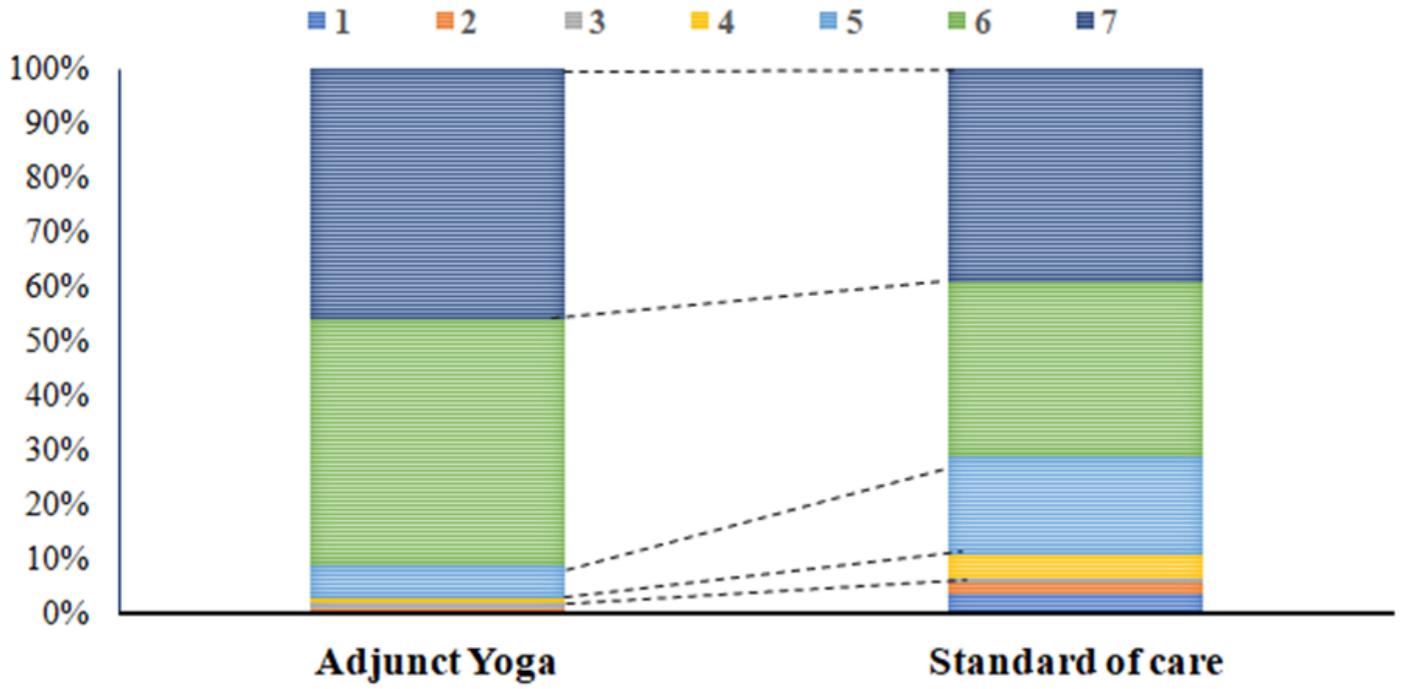


Figure 2

Clinical Status on the Coronavirus Disease (COVID) Outcomes Scale 14 Days post Randomization

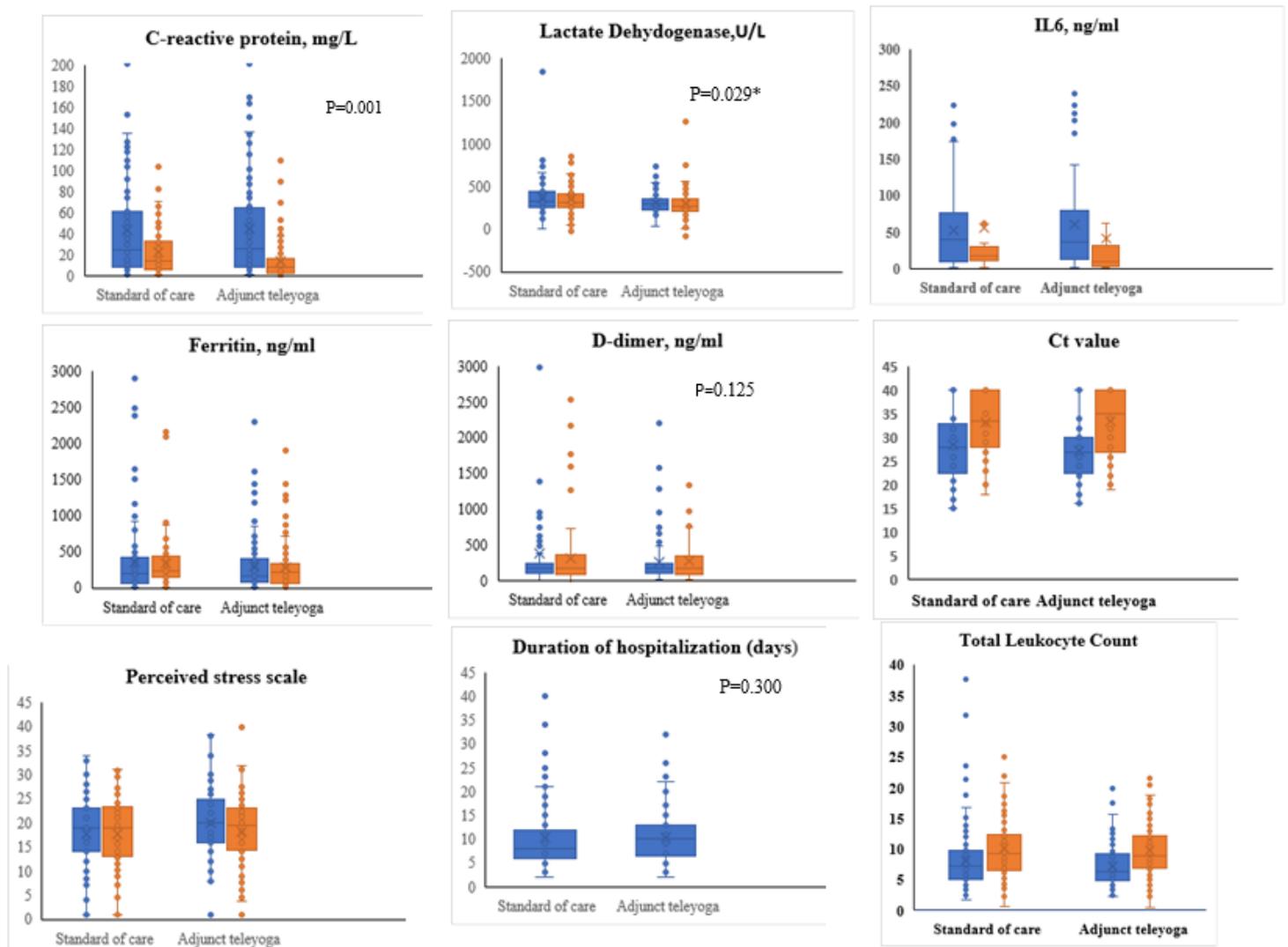


Figure 3

Biomarker levels at day 5 post randomization

Supplementary Files

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- [SupplementrayDataCovidStudyfinal16.03.2022.docx](#)