Article published online: 2022-11-28

Homeopathy as an Adjuvant to Standard Care in Moderate and Severe Cases of COVID-19: A Single-Blind, Randomized, Placebo-Controlled Study

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Homeopathy 2023;112:184–197.

Abstract

Objectives This study aimed to evaluate whether individualized homeopathic medicines have a greater adjunctive effect than adjunctive placebos in the treatment of moderate and severe cases of coronavirus disease 2019 (COVID-19).

Methods The study was a randomized, single-blind, prospective, placebo-controlled clinical trial set in the clinical context of standard care.

Intervention Patients of either sex, admitted in a tertiary care hospital, suffering from moderate or severe COVID-19 and above 18 years of age were included. In total, 150 patients were recruited and then randomly divided into two groups to receive either individualized homeopathic medicines or placebos, in addition to the standard treatment of COVID-19.

Outcome Measures The primary outcome was time taken to achieve RT-PCR-confirmed virus clearance for COVID-19. Secondary outcomes were changes in the Clinical Ordinal Outcomes Scale (COOS) of the World Health Organization, the patient-reported MYMOP2 scale, and several biochemical parameters. Parametric data were analyzed using unpaired *t*-test. Non-parametric data were analyzed using the Wilcoxon signed rank test. Categorical data were analyzed using Chi-square test.

Results In total, 72 participants of the add-on homeopathy (AoH) group showed conversion of RT-PCR status to negative, in an average time of 7.53 ± 4.76 days (mean $\pm$ SD), as compared with 11.65 ± 9.54 days in the add-on placebo (AoP) group ($p = 0.001$). The mean COOS score decreased from 4.26 ± 0.44 to 3.64 ± 1.50 and from

Keywords
- moderate to severe COVID-19
- coronavirus infection
- homeopathy
- integrative care
- pandemic
- RT-PCR

received
February 25, 2022
accepted after revision
June 13, 2022
article published online
November 28, 2022

DOI https://doi.org/10.1055/s-0042-1755365.
ISSN 1475-4916.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

4.3 ± 0.46 to 4.07 ± 1.8 in the AoH and AoP groups respectively ($p = 0.130$). The mortality rate for the AoH group was 9.7% compared with 17.3% in the AoP group. The MYMOP2 scores between the two groups differed significantly ($p = 0.001$), in favor of AoH. Inter-group differences in the pre- and post- mean values of C-reactive protein, fibrinogen, total leukocyte count, platelet count and alkaline phosphatase were each found to be statistically significant ($p < 0.05$), favoring AoH; six other biochemical parameters showed no statistically significant differences.

Conclusion The study suggests homeopathy may be an effective adjunct to standard care for treating moderate and severe COVID-19 patients. More rigorous, including double-blinded, studies should be performed to confirm or refute these initial findings.

Introduction

Background

The novel human coronavirus (SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2]) has resulted in many fatalities,[1] highlighting the risks of highly pathogenic coronaviruses to the human race. Those with co-morbidities seem to be at a higher risk. Wang and colleagues reported findings from 138 cases of coronavirus disease 2019 (COVID-19) and the results suggested that 64 (46.4%) of them had co-morbidities. Patients who were admitted to the intensive care unit (ICU) had a higher incidence of co-morbidity (72.2%) than those not admitted to the ICU (37.3%). Assessing the prevalence of underlying chronic diseases is the basis for mitigating complications in patients infected with SARS-CoV-2. A recent update of a cohort study observed that hypoxia and increased inflammatory laboratory parameters found early after hospital admittance were important markers for critical illness and mortality.[2]

With no definite treatment known for COVID-19 at the time this study was planned, guidelines recommended only supportive care.[3] Various trial drugs were being tested, including a lopinavir–ritonavir combination,[4] and hydroxychloroquine either alone[5,6] or in combination with azithromycin.[7] Bearing in mind the issues pertaining to limited scope of treatment, during the Ebola outbreak of 2014-2016 experts from the World Health Organization, in their statement for containment of Ebola virus disease, had recommended, "In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention".[8] This premise suited the concept of that study well, thus encouraging us to explore the role of homeopathy in COVID-19. Our study was planned in June 2020, just 6 months after the first case had been reported,[3] and it was still too soon to tell how long the pandemic would continue or how remote we were from its effective treatment.

Homeopathy for COVID-19

Homeopathy, a holistic system of medicine, has been in use for epidemic and infectious diseases for a long time.[9] The role of homeopathy in prevention, control and treatment in epidemic disease conditions, including influenza, Japanese encephalitis, dengue and other infectious diseases through historical, clinical and experimental evidence, has been frequently reported.[10–15] The usefulness of this medical system during the pandemic of "Spanish flu" in 1918 has been duly recorded.[16,17]

Homeopathy is viewed by some as "personalized nanomedicine".[18] Given the limitations posed in the treatment of COVID-19, with clinical presentation varying among patients, exploring the role of individualized treatment through homeopathy is crucial. Many trials on this front were ongoing at the time of drafting this manuscript.[19–21]

In this study, individualized homeopathic treatment was given to all the participants of the experimental group (add-on homeopathy, AoH), based on the totality of symptoms inclusive of not only clinical but also holistic or individualizing aspects such as thirst, appetite and frame of mind, wherever possible. In cases that were more severe, such as those in the ICU, it was difficult, however, to elicit their personalized symptoms. Totality of symptoms was thus based mainly on the clinical symptoms and patient's individual medical reports.

This study explored whether homeopathic treatment, when given integratively with standard care in moderate and severe cases of COVID-19, could lead to better clinical outcomes than add-on placebos (AoP).

Methods

Trial Design

This was a single-blind, parallel group, randomized controlled trial. The participants were blinded to group allocation, after having obtained their informed consent that they could randomly receive either individualized homeopathic medicines or placebos in addition to the standard treatment for COVID-19. Randomization to respective groups was performed by a computer-generated randomization list, in the ratio 1:1. Blinding of the trial participants was done with the aim to minimize biases associated with subject awareness and in view of non-feasibility of a double-blinded design.

Eligibility Criteria for Participants

The assessment criteria for inclusion were men or non-pregnant women who were aged at least 18 years, diagnosed

Table 1 Assessment criteria for inclusion of moderate and severe cases

An RT-PCR-positive case of COVID-19 was diagnosed as:		
Moderate if	Pneumonia with no signs of severe disease	*Adolescent or adult* with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90–94%) on room air, respiratory rate more or equal to 24 per minute.
Severe if	Severe pneumonia	*Adolescent or adult* with clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% on room air.
	Acute respiratory distress syndrome	*Onset:* new or worsening respiratory symptoms within 1 week of appearance of clinical symptoms. *Chest imaging* (chest X-ray and portable bed-side lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. *Origin of pulmonary infiltrates*: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor present. *Oxygenation impairment in adults*: Mild ARDS: 200 mmHg <PaO_2/FiO_2 ≤300 mmHg (with PEEP or CPAP ≥5 cm H_2O) Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cm H_2O) Severe ARDS: PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cm H_2O) When PaO_2 is not available, SpO_2/FiO_2 ≤315 suggests ARDS (including in non-ventilated patients).

Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

with moderate or severe COVID-19 by the team of treating doctors, as per the criteria laid down in the guidelines issued by the Ministry of Health and Family Welfare, Government of India, on June 13, 2020,[22] shown in ►**Table 1**.

The exclusion criteria were as follows: COVID-19-positive children and adolescents below 18 years of age; pregnant or lactating women; those not willing to give consent for adjunctive homeopathic treatment; those who notified their inability to be contacted for clinical outcome assessment after being discharged; those cases in whom the medical prognosis was that death was imminent and inevitable within the next 24 hours; those with symptoms of acute respiratory tract infection for more than 10 days before randomization; those with unknown COVID-19 status.

All patients were enrolled in the study only after obtaining their recorded audiovisual consent, except in cases where the patient was either disoriented or not able to provide video consent due to poor health, whereupon informed consent was accorded by a legal representative. Participants' allocation is shown in ►**Fig. 1**.

The study was conducted in accordance with the latest version of the Helsinki Declaration.[23] The trial was approved by the Institutional Ethics Committee of the study site (CCRH and AIIMS, Jhajjar: reference numbers 1–3/2020–

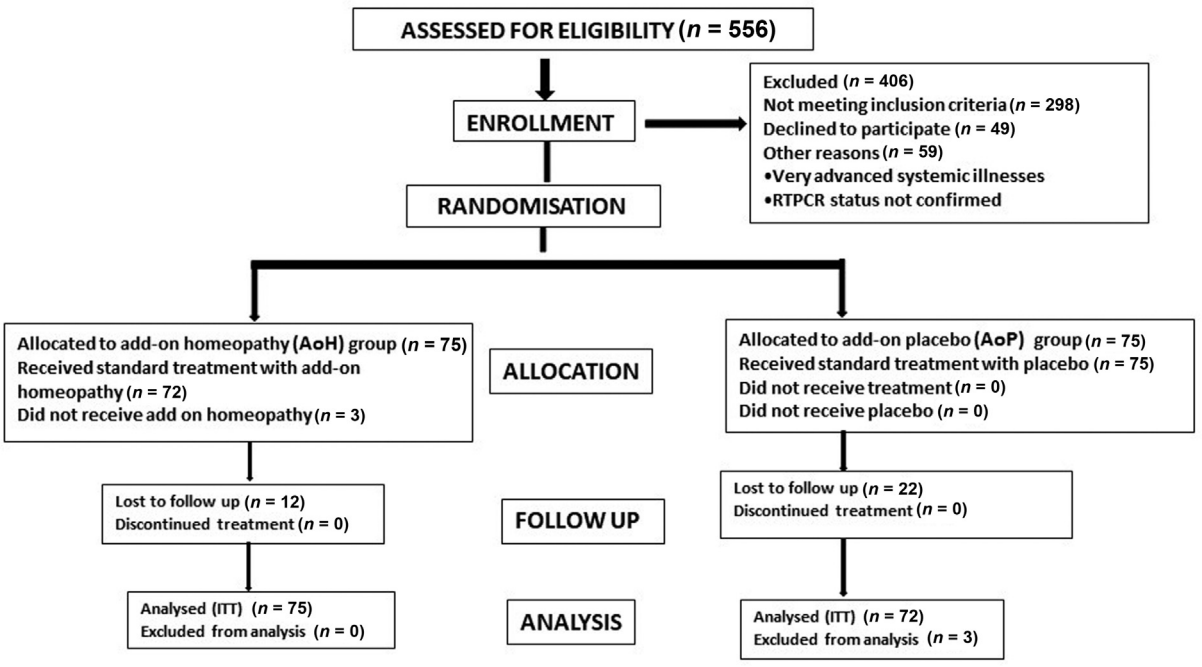

Fig. 1 Participants' allocation.

21/CCRH/Tech./ EC/24 dated 25.8.2020, and IEC-714/07.08.2020, RP-61/2020, respectively) and prospectively registered with the Clinical Trials Registry of India (CTRI/2020/10/028279 [registered on 07.10.2020].

Study Setting

The study was conducted at the National Cancer Institute (NCI), a branch of the All India Institute of Medical Sciences (AIIMS), located in Jhajjar, Haryana. It was declared as a COVID Hospital by the Government of India. Referrals of COVID-19 cases from Delhi were common due to the proximity of the hospital to Delhi, and because of the COVID care facilities available at the NCI. The study duration was 3 months (28 days follow-up) but, due to a sudden surge of cases, the targeted sample size was achieved earlier.

Intervention

Individualized homeopathic treatment was given to the AoH group as an adjunct to standard care, which comprised usually, but not exclusively, non-invasive supplemental oxygen, antibiotics, vasopressor support, dexamethasone and multi-vitamins, as per the institutional management protocol. All homeopathic medicines used in the study were manufactured by GMP-certified pharmaceutical companies and sourced from one supplier. The homeopathic dilutions that were used in the study belonged mostly to the plant kingdom, and less frequently to the animal and mineral kingdoms. Centesimal or millesimal potencies were used throughout the study, ranging from 6C to 1M. In some cases, mother tinctures (Q) were given, which is a solution of a substance and alcohol made according to standards set by the Homeopathic Pharmacopeia (of India, in our case). The control group received placebos, as non-medicated sugar globules or in the form of two drops of dispensing alcohol diluted in 3.5 mL water, along with standard care. The medicine(s) or placebo(s) were given until the end of the patients' hospital stay after enrollment. The duration of follow-up for the trial was 28 days – physically in the Inpatients Department, or telephonically if and when the patients were discharged from the hospital. Except for knowing their ultimate fate, follow-ups were discontinued in cases that were transferred to mechanical ventilation (MV): for the purposes of data analyses, we used the last-observation-carried-forward method in those cases.

The choice of the homeopathic medicine and the frequency of its repetition were based on the condition and perceived susceptibility of each patient, which was assessed by their overall health status score on the Measure Yourself Medical Outcome Profile (MYMOP2) scale.[24] The score was decided by the investigators, based primarily on the quantity of oxygen therapy being given, the mental state of the patient or other individualizing characteristics, and sometimes specific symptoms, if evidenced, such as the nature of a cough or fever, or X-ray/high-resolution computed tomography findings, if available.

In addition to standard care, most patients of the AoH group were prescribed a single, individualized, homeopathic medicine at 2-hour intervals, sometimes along with an indicated homeopathic mother tincture given twice a day for soothing cough symptoms, maintaining blood sugar, or improving oxygen impairment. The dosage comprised four medicated pills at a time, to be taken orally. The tincture was advised to be taken as 10 drops (approximately) in 20 mL drinking water, stirred well before drinking. In many cases, the initial doses were given to the patients by the investigators themselves to help assure subsequent compliance during self-administration of the medicines. For severe cases unable to take medicines on their own, the paramedical staff had the responsibility to assure compliance.

In co-morbid patients with a medical history of diabetes mellitus and for those who expressed the preference, the medicines were dispensed in water form instead of pills by adding five drops of homeopathic dilution in a 3.5 mL capacity glass vial. Patients were asked to take two drops of this dilution every 2 hours.

The AoP group received, in addition to their standard care, a placebo in the form of homeopathic pills at 2-hour intervals and/or two drops of dispensing alcohol in a 3.5 mL capacity glass vial, twice a day.

In both the study arms, the frequency of medicine intake was reduced to four times a day, or less often, as consistent improvement was seen.

Outcome Measures

The primary outcome was identified as time (every 5 days) to achieve RT-PCR COVID-19 negative status. It was not possible to repeat the test every day, considering the judicious use of the PCR kits advised by the Ethical Committee, and in view of their limited availability. In the absence of any prior evidence-based knowledge on the frequency of repetition, an arbitrary decision was made to repeat the PCR test every fifth day in positive cases.

Secondary outcomes were changes in clinical condition assessed through the WHO Clinical Ordinal Outcome Scale (COOS) at Day 2, Day 7, Day 14 and Day 28, and the patient-oriented MYMOP2 scale[24] which was recorded daily. The WHO COOS is an ordinal scale to assess clinical improvement in COVID patients, with scores ranging from 0 to 8, with 0 being uninfected and 8 being death.[25]

Changes in laboratory parameters were also assessed as secondary outcome measures, these being biochemical biomarkers for inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], and ferritin) and coagulation (D-dimer, prothrombin time [PT]), besides other hematological markers including total leukocyte count (TLC) and neutrophils. All the investigations were recorded at baseline and as and when repeated, as per the discretion of the team of conventional doctors. These parameters were followed up in patients until their stay at the hospital ended.

Sample Size

The total sample size was initially calculated to be 128, 64 in each group, assuming that it would provide the trial with 80% power to minimize type II error and at a two-sided significance level of $\alpha = 0.05$. The effect size was arbitrarily calculated as 0.5 due to lack of any prior similar study in

homeopathy. As the planned enrollment of 128 patients in the trial occurred earlier than the expected duration of 3 months, the investigators decided to continue enrollments until the sample size reached 150, considering probable loss to compliance after discharge. This increased sample size was notified to the Ethical Clearance Committee of the study site and agreed upon.

Randomization, Allocation, and Blinding

The patients were recruited as per a randomization table generated by a statistician through computer-based randomization software. While allocating the group to each patient, the investigators strictly adhered to the sequence prescribed in the randomization table. The allocation could not be concealed from the investigators, given the unique situation where the investigators had to recruit the patients in the COVID wards immediately upon obtaining verbal consent through audio/video recordings.

Statistical Methods

The analysis was performed on an intention-to-treat (ITT) basis, with missing values imputed with the last-observation-carried-forward method. Comparison between AoP and AoH groups was performed at baseline using the independent sample *t*-test to assess randomization effect; this test was also used for evaluation of outcomes for time interval to RT-PCR conversion and for WHO-COOS scores. Repeated-measures ANOVA was applied to assess the difference between the two groups at different time points of the MYMOP2 assessments.

Results

Seventy-five participants enrolled in the AoP group and 72 in the AoH group received treatments as per their respective allocation.

Baseline Characteristics

The baseline characteristics of the participants were comparable between the groups, as shown in ►**Table 2**. Out of those enrolled, 100 cases belonged to the moderate category, and 50 to the severe category. The AoP group had more moderate cases ($n = 52$) than the AoH group ($n = 48$). Among the severe, 27 belonged to the AoH group, while 23 belonged

Table 2 Baseline characteristics of the study participants

Baseline feature	AoH	AoP	*p*-Value
Age, years (range)	57.79 (31–85)	58.39 (22–89)	0.796
Sex			
Men	58 (77.3%)	51 (68.0%)	0.200
Women	17 (22.7%)	24 (32.0%)	
Co-morbidities			
No co-morbidities	29 (38.7%)	23 (30.7%)	0.303
Hypertension	25 (41.7%)	35 (58.3%)	
Diabetes	27 (42.9%)	36 (57.1%)	
Respiratory	2 (20%)	8 (80%)	
Renal	2 (28.6%)	5 (71.45)	
Hypertension with diabetes	14 (35.9%)	25 (64.1%)	
Others	7 (50%)	7 (50%)	
Total leukocyte count (TLC) $\times 10^3/\mu L$	($n = 73$)	($n = 71$)	
Mean (range)	10.46 (1.15–84.80)	10.02 (0.01–26.5)	0.76
< 4	6 (8.2%)	3 (4.2%)	
4–10	44 (60.3%)	39 (54.9%)	
> 10	23 (31.5%)	29 (40.8%)	
Neutrophils, %	$n = 74$	$n = 73$	
Mean (range)	81.82 (48.6–95.8)	80.77 (55–96.7)	0.483
< 80	27 (36.5%)	30 (41.1%)	
> 80	47 (63.5%)	43 (58.9%)	
Alkaline phosphatase, IU	$n = 74$	$n = 73$	
Mean (range)	110.30 (46–713)	104.47 (32–524)	0.659
< 116	53 (71.6%)	56 (76.7%)	
> 116	21 (28.4%)	17 (23.3%)	

Table 2 (*Continued*)

Baseline feature	AoH	AoP	*p*-Value
Serum ferritin, ng/mL	$n = 72$	$n = 72$	
Mean (range)	775.98 (16–3709.8)	908.46 (53–4954)	0.298
< 291	18 (25.0%)	18 (25.0%)	
> 291	54 (75.0%)	54 (75.0%)	
C-reactive protein, mg/dL	$n = 71$	$n = 73$	
Mean (range)	9.34 (0.116–21.86)	8.80 (0.012–21.989)	0.653
< 0.16	2 (2.8%)	2.73 (2.7%)	
> 0.16	69 (97.2%)	71 (97.3%)	
LDH, U/L	$n = 62$	$n = 68$	
Mean (range)	573.08 (132–3,121)	678.63 (162–12,740)	0.618
< 246	3 (4.8%)	7 (10.3%)	
> 246	59 (95.2%)	61 (89.7%)	
D-dimer, ng/mL	$n = 69$	$n = 65$	
Mean (range)	668.73 (12.2–7,870)	673.34 (25.8–5,668)	0.98
< 500	50 (72.5%)	41 (63.1%)	
> 500	19 (27.5%)	24 (26.9%)	
Fibrinogen, mg/dL	$n = 64$	$n = 66$	
Mean (range)	430.78 (125.0–690)	482.12 (219–2519)	0.979
< 350	18 (28.1%)	21 (31.8%)	
> 350	46 (71.9%)	45 (68.2%)	
Interleukin-6, pg/mL	$n = 64$	$n = 57$	
Mean (range)	43.60 (0.00–616.40)	34.41 (0.01–368.40)	0.544
< 4.5	25 (39.1%)	12 (21.1%)	
> 4.5	39 (60.9%)	45 (78.9%)	
Platelet count $\times 10^3/\mu L$	$n = 74$	$n = 73$	
Mean (range)	238.12 (11–498)	285.48 (71–716)	0.04*
< 0.15 million	15 (20.3%)	9 (12.3%)	
> 0.15 million	59 (79.7%)	64 (87.7%)	
Prothrombin time	$n = 27$	$n = 34$	
Mean (range)	15.6 (10.9–39)	13.2 (10.6–25.7)	0.42
Blood sugar (random test), mg/dL	$n = 60$	$n = 46$	
Median and mean	111.50 (57.7%)	154.50 (42.3%)	
< 140	20 (33.3%)	18 (39.1%)	0.537
> 140	40 (66.7%)	28 (60.9%)	
WHO-COOS	$n = 72$	$n = 75$	
Mean (range)	4.26 (48.9%)	4.31 (51.1)	
4	53 (73.6%%)	52 (69.3%)	0.569
5	19 (26.4%)	23 30.7%)	

Abbreviations: AoH, add-on homeopathy; AoP, add-on placebo; COOS, Clinical Ordinal Outcomes Scale.
*p-Value was significant; Baseline mean for platelet count was adjusted by applying ANCOVA test.

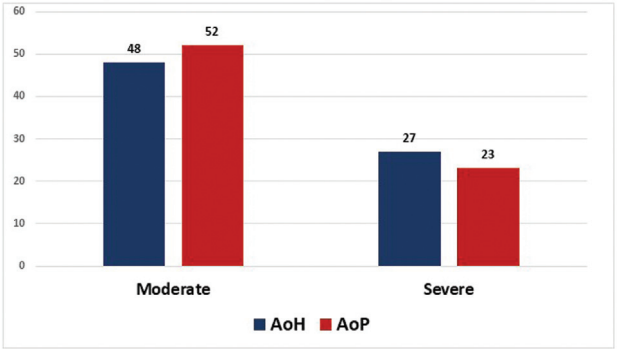

Fig. 2 Distribution of cases by category.

to the AoP group. The distribution of these cases is reflected in ►**Fig. 2**. The presenting complaints of the participants are reflected cumulatively in ►**Fig. 3**, the main ones being cough, breathlessness, fatigue, and anxiety. Interestingly, fever was not reported as frequently, at least not as the most common complaint. It may also be noted that while the AoP group had more co-morbid participants, the AoH group had more severe COVID-19 cases.

Outcomes

A summary of all the outcomes of the study is presented in ►**Table 3**.

Duration for Change in RT-PCR Status from Positive to Negative (Primary Outcome)

Participants who were given adjuvant homeopathy (AoH) demonstrated quicker recovery to RT-PCR negative status (7.53 ± 4.76 days), as compared with those who received placebo (AoP), the latter's time to achieve negative status being 11.65 ± 9.54 days. Those in the AoH group thus showed a faster conversion by approximately 4 days: the difference was statistically significant ($p < 0.001$). Further, more RT-PCR negatives were achieved in the AoH group (72; 97.2%) than in the AoP group (47; 62.7%). Also, total mortalities in the AoH group were 7 (9.7%), compared with 13 (17.3%) in the AoP group. Three cases treated with AoH therapy and seven cases treated with AoP remained RT-PCR positive until the time of their death. However, four out of seven in the AoH and six out of 13 in the AoP group had already become RT-PCR negative before mortality. The data are presented in ►**Table 4**.

Clinical Outcome Ordinal Scale (COOS)

Since all the cases enrolled in the study had compromised oxygen levels, they were either admitted with, or immediately put on, oxygen support; they thus enrolled either at COOS score 4 (on low flow oxygen) or score 5 (on high flow oxygen). Their data were analyzed for the number of days taken to reach a score of 3, meaning not requiring oxygen therapy anymore. Scores of 6 (MV) and above were not recorded further (see Methods). These cases were observed further solely with the purpose of recording their

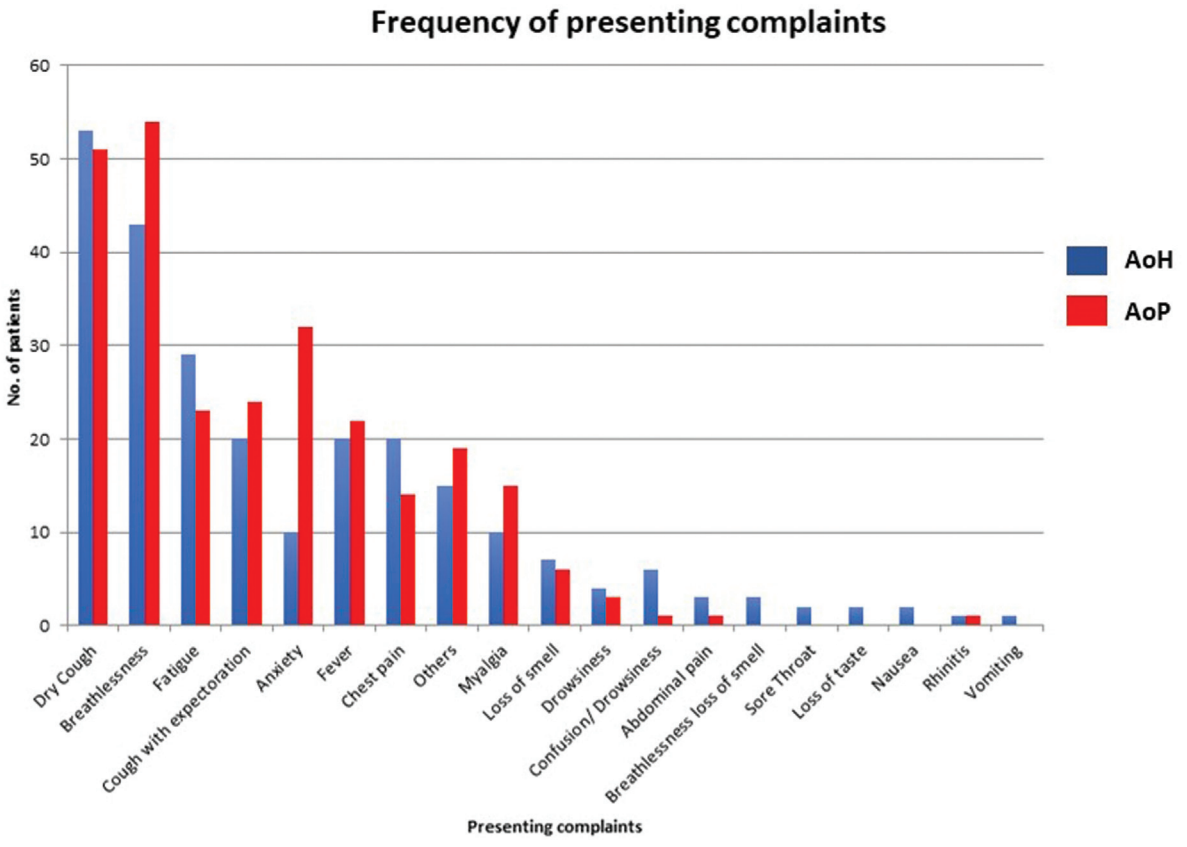

Fig. 3 Baseline symptoms of the participants in both the groups.

Table 3 Overall outcomes of the study

Variable	Test applied	AoH (Mean ± SD/SEM)/%	AoP (Mean ± SD/SEM)/ %	*p*-Value (significant*)
Primary outcome		Mean difference from baseline to last follow-up (between groups)		
RT-PCR (Primary outcome)	Independent *t*-test	72 (7.53 ± 4.75)	75 (11.65 ± 9.54)	0.001*
RT-PCR positive	Chi-square test	2 (2.8)	28 (37.3)	0.0001*
RT-PCR negative		70 (97.2)	47 (62.7)	
Secondary outcomes		Mean difference from baseline to last follow-up (between groups)		
WHO-COOS (days)	Independent *t*-test	72 (0.63 ± 0.16)	75 (0.24 ± 0.19)	0.13
Mortalities	Chi-square test	7 (9.7%)	13 (17.3%)	0.13
		Mean difference from baseline to last follow-up (within group)		
MYMOP2	Repeated measures ANOVA	73 (1.82 ± 0.22)	72 (1.35 ± 23)	0.0001*
Laboratory values		Mean difference from baseline to last follow-up (between groups)		
TLC	Repeated measures ANOVA	51 (−2.04 ± 0.88)	50 (−3.62 ± 0.96)	0.00001*
CRP	Repeated measures ANOVA	52 (7.61 ± 0.99)	47 (6.16 ± 1.08)	0.00001*
Platelets	Repeated measures ANCOVA	53 (−36.84 ± 17.25)	52 (23.25 ± 20.17)	0.03*
Fibrinogen	Repeated measures ANOVA	18 (82.75 ± 25.48)	24 (176.13 ± 95.33)	0.05*
Alkaline phosphatase	Repeated measures ANOVA	61 (20.93 ± 6.93)	57 (2.12 ± 5.57)	0.03*
IL-6	Repeated measures ANOVA	42 (33.59 ± 15.76)	39 (−44.29 ± 47.22)	0.37
D-dimer	Repeated measures ANOVA	31 (78.23 ± 184.28)	31 (−90.74 ± 110.24)	0.34
Ferritin	Repeated measures ANOVA	36 (−22.61 ± 155.28)	43 (−504.11 ± 299.53)	0.14
LDH	Repeated measures ANOVA	27 (195.15 ± 107.67)	26 (−20.00 ± 47.09)	0.07
Prothrombin time	Repeated measures ANOVA	51 (−3.9 ± 3.48)	49 (−4.5 ± 5.14)	0.43
Neutrophils	Repeated measures ANOVA	32 (−0.43 ± 1.19)	29 (−1.67 ± 1.67)	0.52

Abbreviations: ANOVA, analysis of variance; COOS, Clinical Ordinal Outcomes Scale. *indicates significant *p* value.

subsequent fate, which happened to be demise for all such individuals in this study.

At the end of 28 days' follow-up, reduction in the mean COOS score was greater in the AoH group, from 4.26 ± 0.44 to 3.64 ± 1.50, with mean difference 0.62 ± 1.35; the corresponding reduction was 4.3 ± 0.46 to 4.07 ± 1.8 in the AoP group, with mean difference 0.24 ± 1.68 (►**Fig. 4**). The two groups did not differ significantly in their last follow-up scores ($p = 0.130$) (►**Table 5**). During the study, four patients in the AoH group and eight in the AoP group worsened, necessitating the use of MV. Eventually, all those who were put on MV had unfavorable and subsequently life-ending outcomes.

Patient-Reported Improvement: MYMOP2 Scale

Repeated-measures ANOVA, with Greenhouse-Geisser correction, was applied to measure the difference in mean scores within the groups. The participants of both groups reported improvement over the follow-up period (►**Fig. 5**). However, the mean difference in the scores of the AoH group

Table 4 RT-PCR outcome (from positive to negative, in days)

Variable	Test	AoH (Mean ± SD/SEM)/ %	AoP (Mean ± SD/SEM)/ %	p-Value (Significant*)
RT-PCR	Independent *t*-test	72 (7.53 ± 4.75)	75 (11.65 ± 9.54)	<0.001*
RT-PCR positive	Chi-square test	2 (2.8)	28 (37.3)	<0.0001*
RT-PCR negative		70 (97.2)	47 (62.7)	

Abbreviations: AoH, add-on homeopathy; AoP, add-on placebo; COOS, Clinical Ordinal Outcomes Scale; RT-PCR, reverse transcription polymerase chain reaction; SD, standard deviation; SEM, standard error of the mean. *indicates significant *p* value.

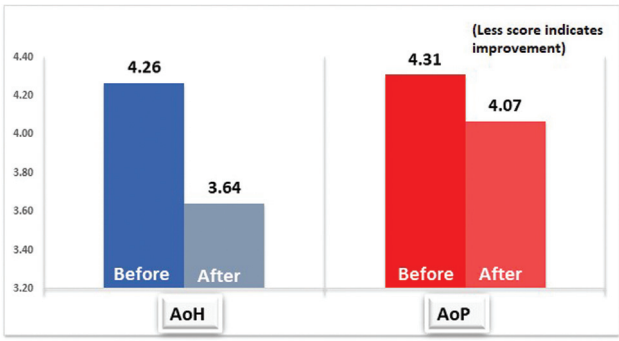

Fig. 4 Mean COOS scores. COOS, Clinical Ordinal Outcomes Scale.

was statistically significant when compared with the baseline ($p = 0.0001$). Further, the difference was also significant between the groups ($p = 0.0001$).

Laboratory Parameters

The AoH group showed a statistically significant improvement in 5 out of 11 parameters analyzed in the study: CRP ($p < 0.001$), TLC ($p < 0.001$), platelet count ($p = 0.03$), serum fibrinogen ($p = 0.05$), and serum alkaline phosphatase ($p = 0.03$), through repeated-measures ANOVA used for sub-group analysis between the groups. Other parameters (IL-6, D-dimer, ferritin, neutrophil count, LDH, PT) showed a positive trend in favor of AoH but were statistically non-significant (►**Supplementary Fig. S1**, available online only).

Homeopathic Treatment

The most frequently used medicines in the study were *Veratrum viride*, *Arsenicum album*, *Bryonia alba,* and *China officinalis*. In moderate cases, *Veratrum viride* and *Arsenicum album* were used the most and, in severe cases, *Veratrum viride* and *China* were the most prescribed drugs. Among tinctures, *Aspidosperma* was prescribed most frequently, followed by *Lobelia* (►**Tables 6** and **7**). *Veratrum viride* 200 C and mother tincture *Aspidosperma* were among the

Table 5 Independent sample *t*-test results of WHO-COOS mean scores

Group		*N*	Mean score	Std. deviation	Std. error of mean	*p*-Value
COOS at baseline	AoH	72	4.26	0.444	0.052	0.569
	AoP	75	4.31	0.464	0.054	
COOS at last follow-up	AoH	72	3.64	1.504	0.177	0.130
	AoP	75	4.07	1.870	0.216	

Abbreviation: COOS, Clinical Ordinal Outcomes Scale.

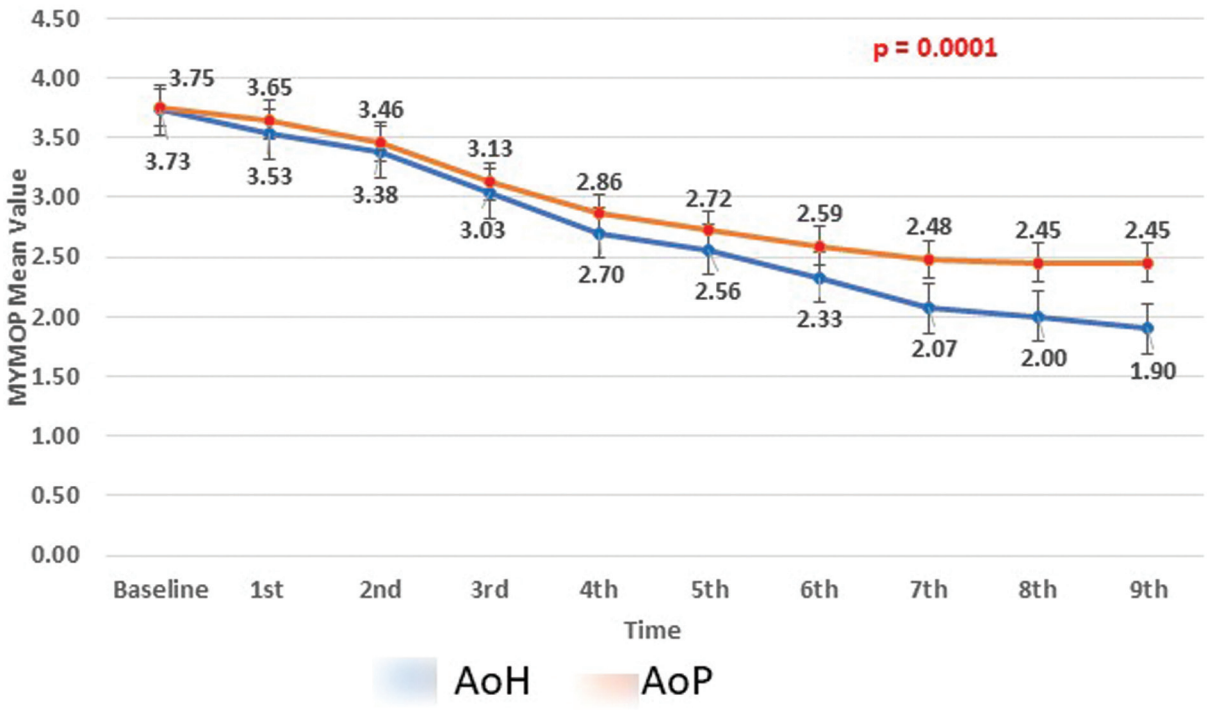

Fig. 5 Trend lines for clinical condition of participants as per MYMOP2 scale.

top medicines prescribed with the sole indication of depleted oxygen saturation (≤92%). Homeopathic mother tinctures, when administered, seemed to help stabilize oxygen levels, soothing down cough frequency and intensity and improving the general recovery from COVID illness.

Discussion

RT-PCR Status as the Primary Outcome

Time for RT-PCR conversion to negative was the primary outcome of the study. The authors report in this paper the statistically significant finding that more RT-PCR negatives were achieved in the AoH group than in the AoP group, and in less time. It is worth mentioning that this study was conceived in June 2020 when India was officially only 3 months into the pandemic, and eventually it was realized that RT-PCR negative status does not necessarily alleviate the morbidity or, more specifically, the mortality risk of a patient, with many patients who eventually succumb to the disease being COVID-negative for a considerable time before passing away. Even for moderate cases, it is doubted as a parameter of total recovery, with many patients regarded fit for discharge even before they test negative for RT-PCR.[26] Even in our study site, negative RT-PCR was not a criterion for discharge once the patient was clinically improved on the basis of other parameters such as stable breathing on room air, mostly for two consecutive days. This made way for those who were more in need of hospitalization. Discharge of COVID-positive patients from the hospital was sometimes followed by delay in post-discharge RT-PCR sample collection from home. This could have impacted the study results in some way.

Table 6 Most frequently used medicines

No.	Name of medicine	No. of patients	Moderate	Severe
1.	*Veratrum viride*	22	13	9
2.	*Arsenicum album*	19	15	4
3.	*Bryonia alba*	14	9	5
4.	*China*	10	4	6
5.	*Gelsemium*	6	3	3
6.	*Kali carb.*	6	3	3
7.	*Carbo veg.*	5	3	2
8.	*Phosphorus*	5	2	3
9.	*Pyrogenium*	5	5	0
10.	*Lycopodium*	4	4	0
11.	*Sulphur*	4	3	1
12.	*Vanadium*	4	2	2
13.	*Merc. sol.*	4	1	3
14.	*Hepar sulph.*	3	3	0
15.	*Ipecacuanha*	3	2	1
16.	*Nux vomica*	3	2	1
17.	*Antimonium arsenicum*	2	2	0
18.	*Antimonium tart.*	2	0	2
19.	*Camphora*	2	1	1
20.	*Crotalus horridus*	2	2	0
21.	*Lachesis*	2	1	1
22.	*Rumex*	2	2	0
23.	*Senega*	2	1	1
24.	*Arnica montana*	2	0	2
25.	*Cuprum met.*	1	0	1
26.	*Mephitis*	1	1	0
27.	*Spongia tosta*	1	1	0
28.	*Pulsatilla*	1	0	1
29.	*Influenzinum*	1	1	0
30.	*Belladonna*	1	0	1
31.	*Sarcolactic acid*	1	1	0

Table 7 Most frequently used mother tinctures

No.	Name of mother tincture	No. of patients	Moderate	Severe
1.	*Aspidosperma Q*	19	15	4
2.	*Lobelia i. Q*	7	6	1
3.	*Acid phos Q*	4	4	0
4.	*Viola o. Q*	4	3	1
5.	*Avena s. Q*	2	0	2
6.	*Glycyrrhiza Q*	2	1	1
7.	*Justicia a. Q*	2	2	0

Co-morbidities, Clinical Improvement and Mortalities

Our research resonates with several other studies[27,28] that speak of multi-morbidity as a major risk factor for severity in COVID-19. Of the 23 participants who were enrolled in the study from the ICU, 14 had more than two co-morbidities, seven in each group. Out of 150, 53 (35.3%) patients had more than one morbidity, of which 39 (26%) reported the combined morbidity of Type II diabetes mellitus and hypertension. Corrective measures to reduce these two conditions to help limit severe COVID-19, therefore, seem to be a step in the right direction.[29] WHO-COOS, the 8-point ordinal scale for clinical outcome assessment, was an effective tool to measure clinical improvement or deterioration. Better improvement was seen in the AoH group, whose participants were free of oxygen therapy earlier within the follow-up period of 28 days, and with fewer mortalities, speaking in favor of enabling integrated homeopathic treatment in the COVID treatment centers, including intensive care set-ups. More participants in the AoH group were free of oxygen support therapy at the end of 28 days: that is SpO_2 in room air or reduced to low flow from high flow oxygen. Overall well-being, reflected via MYMOP2, also showed a significant finding in favor of the AoH group.

In common with another study,[30] medicines reported as useful in the study included *Bryonia*, *Arsenicum album*,

Gelsemium and *Phosphorus*. However, our study focused on moderate and severe cases, and patients also responded well to other medicines, with *Veratrum viride* 200 C and mother tincture *Aspidosperma* deserving special mention. Our study also suggested a role of homeopathy mother tincture(s) in the management of oxygen levels and cough paroxysms in COVID-19 patients, thus warranting more research on their use along with studies on ultra-diluted, individualized, homeopathic medicines that perhaps have a longer and more far-reaching role in overall recovery.[31]

This study reports 13.6% total mortality rate. Though the work was concentrated on moderate and severe cases only, the mortality rate is lower than reported in hospitalized patients from other studies.[32,33] The AoH group had 44% fewer casualties than the AoP group. Whether this can be attributed to holistic treatment through homeopathy, especially when the body's immunity is weakened,[34] remains a subject of further, more rigorous research.

Trends in Laboratory Parameters

Five important parameters were found to be statistically significantly improved in the AoH group as compared with the AoP group in the study: viz., CRP, fibrinogen, TLC count, alkaline phosphatase, and platelet count. The statistical trends in other parameters also favored the AoH group in terms of better improvement.

Some hematological parameters, including white blood cells, lymphopenia, CRP, and some biochemical parameters such as LDH, creatine kinase (CK) and troponin, have been reported to be associated with COVID-19 severity.[35] The CRP marker has been found to be significantly increased in the initial phases of the infection for severe to critical COVID-19 patients – in fact, even before tomography has shown diffused pneumonia patches in the lungs, demonstrating the level of severity. Studies reveal CRP is an early predictor of onset of inflammation in the body, followed later by IL-6 and serum ferritin.[35–37] Studies reveal CRP is an early predictor of onset of inflammation in the body, followed later by IL-6 and serum ferritin.[35–37] The significant regression of CRP to normal in the AoH group should be investigated further before stating the possible role of homeopathy in limiting the inflammation in the early stages of COVID-19. However, a recent study found that IL-6 is one of the most robust prognostic markers of survival, eclipsing or outperforming CRP, D-dimer and ferritin.[38] D-dimer, a coagulation biomarker, is an equally important parameter. Therefore, the positive trend seen in IL-6 and D-dimer in the AoH group compared with the AoP group necessitates further assessment of the role of homeopathy to limit the coagulopathy, inflammation and associated mortalities resulting from COVID-19.[39] Significant decreases in platelet count and fibrinogen also speak of an anti-coagulant role[40,41] of homeopathic medicines, thus advocating additional studies.

Raised TLC count is another measure associated with higher chances of developing severe illness from COVID-19.[42] Significant control of this measure in the AoH group, as opposed to the AoP group, is worth exploring further to understand whether homeopathic medicines could play a role in checking the progress of COVID-19 toward severity. Another important finding in the study is the significant reduction in alkaline phosphatase, which indicates lesser liver toxicity[43] in the AoH group. This outcome may be evaluated in future studies to understand whether homeopathic medicines are able to reduce liver damage directly, or indirectly as a result of a reduced need for conventional medicines with known adverse effects on the liver.

Individualized homeopathic medicines had an overall positive effect on the biochemical and hematological parameters used for assessing patients' clinical status.

Blinding and Controlled Studies

Single-blinded design, though a source of potential bias, could not be avoided in the study's clinical setting since we were dealing with high-risk cases, and it was important for all investigators and treating doctors to know whether the patients were being given any medicine other than the standard care at all given points of time. This did help in two cases, one of them when the patient suddenly became non-compliant and started reporting problems after the medicine (he belonged to the control group), which was then clarified to the medics on duty. In the second instance, the patient, belonging to the AoH group, had to be immediately transferred to ICU to treat a sudden drop in glucose levels. A complete medical history was required instantly. Had the investigators been blinded, such information would have had to wait to be passed on to the resources who required it for immediate interpretation. In such situations therefore it was deemed appropriate to have the investigators aware of the group to which the cases belonged, thus saving precious time, as has also been recommended as proper practice when double blinding is impossible or unethical.[44] However, the single-blinded design is an obvious limitation of our study and investigator bias cannot be ruled out, which could be the reason for relatively more co-morbid participants in the control group. Nevertheless, single blinding of the trial participants themselves minimized biases associated with subject awareness. If a double-blind trial could be made possible in future, the results of such a study would be more reliable.

Even though the external validity of placebo-controlled trials is generally low,[45] this trial was different in the sense that even though controlled, it was performed in the relatively pragmatic setting of intensive care COVID wards. The standard treatment varied between patients, and that could not be controlled as it fell under the domain of the institutional management protocol which, as per the study design, was left to the discretion of the doctors delivering standard care. Even the laboratory tests were repeated in the patients only when those doctors deemed fit. This meant fewer follow-up readings available for periodic blood tests, which in turn affected the consistency in results for analysis. Out of the 147 patients enrolled, laboratory parameters could be assessed only for those who were so advised, and at that frequency of measurement. Another reason for broader generalizability of the study to the wider population is that the inclusion criteria for participation were broad,

with all adult ages allowed, and with co-morbidities not excluded.

Serving in Adversity – A Challenge or an Opportunity?
This study was conducted amid a very challenging time when India was witnessing the pandemic at its peak, with Delhi alone reporting more than 8,000 cases in a single day.[46] This worked both as a merit and a limitation of the study. On one hand, due to this peak, the number of patient enrollments could be achieved faster than expected; on the other hand, due to a high admission rate, the patients were being shifted across four COVID wards in the hospital (based on their clinical condition) to accommodate higher patient inflow. This led to some time lost at the end of investigators in tracing patients in a 200-bedded COVID ward. Moreover, the compliance for taking the medicines could be assured only once a day during the daily follow-up. Since the paramedical staff were overburdened with the patient rush, it was not practical to request them to assure compliance to an add-on medicine. Further, in the ICU, the investigators faced a different set of challenges. For example, most patients were disoriented and not in a position to talk, either due to the high flow nasal therapy through non-invasive ventilators, or because of the medicines they were taking as a part of standard care. Hence, in most cases, the medicines were prescribed on the observed signs and clinical condition alone, without any characterization of the subjective symptoms that a homeopath would otherwise normally elicit through a one-to-one interaction.[47] Nevertheless, the medicines prescribed on objective symptoms and pathological stage seemed to provide clinical relief. Also, in cases of compromised compliance, the infrequent doses seemed to bring relief to many patients, even though the investigators would have liked to follow the approach of giving medicines every 2 hours. The more oriented and compliant patients, however, did seem to have fared better in terms of speedier and better recovery.

Delivering integrated homeopathy treatment, especially in tertiary and intensive care set-ups, was both a challenge and a privilege at the same time. Nevertheless, the investigators had a gratifying experience, with the AoH group's patients reporting relief, sometimes immediately after the medicine, which mostly included easier breathing, reduced cough, better sleep, calmer mind, and improvement in overall wellbeing. The homeopathic mother tinctures, whenever given, either as a cough pacifier or to boost oxygen levels, seemed to work as per expectation in most cases.

Our study, exploring whether integrative homeopathy could be successful in treating moderate to severe COVID-19 patients, was merely a small effort in that direction. More rigorous, including double-blinded, trials would be instrumental in confirming or refuting the present findings. With positive outcomes documented in the viral clearance time, mortality rate and some important laboratory parameters, the study suggests a useful role for AoH in COVID-19 management, albeit in a preliminary manner.

Conclusion

The study suggests that homeopathy may be an effective adjunct to standard care for treating moderate and severe COVID-19 patients. More rigorous studies are warranted to confirm or refute these initial findings.

Highlights
- The trial explored whether homeopathic treatment, when given in conjunction with standard care (AoH group) in moderate and severe cases of COVID-19, could lead to better clinical outcomes than in corresponding cases given placebo with standard care (AoP).
- AoH patients showed faster conversion of RT-PCR to negative, lesser mortality rate, and better clinical and patient-reported improvement compared with the AoP group.
- Further research is indicated on the use of AoH in hospitalized patients with moderate or severe COVID-19.

Supplementary material

Supplementary Fig. S1. Laboratory values in AoH and AoP groups.

Data Sets
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
Harleen Kaur conceptualized and designed the study, in consultation with Arvind Dayal, the statistician. She drafted the protocol, sought approvals from the concerned committees, executed the study as the Team Leader, and was involved in final compilation and analysis of the data. There were two teams that alternated for duties, with a period of 15 days home quarantine following 15 days COVID duty. Team A was led by Harleen, and Team B was led by Subhash Kaushik. Besides, Subhash was instrumental in effecting homeopathic prescriptions in treating moderate and severe COVID-19 cases. Sushma Bhatnagar and Anil Khurana played a pivotal role by mentoring the teams for the study, and guiding them from time to time. Naval Kumar Verma provided his clinical acumen on a case-to-case basis, as and when consulted, and also shared a reference compendium of medical literature for quick reference. Khushbu Gautam, Gurpreet Singh and Shweta Singh, and Maneet Parewa, Tania Chatterjee and Syed Ali were the three assisting homeopathy doctors in Teams A and B respectively. Arvind Dayal helped in statistical analysis of the huge

data generated from the study, along with Harleen, Gurpreet and Shweta. Suraj Pal Singh and Varun Shekhar were instrumental in all study-related coordination with AIIMS' clinical and paramedical staff for execution of the study. All the authors read the draft manuscript and provided their inputs for its refinement or modification. All authors assure the completeness and accuracy of the data and the adherence of the trial to the protocol.

Funding
The study was funded by the Central Council for Research in Homoeopathy, Ministry of AYUSH, Government of India. The funder approved the study through its review committees, delegated/recruited staff for conducting the study, and facilitated all collaborative procedures.

Conflict of Interest
None declared.

Acknowledgements
The authors are indebted to Dr. V.K. Gupta, Chairman, Scientific Advisory Board, CCRH, for his guidance during the drafting of the protocol. Thanks are due to Dr. Jaswant Patil, Pulmonologist-cum-Homeopath, Mumbai, for his practical guidance in developing expertise in managing hospitalized COVID-19 cases, and guiding prescriptions in difficult cases. Dr. Saurabh Vig, Dr. Ram Singh, Dr. Prashant Sirohia and Dr. Shruti Gairola of AIIMS are gratefully acknowledged for their guidance during the handling of patients in the ICU. The kind efforts of Dr. Jyoti Sachdeva, Research Associate (Homoeopathy) at CCRH are acknowledged for management of the data, along with Ms. Kanchan Sharma, Office Assistant at CCRH. The invaluable and critical feedback of Dr. Daisy Katarmal, Senior Research Fellow (Homoeopathy) and Dr. Surbhi Jain, Research Associate (Homoeopathy), on the study protocol before its execution, and their assistance in reviewing the Materia Medica for COVID-19-like symptoms along with Dr. Sachdeva, are deeply appreciated. Dr. Katarmal also reviewed the manuscript critically before submission. Rejoice Health Foundation, a non-government organization, is acknowledged for administrative support. The authors also thank Dr. Supriya Bhalerao and Dr. Ramesh Bawaskar, who provided their expert advice in revising the manuscript text to suit the journal style.

References

1 World Health Organization. Weekly epidemiological update on COVID-19. Accessed January 21, 2022 at https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2 Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966
3 Palacios Cruz M, Santos E, Velázquez Cervantes MA, León Juárez M. COVID-19, a worldwide public health emergency. Rev Clin Esp (Barc) 2021;221:55–61
4 Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020; 382:1787–1799
5 Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents 2020;55:105932
6 Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:732–739
7 Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; 56:105949
8 World Health Organization. Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD). WHO, 2016. Accessed February 27, 2021 at: https://www.who.int/news/item/12-08-2014-ethical-considerations-for-use-of-unregistered-interventions-for-ebola-virus-disease-(evd)
9 Varanasi R, Nayak D. Homoeopathy in the management of infectious diseases: different facets of its use and implications for the future. Indian J Res Homoeopathy 2020;14:110–121
10 Teixeira MZ. Homeopathy: a preventive approach to medicine? Int J High Dilution Res 2009;8:155–172
11 Mathie RT, Baitson ES, Frye J, Nayak C, Manchanda RK, Fisher P. Homeopathic treatment of patients with influenza-like illness during the 2009 A/H1N1 influenza pandemic in India. Homeopathy 2013;102:187–192
12 Jacobs J. Homeopathic prevention and management of epidemic diseases. Homeopathy 2018;107:157–160
13 Manchanda R, Oberai P, Prasad R, et al. Evaluation of homoeopathic medicines as add-on to institutional management protocol in acute encephalitis syndrome: an exploratory observational comparative study. Indian J Res Homoeopath 2015;9:34–41
14 Nayak D, Chadha V, Jain S, et al. Effect of adjuvant homeopathy with usual care in management of thrombocytopenia due to dengue: a comparative cohort study. Homeopathy 2019;108:150–157
15 Golden I. Large scale homœoprophylaxis: results of brief and long-term interventions. Am J Homeopath Med 2019;112:31–36
16 Shinde V. Homoeopathy in pandemic Spanish flu 1918. Indian J Res Homoeopath 2020;14:152–159
17 Winston J. The Faces of Homeopathy. Wellington, New Zealand: Great Auk Publishing; 1999
18 Rajendran ES. Homeopathy seen as personalised nanomedicine. Homeopathy 2019;108:66–70
19 Tramontana A. COVID-19 pneumonia: a potential role of homeopathy. Homeopathy 2021;110:70–71
20 Masiello DJ. The COVID-19 pandemic: a view from New York City. Homeopathy 2020;109:163–166
21 Adler UC, Adler MS, Hotta LM, et al. Homeopathy for Covid-19 in primary care: a structured summary of a study protocol for a randomized controlled trial. Trials 2021;22:109
22 Govt. of India. Ministry of Health & Family Welfare. Clinical Management Protocol: COVID-19. 2020, Version 4; Accessed June 27, 2020 at: https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf
23 World Medical Association. WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. 64th WMA General Assembly. Fortaleza, Brazil: 2013
24 Paterson C, Britten N. In pursuit of patient-centred outcomes: a qualitative evaluation of the 'Measure Yourself Medical Outcome Profile'. J Health Serv Res Policy 2000;5:27–36
25 World Health Organization. COVID-19 Therapeutic Trial Synopsis. World Health Organization2020; Geneva, Switzerland:1–9. February 18, 2020. Available at: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis
26 Chu CM, Leung WS, Cheng VCC, et al. Duration of RT-PCR positivity in severe acute respiratory syndrome. Eur Respir J 2005;25:12–14
27 Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 2020;65:533–546

28 Khedr EM, Daef E, Mohamed-Hussein A, et al. Impact of Comorbidities on COVID-19 Outcome. medRχiv; 2020
29 Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21
30 Rutten L, Smedley T, Ives G, et al. Data collection during the COVID-19 pandemic: learning from experience, resulting in a Bayesian repertory. Homeopathy 2021;110:94–101
31 Mathie RT, Lloyd SM, Legg LA, et al. Randomised placebo-controlled trials of individualized homeopathic treatment: systematic review and meta-analysis. Syst Rev 2014;3:142
32 Van Halem K, Bruyndonckx R, van der Hilst J, et al. Risk factors for mortality in hospitalized patients with COVID-19 at the start of the pandemic in Belgium: a retrospective cohort study. BMC Infect Dis 2020;20:897
33 Olivas-Martínez A, Cárdenas-Fragoso JL, Jiménez JV, et al. In-hospital mortality from severe COVID-19 in a tertiary care center in Mexico City; causes of death, risk factors and the impact of hospital saturation. PloS One 2021;16:e0245772
34 Mudd PA, Crawford JC, Turner JS, et al. Targeted Immunosuppression Distinguishes COVID-19 from Influenza in Moderate and Severe Disease. medRχiv; 2020
35 Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020;57:389–399
36 Bilgir O, Bilgir F, Calan M, Calan OG, Yuksel A. Comparison of pre- and post-levothyroxine high-sensitivity c-reactive protein and fetuin-a levels in subclinical hypothyroidism. Clinics (São Paulo) 2015;70:97–101
37 Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55:105954–105960
38 Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020;26:1636–1643
39 Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324–1329
40 Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology 2021;88:15–27
41 Aggarwal M, Dass J, Mahapatra M. Hemostatic abnormalities in COVID-19: an update. Indian J Hematol Blood Transfus 2020; 36:1–11
42 Zhu B, Feng X, Jiang C, et al. Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study. BMC Infect Dis 2021;21:574
43 Kumar A, Kumar P, Dungdung A, Gupta AK, Anurag A, Kumar A. Pattern of liver function and clinical profile in COVID-19: a cross-sectional study of 91 patients. Diabetes Metab Syndr 2020; 14:1951–1954
44 Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. BMJ 2000;321:504
45 Canevelli M, Trebbastoni A, Quarata F, et al. External validity of randomized controlled trials on Alzheimer's disease: the biases of frailty and biological aging. Front Neurol 2017;8:628
46 The New Indian Express. Delhi records over 8,000 COVID-19 cases for first time, 4.59 lakh cases in capital. November 12, 2020
47 Schmacke N, Müller V, Stamer M. What is it about homeopathy that patients value? What can family medicine learn from this?. Qual Prim Care 2014;22:17–24

