Clinical characteristics based homeopathic Remedy Profiling of COVID-19 Patients: A Retrospective Cohort Study

Research Article

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Abstract

Objective: The objective of the study was to recognize core symptoms associated with COVID-19 positivity, its impact on mental health of patients and to identify indicated homeopathic remedies for COVID-19. Methods: In this pilot study, 25 confirmed COVID-19 patients admitted at Dedicated COVID Hospital (DCH) established under Dr. D Y Patil Vidyapeeth campus took part in survey questionnaire entitled as "Health impact survey for clinical features and patient profiles of COVID 19: Based on Homoeopathic perspective" observed by three independent observers. Based on the survey, specificity and sensitivity of symptoms was analyzed by three independent physicians to perform remedy analysis in order to identify indicated homeopathic medicines for COVID-19 in mild to moderate cases. Results: A total of 25 patients were included in study. Out of 25, 16 patients did not have any co-morbidity while 9 patients had diabetes, blood pressure or thyroid as one of the co-morbidities. The mean age of the patients was 39.4 years ± 12.6 where mean age of patients without co-morbidity was significantly lower than the patients with co-morbidities. The major symptoms were found to be fever (76%), cough (76%), shortness of breath (72%), sore throat (56%), fatigue (80%), loss of smell (40%) and Loss of taste(48%). Likelihood ratio of a positive test was found to be higher for Loss of smell, Loss of taste and Cough. Mixed and contrasting responses were reported by the study subjects on mental health impact. Majority of patients showed mild negative impact on mental health. In remedy analysis total 6 homeopathic medicines were observed with most commonly indicated being *Carbo vegetabilis* (70.66%), *Antimonium tartaricum* (10.66%), *Arsenic album* (9.33%) and *Bryonia alba Linn.* (4%) in 30C potency. Conclusion: The observation from current study demonstrate that fever, cough, shortness of breath, sore throat, fatigue, loss of smell and Loss of taste are most common symptoms associated with COVID-19 and *Carbo vegetabilis, Antimonium tartaricum, Arsenic album* and *Bryonia alba Linn.* are most frequently indicated homeopathic medicines for COVID-19.

Key Words: COVID-19, Major symptoms, Mental impact, Homoeopathy.

Introduction

COVID-19 is a pandemic caused by novel corona virus SARS-CoV-2. It started in December, 2019 from China and since then it has infected more than 200 million people and caused millions of casualties around the globe (1).As of August, 2021, there were over 32 million confirmed cases of COVID-19 with more than 4 lakh deaths in India (2).

SARS-CoV-2 is a positive stranded beta corona virus. Extensive research has shown that SARS-CoV-2 infect host cells by binding to host Angiotensin-Converting Enzyme-2 (ACE2) receptor through its spike proteins (3). The infection starts from nasal cavity and progress through upper to lower respiratory tract. In severe cases, virus infect alveolar type II cells in lungs which leads to cellular damage causing aberrant wound healing, leading to more severe scarring and fibrosis than other forms of acute respiratory distress syndrome. It can also cause extra-pulmonary manifestation in ACE-2 receptor expressing tissues other than lungs (4). COVID-19 clinical symptoms display mild cold to severe pneumonia-like symptoms. These include a wide range of symptom such as breathing difficulties, muscle pain, respiratory disorders, low to high-grade fever (mainly persisting for 3-4 days), headache, mild conjunctivitis, etc. Severe cases present pneumonia is a prime symptom (3-4). Further, persistent lockdowns imposed to prevent the spread of virus also impacted mental health of large population including COVID-19 patients all around the world.

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Since last 18 months, pandemic has pushed scientific and medical community to identify and develop therapeutic approaches for the prevention and management of COVID-19. Various therapeutic agents ranging from remdesivir, lopinavir/ritonavir with interferon β-1a, chloroquine, and hydroxychloroquine has to convalescent plasma been used for COVID-19 therapy (3-7). Recently, many vaccines has also been developed and approved for prevention of COVID-19.Along with these, medical community also tried traditional medicine for management of COVID-19 associated symptoms (8).

Homoeopathy has a well-established history in epidemic management (9, 10).In case of COVID-19, homoeopathy medicines has been tested for preventive measures with a focus has been on identifying an effective universal prophylactic medicine or as personalized homeopathic treatment for patients or as an adjuvant therapy (11-12). Identification of potential homeopathic medicine for treatment of COVID-19 needs a stepwise process where the first step is characterization of clinical symptoms of COVID-19-positive patients and identification of probable effective remedies. It should be followed by evaluation of therapeutic efficacy of these remedies against COVID-19 through a high-quality randomized controlled trial (RCT). The potential remedies with anti-COVID-19 effect must be integrated in the treatment regimens of COVID-19 patients and their preventive potential should be assessed through rigorous RCTs in high-risk population groups and disease hot spots.

In this study, we have addressed the first step where we systemically characterized major clinical symptoms of COVID-19 along with its impact on mental health of patients. We have further identified potential homeopathic medicine based on those clinical features. This will lead to future studies for wide-range validation and incorporation in treatment regimens.

Methods
Study design
A single centric pilot study was conducted in Dedicated COVID-19 Hospital (DCH) established under Dr. D Y Patil Vidyapeeth campus, Pune, Maharashtra, India. In this study, a survey questionnaire entitled as "Health impact survey for clinical features and patient profiles of COVID 19: Based on Homoeopathic perspective" was carried out by physicians. A comprehensive questionnaire was designed by faculty members of Dr. D Y Patil Homoeopathic Medical College and Research Centre, Pune entitled as "Dr. D. Y. Patil Homoeopathic Medical College and Research Centre Modified Corona virus Health impact survey for clinical features and patient profiles of COVID 19" to collect information about the clinical symptoms and mental health issues in COVID-19 patients. From the survey, the specificity and sensitivity of symptoms was analyzed by three independent observers and then further converted into rubrics. Based on the rubric analysis, potency indicator and remedy analysis was performed by three independent physicians for identification of most indicated homeopathic medicines and their optimum potency for COVID-19 interventions.

Participants
25 RT-PCR confirmed COVID-19 symptomatic patients admitted to dedicated COVID Hospital established under Dr. D Y Patil Vidyapeeth campus, Pune, Maharashtra, India were included in the study after signing an informed consent form for subsequent data analysis and publication.

Data Sources
Case record form were studied to collect clinical characteristics of patients. Faculty members from Dr. D Y Patil Homoeopathic Medical College and Research Centre, Pune collected the symptoms and mental health impact based on a designed questionnaire entitled as "Dr. D. Y. Patil Homoeopathic Medical College and Research Centre Modified Corona virus Health impact survey for clinical features and patient profiles of COVID 19".

Results
Demographics
A total of 25 confirmed COVID-19 symptomatic patients were included in the study. Out of these, 14 (56%) were male while 11 (44%) were female patients. The mean age of patients was 39.4 years (S.D., 12.6; range, 19-72). 16 patients did not have any co-morbidity while remaining 9 patients have either diabetes or blood pressure or thyroid as one of the co-morbidity. The mean age of patients without co-morbidities was significantly lower (33.38 ± 7.65) than patients with co-morbidities (54.6 ± 12.85; 54.6 ± 10.13 and 44.5 ± 10.5) **(Table 1).**

Table 1: Demographic details of patients

	Total (n=25)	Without Co-morbidity (n=16)	With diabetes as one of co-morbidity (n=5)	With blood pressure as one of co-morbidity (n=5)	With thyroid as one of co-morbidity (n=2)
Age					
Mean	39.4 ± 12.6	33.38 ± 7.65	54.6 ± 12.85	54.6 ± 10.13	44.5 ± 10.5
Median	35	34	57	55	44.5
Gender					
Male	14 (56%)	10	3	3	0
Female	11 (44%)	6	2	2	2

Effect of exposure to COVID+ patients and symptoms

Majority of the subjects had history of exposure to COVID+ patients (76%), fever (76%), cough (76%), shortness of breath (72%), sore throat (56%), and fatigue (80%), but a few had history of loss of smell (40%),loss of taste (46%), eye infection (4%), diarrhoea (8%) and others (8%) (Table 2).

Table 2: Details of clinical symptoms of COVID-19 in patients

Symptoms	Absent (n)	Present (n)
Exposure to someone likely to have Corona virus/COVID-19	6 (24%)	19 (76%)
Fever	6 (24%)	19 (76%)
Cough	6 (24%)	19 (76%)
Shortness of breath	7 (28%)	18 (72%)
Sore throat	11 (44%)	14 (56%)
Fatigue	5 (20%)	20 (80%)
Loss of smell	15 (60%)	10 (40%)
Loss of taste	13 (52%)	12 (48%)
Eye infection	24 (96%)	1 (4%)
Diarrhoea	23 (92%)	2 (8%)
Others	23 (92%)	2 (8%)

Of the above reported symptoms, three symptoms e.g. Loss of smell, Loss of taste and Cough demonstrated Likelihood Ratio for positive test greater than 1, indicative of the fact that history of exposure to COVID+ patient has increased itself the likelihood of these three symptoms among the study subjects. Diagnostic accuracy of Cough was the highest (68%) while it was 56% for other two symptoms (Table 3) Likelihood Ratio of COVID-19 symptoms.

Table 3: Likelihood Ratio of COVID-19 symptoms

Symptoms	Likelihood ratio of a Positive Test	Likelihood ratio of a Negative Test	Diagnostic Efficacy
Fever	0.6842 (Undefined)	Undefined	52% (33.5-69.97)
Cough	1.184 (0.7006 - 2.002)	0.6316 (0.0545 - 7.319)	68% (48.41-82.8)
Shortness of breath	0.8211 (0.5175 - 1.303)	1.895 (0.00007579 - 47370)	56% (37.07-73.33)
Sore throat	0.7895 (0.4054 - 1.537)	1.421 (0.161 - 12.54)	48% (30.03-66.5)
Fatigue	0.9474 (0.6182 - 1.452)	1.263 (0.00004291 - 37180)	64% (44.52-79.75)
Loss of smell	2.842 (0.3143 - 25.7)	2.842 (0.3143 - 25.7)	56% (37.07-73.33)
Loss of taste	1.579 (0.4968 - 5.019)	0.7105 (0.4473 - 1.129)	56% (37.07-73.33)
Eye infection	Undefined	0.9474 (0.8496 - 1.056)	28% (14.28-47.58)
Diarrhoea	0.3158 (Undefined)	1.137 (0.9427 - 1.371)	24% (11.5-43.43)
Others	0.0 (Undefined)	1.5 (Undefined)	16% (6.403-34.65)

Impact of COVID-19 on mental health of patients

The impact of COVID-19 on mental health of patients was assessed by survey questionnaire. The results reported mixed and contrasting responses by the study subjects on mental health impact. Majority (76%) of the subjects accepted that quality of relationship with family members changed(mostly mildly)and these changes in family and social contacts were stressful for 56%and 48% participants respectively. Only 56% were moderately while 36% were mildly hopeful that COVID-19 crisis will end in their area but most of them were generally worried (64%). Though majority of them remained happy (96%) and relaxed (72%), but 88% were restless, 92% felt fatigued/tired and 96% were not able to concentrate, however only 28% got easily irritated/angered. Almost half (44%) felt lonely and majority of them (9/11) with moderate to severe intensity.

Table 4: Impact of COVID-19 on mental health of patients

Mental and personal effects	Absent	Mild	Moderate	Moderately Severe	Severe
Effect on family relation	6 (24%)	16 (64%)	3 (12%)	-	-
Stress due to changes in family contacts	11 (44%)	3 (12%)	11 (44%)	-	-
Stress due to changes in social contacts	12 (48%)	9 (36%)	3 (12%)	1 (4%)	
Hopes of COVID-19 ending soon	2 (8%)	9 (36%)	14 (56%)	-	-
Wariness	9 (36%)	3 (12%)	8 (32%)	5 (20%)	-
Sadness	1 (4%)	23 (92%)	1 (4%)	-	-
Anxious	2 (8%)	16 (64%)	6 (24%)	1 (4%)	-
Fidgety or restlessness	3 (12%)	16 (64%)	6 (24%)	-	-
Fatigue	2 (8%)	6 (24%)	11 (44%)	6 (24%)	-
Concentration	1 (4%)	20 (80%)	3 (12%)	1 (4%)	-
Irritation or anger	18 (72%)	5 (20%)	2 (8%)	-	-
Loneliness	14 (56%)	2 (8%)	7 (28%)	1 (4%)	1 (4%)

Analysis of the specificity and sensitivity of symptoms by rubric profiling

From the survey, the specificity and sensitivity of symptoms were analysed by three independent observers which then further converted into rubrics. This information was compiled for the 64 clinical symptoms and homeopathic rubric profile by means of yes proportion is represented in **Table 5**.

Table 5: Rubric profiling of symptoms in COVID-19 patients

Serial No	Rubric	Yes proportion		
		Profile 1	Profile 2	Profile 3
1	Respiration- Accelerated	100	100	92
2	Respiration-Difficult (Dyspnoea)	96	96	96
3	Respiration-Difficult (Dyspnoea)- Fans wants to be	88	68	88
4	Respiration-Difficult (Dyspnoea)- Lying down aggravates	88	88	92
5	Respiration- Wheezing	56	56	64
6	Respiration- Arrested- Sleep during	108	108	112
7	Respiration-Deep- Desire to breathe	96	96	96
8	Respiration-Difficult (Dyspnoea)- Cough with	100	100	100
9	Respiration-Difficult (Dyspnoea)- motion	100	100	100
10	Respiration-Difficult (Dyspnoea)- Open wants doors and windows	96	80	96
11	Respiration-Difficult (Dyspnoea)- better by sitting	96	96	96
12	Respiration- Loud	88	88	88
13	Respiration- Rattling	72	72	72
14	Respiration- Accelerated- lying down while	104	104	104
15	Respiration- Arrested	120	128	120
16	Respiration- Arrested- Coughing	116	116	116
17	Respiration- Asphyxia	24	24	36
18	Respiration- Deep	92	92	92
19	Respiration- Impeded-Obstructed	104	88	104
20	Chest- Pain- Respiration- Deep	92	92	92
21	Chest- Weakness- Respiration- Deep	96	96	96
22	Chill- Icy Coldness- Whole Body- Cold Breath	36	52	36
23	Chest-Pain- Inspiration during	88	92	88
24	Chest-Pain Stitching- Sides- Inspiration	76	76	76
25	Back-Pain- Breathing When	36	36	36
26	Chest- Oppression	96	96	96
27	Chest- Inflammation- Lungs	144	144	144
28	Chest- Weakness	104	100	104
29	Cough- Irritation- Chest in	88	88	88
30	Chest- Congestion	92	92	92
31	Chest- Fullness	104	104	104
32	Chest- Inflammation- Bronchial Tubes	156	156	156
33	Chest- Oedema- Pulmonary	164	167	164
34	Chest- Pain	80	80	80
35	Chest- Pain- Pressing	40	40	40
36	Chest- Pain- Stiching	80	80	80
37	Chest- Paralysis- Lung Old People	12	12	12
38	Cough- Constriction- Chest	88	88	88
39	Chest- Catarrh	72	72	72
40	Chest- Weakness- Respiration-deep	88	88	88
41	Fever- Burning Heat	72	72	72
42	Fever -Continuous Chill	24	24	24
43	Generalities- Weakness- Fever during	76	76	76
44	Cough- Paroxysmal	84	84	84
45	Cough Spasmodic	100	100	100
46	Cough- Suffocative	100	100	100
47	Cough- Violent	96	96	96
48	Cough- Constant	28	28	28
49	Cough- Exhausting	96	96	96
50	Cough- Hard	92	92	92
51	Cough- Rattling	72	72	68
52	Cough- lying aggravates	96	96	96
53	Extremities- Pain- Fever during	20	20	20
54	Fever- Internal heat	68	68	68
55	Cough- fever-during	64	64	64
56	Throat- Pain- Sore	52	52	52
57	Throat- Swallowing difficult	44	44	44
58	Larynx & Trachea- Catarrh	20	20	20
59	Larynx & trachea- Pain- soreness	16	16	16

60	Larynx & trachea- Voice- Hoarseness	4	4	4
61	Nose Obstruction	40	40	48
62	Nose- Catarrh	48	48	48
63	Nose- Sneezing- frequent	36	36	36
64	Nose- Coryza	68	68	68

We further performed correlation study to examine intra and inter-observer correlation among the three observers in assessment of rubric profile. Almost perfect inter-observer correlation was found among the three observers (P1, P2 and P3) in assessment of rubric profile of 25 patients each. Pearson's correlation coefficient (r) for all 3 pairs P1/P2, P1/P3 and P2/P3 were more than 0.98 (Table 6).

Table 6: Correlation among the three observers in assessment of rubric profile

	P1	P2	P3
	P1	P2	P3
P1	1		
P2	0.9913, P= 0.00	1	
P3	0.9975, P= 0.00	0.9886, P= 0.00	1

Intra-observer agreement for individual patients was also good for all the three observers. Degree of concordance assessed by Cohen's kappa (k) was always k >0.85 (Lowest for first patient k=0.68, highest for last patient k=0.97)(Supplementary Data 1).

Supplementary Data-1
Inter-observer agreement analysis using Cohen's Kappa statistic (k)
Agreement between 3 observers in doing Rubric classification for each patient by 3 categories (Yes, No and don't know)

```
. kap  r1p1 r2p1 r3p1
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.7020     9.73    0.0000
           1 |   0.6889     9.55    0.0000
           2 |   0.3840     5.32    0.0000
----------------+-----------------------------
    combined |   0.6791    10.17    0.0000
```

```
. kap  r1p2 r2p2 r3p2

There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.9285    12.87    0.0000
           1 |   0.8939    12.39    0.0000
           2 |   0.8873    12.29    0.0000
----------------+-----------------------------
    combined |   0.9037    17.48    0.0000
```

```
. kap  r1p3 r2p3 r3p3

There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.9133    12.65    0.0000
           1 |   0.9156    12.69    0.0000
           2 |   1.0000    13.86    0.0000
----------------+-----------------------------
    combined |   0.9327    17.19    0.0000
```

```
. kap  r1p4 r2p4 r3p4
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.9106    12.62    0.0000
           1 |   0.9166    12.70    0.0000
           2 |   0.7947    11.01    0.0000
----------------+-----------------------------
    combined |   0.8930    15.77    0.0000
```

```
. kap  r1p5 r2p5 r3p5
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.8406    11.65    0.0000
           1 |   0.8514    11.80    0.0000
           2 |   1.0000    13.86    0.0000
----------------+-----------------------------
    combined |   0.8665    14.52    0.0000
```

```
. kap  r1p6 r2p6 r3p6
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.8819    12.22    0.0000
           1 |   0.8889    12.32    0.0000
           2 |   1.0000    13.86    0.0000
----------------+-----------------------------
    combined |   0.8957    14.16    0.0000
```

```
. kap  r1p7 r2p7 r3p7
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.9490    13.15    0.0000
           1 |   0.9519    13.19    0.0000
           2 |   1.0000    13.86    0.0000
----------------+-----------------------------
    combined |   0.9539    14.59    0.0000
```

```
. kap  r1p8 r2p8 r3p8
There are 3 raters per subject:
     Outcome |   Kappa       Z      Prob>Z
----------------+-----------------------------
           0 |   0.8739    12.11    0.0000
           1 |   0.8837    12.25    0.0000
           2 |   1.0000    13.86    0.0000
----------------+-----------------------------
    combined |   0.8904    14.15    0.0000
```

. kap r1p9 r2p9 r3p9
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8545   11.84   0.0000
          1 |  0.8876   12.30   0.0000
          2 |  0.8945   12.39   0.0000
----------------+----------------------------
   combined |  0.8740   14.01   0.0000
```

. kap r1p10 r2p10 r3p10
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8332   11.54   0.0000
          1 |  0.8500   11.78   0.0000
          2 |  0.9175   12.71   0.0000
----------------+----------------------------
   combined |  0.8501   13.91   0.0000
```

. kap r1p11 r2p11 r3p11
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.9291   12.87   0.0000
          1 |  0.9359   12.97   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.9431   16.25   0.0000
```

. kap r1p12 r2p12 r3p12

There are between 0 and 3 (median = 3.00) raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8597     .      .
          1 |  0.8867     .      .
          2 |  1.0000     .      .
----------------+----------------------------
   combined |  0.8934     .      .
```

Note: number of ratings per subject vary; cannot calculate test statistics.

. kap r1p13 r2p13 r3p13

There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.7619   10.56   0.0000
          1 |  0.8170   11.32   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.8243   13.97   0.0000
```

. kap r1p14 r2p14 r3p14
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8476   11.74   0.0000
          1 |  0.8665   12.01   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.8732   14.14   0.0000
```

. kap r1p15 r2p15 r3p15
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.9410   13.04   0.0000
          1 |  0.9496   13.16   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.9528   15.92   0.0000
```

. kap r1p16 r2p16 r3p16
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.9672   13.40   0.0000
          1 |  0.9730   13.48   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.9746   16.46   0.0000
```

. kap r1p17 r2p17 r3p17
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8902   12.34   0.0000
          1 |  0.9086   12.59   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.9127   15.06   0.0000
```

. kap r1p18 r2p18 r3p18
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8396   11.63   0.0000
          1 |  0.8815   12.21   0.0000
          2 |  1.0000   13.86   0.0000
----------------+----------------------------
   combined |  0.8859   15.18   0.0000
```

. kap r1p19 r2p19 r3p19
There are 3 raters per subject:

```
    Outcome |  Kappa      Z    Prob>Z
----------------+----------------------------
          0 |  0.8449   11.71   0.0000
          1 |  0.8781   12.17   0.0000
          2 | -0.0052   -0.07   0.5289
----------------+----------------------------
   combined |  0.8486   12.03   0.0000
```

. kap r1p20 r2p20 r3p20
There are 3 raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.8944    12.39   0.0000
          1 |   0.8957    12.41   0.0000
          2 |   1.0000    13.86   0.0000
----------------+------------------------------
   combined |   0.9084    15.13   0.0000
```

. kap r1p21 r2p21 r3p21
There are 3 raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.8615    11.94   0.0000
          1 |   0.9156    12.69   0.0000
          2 |   0.8832    12.24   0.0000
----------------+------------------------------
   combined |   0.8887    15.40   0.0000
```

. kap r1p22 r2p22 r3p22
There are 3 raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.9356    12.96   0.0000
          1 |   0.9515    13.18   0.0000
          2 |   1.0000    13.86   0.0000
----------------+------------------------------
   combined |   0.9561    17.21   0.0000
```

. kap r1p23 r2p23 r3p23
There are between 0 and 3 (median = 3.00) raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.9350      .       .
          1 |   0.9334      .       .
          2 |   1.0000      .       .
----------------+------------------------------
   combined |   0.9381      .       .
```

Note: number of ratings per subject vary; cannot calculate test
statistics.

. kap r1p24 r2p24 r3p24
There are 3 raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.9410    13.04   0.0000
          1 |   0.9524    13.20   0.0000
          2 |   1.0000    13.86   0.0000
----------------+------------------------------
   combined |   0.9566    16.81   0.0000
```

. kap r1p25 r2p25 r3p25

There are 3 raters per subject:

```
    Outcome |   Kappa      Z    Prob>Z
----------------+------------------------------
          0 |   0.9615    13.32   0.0000
          1 |   0.9700    13.44   0.0000
          2 |   1.0000    13.86   0.0000
----------------+------------------------------
   combined |   0.9717    16.67   0.0000
```

Based on rubric profiling of symptoms, analysis of 6 homeopathic remedies was performed by 3 independent physicians. The data in **Table 7** suggests that out of 6 prescribed homeopathic medicines, *Carbo vegetabilis* (70.66%), *Antimonium tartaricum* (10.66%), *Arsenicum album* (9.33%) and *Bryonia alba Linn.* (4%) were most commonly indicated medicines. Further, potency indicator analysis demonstrated that 30C was the most commonly employed potency. Further, correlation analysis exhibited weak, negative and non-significant correlation in potency indicator classification between observers 1 & 2 (Spearman's coefficient = -0.1951, $P > 0.05$)and observers 1 & 3 (Spearman's coefficient = -0.2228, $P > 0.05$). However, weakly positive although non-Significant correlation was found in potency indicator classification between two observers 2 & 3 (Spearman's coefficient = 0.1138, $P > 0.05$)**(Supplementary Data 2)**.

Table 7: Prescribing indications of homeopathic remedies

Homeopathic medicine	No of patients			
	Physician			Average (%)
	1	2	3	
Carbo vegetabilis	21 (84%)	16 (64%)	16 (64%)	70.66%
Arsenic album	1 (4%)	2 (8%)	4 (16%)	9.33%
Camphor	-	1 (4%)	-	1.33%
Bryonia alba Linn.	1 (4%)	1 (4%)	1 (4%)	4%
Antimonium tartaricum	2 (8%)	2(8%)	4 (16%)	10.66%
Phosphorus	-	3 (12%)	-	4%

Supplementary Data 2
Potency Indicator

. tab Potency1

```
        P1 |   Freq.    Percent     Cum.
------------+-----------------------------------
          1 |     24      80.00      80.00
          2 |      5      16.67      96.67
          3 |      1       3.33     100.00
------------+-----------------------------------
      Total |     30     100.00
```

. tab Potency2

```
     P2 |    Freq.    Percent     Cum.
------------+-----------------------------------
       1 |     26     86.67     86.67
       2 |      3     10.00     96.67
       3 |      1      3.33    100.00
------------+-----------------------------------
   Total |     30    100.00
```

. tab Potency3

```
     P3 |    Freq.    Percent     Cum.
------------+-----------------------------------
       1 |     25     83.33     83.33
       2 |      5     16.67    100.00
------------+-----------------------------------
   Total |     30    100.00
```

. spearman Potency1 Potency2 Potency3, pw star(.05)
(obs =varies)

```
         | Potency1 Potency2 Potency3
-------------+---------------------------
  Potency1 |   1.0000
  Potency2 |  -0.1951   1.0000
  Potency3 |  -0.2228   0.1138   1.0000
```

Further, Spearman's rank-order-correlation coefficient (Rho) was used to find inter-observer agreement for 3 observers while doing remedy analysis. Weak, positive, non-Significant correlation was found in Remedy analysis between two observers 1 & 2 (Rho =0.14, P > 0.05).Weak, negative, non-Significant correlation was found in Remedy analysis between two observers 1 & 3 Rho = -0.24, P > 0.05).Moderate, negative, but Significant correlation was found in Remedy analysis between two observers 2 & 3 Rho = -0.47, P < 0.05)**(Table 8)**.

Table 8: Correlation among the three physicians in remedy analysis

	P1	P2	P3
P1	1		
P2	0.1433, P > 0.05	1	
P3	-0.2057 , P > 0.05	-0.4670, P < 0.05	1

Discussion

Since last one and half year, COVID-19 pandemic has severely affected physical and mental health of masses all around the world. While western world relied upon allopathic medicine, unique health care system in India applied a pluralistic approach involving Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH) systems along with allopathy against COVID-19. Various reports suggested that integration of traditional medicines with western medicine enhances the cure rate and results in better management of COVID-19 symptoms (13-17). Similarly homeopathic medicine may prove to be potential candidates in combination with conventional therapy (12, 18).

Current study has identified highly indicated homeopathic medicines which may be used in conjunction with medically approved therapy to COVID-19 patients. These medicines were found to be highly indicated after careful analysis of sensitivity and specificity of clinical symptoms of COVID-19. The datasets of clinical symptoms of 25 confirmed COVID-19 symptomatic patients were compiled through a survey questionnaire. The major symptoms were found to be fever, cough, shortness of breath, sore throat, fatigue, loss of smell and Loss of taste. Earlier, Jethani et al also demonstrated similar set of symptoms to be dominant in 196 COVID-19 patients (19). Various other studies also shared similar observation as ours (20, 21). Further, we examined the likelihood ratio for COVID-19 positivity and these symptoms. The likelihood ratio (LR) gives the probability of correctly predicting disease in ratio to the probability of incorrectly predicting disease. The LR indicates how much a diagnostic test result will raise or lower the pre-test probability of the suspected disease. In our study, likelihood of a positive test was found to be higher for loss of smell, loss of taste and cough.

We also examined impact of COVID-19 on mental health of patients. We got mixed and contrasting responses by the study subjects on mental health impact. Majority of patients showed mild negative impact on mental health. A large number of studies regarding the effect of COVID-19 pandemic on mental health of general population has been reported however very few studies have described mental health of COVID-19 patients. Previously, Hasan et al studied the mental wellbeing of 237 COVID-19 patients and found that disease induced mild anxiety and depression in the patients (22). Further, Taquet et al demonstrated that COVID-19 was associated with increased incidence of a first psychiatric diagnosis in patients. These studies corroborate with our findings (23).

Based on analysis of sensitivity and specificity of clinical symptoms of COVID-19, we performed remedy analysis of 6 *Carbo vegetabilis* homeopathic medicine by three independent physicians. The most frequently indicated medicines were found to be, *Antimonium tartaricum*, *Arsenicum album* and *Bryonia alba Linn*. Previously, Takacs et al have shown that *Carbo vegetabilis, Antimonium tartaricum, Arsenicum album* were among most prescribed homeopathic medicines (24). Similarly, in another report *Bryonia alba Linn.* and *Arsenicum album* have been shown to be frequently prescribed (25).

The use and success of homeopathic medicine depends upon effective identification of a combination of symptoms for indication of specific medicine or combination of medicines. Hence identification of clinical symptoms is the first step leading to indication of plausible therapeutic candidates which can further be examined in randomized clinical trials. Here, we provide crucial information which may lead to multicentre, prospective, randomized double-blind

controlled trial of homeopathic medicines for COVID-19 patients using the identified medicines.

Conclusion

Observations from current study suggest that fever, cough, shortness of breath, sore throat, fatigue, loss of smell and Loss of taste are most common symptoms in COVID-19 and patients with loss of smell, loss of taste and cough are more likely to be COVID-19 positive. Further, COVID-19 patients have been shown to possess mild mental health problems. Most importantly, *Carbo vegetabilis*, *Antimonium tartaricum*, *Arsenicum album* and *Bryonia alba Linn.* were found to be most frequently prescribed homeopathic medicines and a randomized controlled clinical trial is desirable to assess the true potential of these medicines in COVID-19 management.

Highlights

- Effect of COVID-19 on mental health of clinically confirmed patients was assessed
- Clinical presentation of COVID-19 was studied in clinically confirmed symptomatic patients as a first step to identify potential homeopathic treatments
- Based on symptom profile, 4 homeopathic drugs were chosen for further assessment.

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