Ayurveda and Management of COVID-19 in Rural Indian Population: A pilot, double blind, randomized control trial

Dr. K P Bharath Chandra  
Doctors For You, Hashan, India

Saumya Subramanian  
SRI SRI INSTITUTE FOR ADVANCED RESEARCH

Rohini Wadhawan  
Doctors For You, Hashan, India

Dr. Akhilesh Mohan Wodeyar  
Doctors For You, Hashan, India

Dr. Alefia Zakir Marfatia  
Doctors For You, Hashan, India

Dr. Jeetu Pathak  
SRI SRI INSTITUTE FOR ADVANCED RESEARCH

Divya Kanchibhotla (divya.kanchibhotla@artofliving.org)  
SRI SRI INSTITUTE FOR ADVANCED RESEARCH

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Abstract

Background
The SARS-CoV-2 virus responsible for the COVID-19 pandemic is a highly contagious and rapidly mutating virus. The COVID-19 pandemic has affected millions globally over the last 18 months and continues to overwhelm the healthcare system in several countries to date. The healthcare and scientific community has been vigorously searching for ways to manage the disease. Several solutions based on traditional systems of medicine like Ayurveda are also being explored for their effectiveness in managing COVID-19. The study explored the efficacy of a 19 ingredient Ayurvedic polyherbal formulation called NOQ19, on the recovery of mild, RT-PCR positive COVID-19 patients.

Methods
This was a prospective, double blind, randomized control trial that included 92 patients with a RT-PCR positive mild case of COVID-19. The patients were enrolled from rural areas of Karnataka, a state in India. The patients were randomized between the NF2 and placebo arms, in a 1:1 ratio, and were provided their respective intervention, along with the standard of care treatment (SOC). The trial took place at the Community Care Center, Konnanuru, Hassan, Kamataka. The study duration was around 2 months and the follow-up period for an individual patient was 14 days. RT-PCR analysis was done at baseline, Day 3, 7 and 10. Blood markers to track inflammation were assessed at baseline, Day 3 and 7.

Result
A statistically significant difference was observed between the two groups with regards to the percentage of population who turned RT-PCR negative on Day 3 and Day 10. On all three assessment time points (Day 3, 7 and 10), the NF2+SOC arm showed a greater percentage of population who were RT-PCR negative compared to the placebo+SOC arm: Day 3 (NF2 -19%, Placebo - 0%) ; Day 7 (NF2- 41%, Placebo - 19%) ; Day 10 (NF2-73%, Placebo 44%). No significant changes were observed in blood markers for both the groups.

Conclusion
NF2 administered along with standard of care treatment aided early recovery from COVID-19 as demonstrated by a higher percentage of population who were RT-PCR negative on Day 3, 7 and 10. No side effects were observed during the entire study duration. Early recovery of patients is essential for rational usage of limited healthcare resources in a pandemic.

1.0 Introduction
Numerous research studies have been conducted over the last two years in the quest for an effective cure and treatment for the coronavirus disease (COVID-19). Hundreds of accelerated clinical trials have been undertaken to meet the global demand [1]. The ongoing COVID-19 global health crisis is caused by the Severe Acute Respiratory
Syndrome Coronavirus (SARS-CoV-2), a novel coronavirus. The disease presents with flu-like symptoms of fever, sore throat, dry cough, shortness of breath, fatigue, headache, conjunctivitis and gastrointestinal issues [2].

The virus first emerged in China during December 2019 and rapidly spread across the world. It was declared a pandemic by the World Health Organization (WHO) on March 11, 2020[3].

While some of the infected individuals remain asymptomatic or experience mild flu-like symptoms, others present with more severe symptoms including the severe acute respiratory distress syndrome (ARDS) which requires hospitalization, management in intensive care and can lead to further complications and adverse outcomes [4]. Various clinical trials are being conducted to identify potential therapeutic options for treating COVID-19. Several antiviral drugs e.g., remdesivir and lopinavir; immunomodulatory drugs e.g., tocilizumab, corticosteroids, hydroxychloroquine; anticoagulants; anti-inflammatory drugs and hyperimmune immunoglobulins have been proposed as treatments for COVID-19 but none of them are being used currently [5]. Although symptomatic relief from ailments is obtained, due to extensive side effects, antiviral therapy cannot be continued in the long run [6]. There is a need to identify solutions present in other health care systems such as Ayurveda, Siddha, Herbal medicine etc. which can support the current approach for COVID-19 management.

Traditional systems of medicine like Ayurveda have the potential to treat various viral infections and many herbs have been used in the treatment of epidemics in the past [7]. Several health authorities have recognized medicinal herbs from the Ayurvedic system of medicine to be reliable, evidence-based treatments for respiratory disorders [8]. The present study investigates the efficacy of an Ayurvedic formulation called NF2 in the management of COVID-19. NF2 contains 19 ingredients from 13 Ayurvedic herbs including Ashwagandha (*Withania somnifera*), Vasaka (*Adhatoda vasica*), Guduchi (*Tinospora cordifolia*), Yashtimadhu or Licorice (*Glycyrrhiza glabra*) etc. Several research studies have been conducted on individual constituents of NF2 to explore their efficacy and safety with good results. Scientists have targeted the main SARS-CoV-2 enzyme for splitting proteins, known as the Main protease (Mpro), which plays a key role in viral replication. A research study investigating the impact of active phytochemicals in *Withania somnifera* (Ashwagandha, one of the constituent of NF2) on targeting COVID-19 (SARS-CoV-2) main protease determined that Ashwagandha can be used as a potent medicine for the treatment of COVID-19 due to its inhibitory effect on SARS CoV-2 Mpro. It hinders the viral translation, thus preventing the damage to the vital organs [9]. Highest binding affinity to PLpro, 3CLpro, and spike protein were shown by Withanolide_G, Withanolide_I, and Withanolide_M from *Withania somnifera* respectively [10]. A randomized controlled clinical trial comparing HCQ (Hydroxychloroquine) and *Withania somnifera* suggested that *W. somnifera* is in no way inferior to HCQ for prophylaxis of COVID-19 and could be a safer chemo prophylactic option as well [11].

Another constituent of NF2, *Aegle marmelos* (Bilwa) showed significant anti-inflammatory properties in animal models [12]. A study on the anti-inflammatory properties of Bilwa revealed that by suppressing the pro-inflammatory cytokines and by inducing anti-inflammatory cytokines, Bilwa can act a potent anti-inflammatory Ayurvedic medicine [13]. A pharmacological study on *Glycyrrhiza glabra* (Yashtimadhu, another constituent of NF2) showed that it regulates cell growth, cell cycle and the inflammatory pathways. Yashtimadhu helps in regulation of cell cycle, MAPK1/3, PI3K/AKT pathways [14]. Another study highlighted that Yashtimadhu helps prevent apoptosis and mitochondrial stress by inhibiting the MEK-ERK-1/2 hyper-phosphorylation pathway [15].
*Adhatoda vasica* (Vasaka) contains many bioactive compounds such as vasicine and vasicinone. Vasicine has shown bronchodilator activity under both *in vitro* and *in vivo* conditions and vasicinone has shown bronchoconstriction under *in vivo* conditions. A combination of vasicine and vasicinone has shown marked reduction in cardiac depression\[^{[16]}\]. A study on Pyrroloquinazoline alkaloids derived from the extracts of *Adhatoda vasica* showed most potent anti-inflammatory effects and anti-microbial properties on a CFA-model induced with edema\[^{[17]}\]. In another *in vivo* study on guinea pigs and rabbits, coughing was induced by irritant aerosols and the intervention of *Adhatoda vasica* extracts showed potent antitussive properties similar to that of codeine\[^{[18]}\].

*Ocimum sanctum* (Tulsi - a constituent of NF2) has 46 active phytochemicals, among which Vicenin, Isorientin 4′-O-glucoside 2"-O-p-hydroxybenzoagte and Ursolic acid are found to have strong binding affinity to SARS-CoV-2 M\(^\text{pro}\)\[^{[19]}\]. These compounds are reported to have antiviral, anti-inflammatory, antitumor, antimicrobial and hepatoprotective properties. The SARS-CoV-2 M\(^\text{pro}\) can be regarded an important target for drugs as it regulates translation, transcription and replication of the virus. Tulsi is also known for its immune boosting properties\[^{[20]}\]. The phytocompounds isolated from Tulsi have been used in the treatment of swine flu and showed binding properties similar to Oseltamivir and Zanamivir, which are known antiviral drugs. Tulsi could be used as a potent antiviral agent\[^{[21]}\].

*Piper longum* (Pipalli - a constituent of NF2) is known for its medicinal properties to treat respiratory disorders caused by viral infections. The antiviral assays on *Piper longum* in methanol and chloroform extracts have shown high antiviral activity\[^{[22]}\]. Piperine, a key compound present in Pipalli with antioxidant properties, can increase WBC count, enhance immunomodulatory effect and boost enzymatic activity, as seen in cell-based study. Animal and human based studies have highlighted the anti-asthmatic, antitussive, antioxidant, anti-inflammatory, antimicrobial, and bioavailability enhancement properties of piperine\[^{[23]}\]. Piperine plays an important role in inhibiting the entry of SARS-CoV-2 into the cell by increasing the curcumin and catechin in plasma. This role is attributed to the bioavailability enhancement property of piperine\[^{[24]}\]. Previous *in vitro* studies on NF2 have shown 100% antiviral efficacy in a Vero E6 cell line-based assay\[^{[25]}\]. The *in vivo* study in a hamster model showed a 78.2% reduction in lung viral load in the NF2 group when compared to untreated controls\[^{[26]}\]. An open label feasibility study on 161 mild COVID-19 patients demonstrated that 74% (on day 5) and 98% (on day 10) of the patient population turned RTPCR negative by taking NF2 along with standard of care treatment including Vit. C, Zinc and antipyretic as (if necessary)\[^{[27]}\]. No adverse events were reported. This pilot, double blind, randomised, control trial aims to assess the effect of NF2 along with the standard of care treatment on rural patients with mild COVID-19, by specifically measuring the conversion of RTPCR from positive to negative.

2.0 Materials And Methods

2.1 Study Design

A pilot, double blind, randomized placebo control clinical trial design was chosen for this study. The study was conducted at the Community Care Center, Konnanuru, Hassan, Karnataka. The study was approved by the Doctors For You (DFY) Ethics Committee (Ref. Number- DFY/ DELHI/R/ B407/2021-22). The protocol of the study was in compliance with Helsinki ethical standards and Good Clinical Practice. The study was conducted from 5\(^\text{th}\) July to 29\(^\text{th}\) August 2021 and participants were recruited during the entire study period as and when they reported to the hospital. The follow up period was 14 days for each patient.
2.2 Participants

The participants in the study were predominantly from rural areas near the study site. Patients, with a confirmed symptomatic or asymptomatic case of COVID-19 from nearby rural areas, who reported to the study hospital were invited to participate in the study. They were informed about the purpose of the trial, and enrolled once informed consent was provided. Participants were made aware that they could withdraw from the study at any time without any loss. Baseline assessments were obtained through study proforma, including demographic information and other subjective and objective parameters of assessment. A total of 92 IPD Patients from Community Care Center, Konnanuru, Hassan, Karnataka were enrolled in the study after receiving their written consent.

2.2.1. Inclusion Criteria

a. Symptomatic RT-PCR positive mild to moderate COVID-19 cases with or without comorbidities) as per the GOI norms
b. Patients of both genders between the ages of 18-70 years
c. Indian Nationals
d. Willingness to participate in the study and provide a written consent.

2.2.2. Exclusion Criteria

a. Not willing to provide consent or participate in the clinical trial
b. Age less than 18 years or more than 70 years
c. Pregnant women or lactating mothers

2.3 Intervention

Post enrollment, each patient was monitored for 14 days. Follow up assessments were conducted on day 3, day 7 and day 10. One nasal and one throat swab for RT-PCR was obtained and analyzed on day 3, day 7 and day 10 by an ICMR accredited laboratory. The patients were monitored daily in person for compliance and were advised to inform the study team immediately in case of any adverse events and/or aggravation of symptoms.

2.3.1. NF2 preparation

NF2 is a polyherbal formulation of 19 ingredients containing 13 potent Ayurvedic herbs including Ashwagandha (*Withania somnifera*) powder and extract, Bilwa (*Aegle marmelos*), Yashtimadhu (*Glycyrrhiza glabra*) powder and extract, Rasna (*Pluchea lanceolata*), Bhunimba (*Andrographis paniculata*) powder and extract, Pippali (*Piper longum*), Haridra (*Curcuma longa*), Patha (*Cissampelos pareira*), Bhumiamla (*Phyllanthus fraternus*) powder and extract Saptaparna (*Alstonia scholaris*), Tulasi (*Ocimum sanctum*), Vasaka (*Adhatoda vasica*) powder and extract and Guduci (*Tinospora cordifolia*) powder and extract. NF2 was manufactured by Sriveda Sattva Pvt Ltd, Bangalore (Sri Sri Tattva). The drug was licensed by the Ministry of AYUSH, Govt. of India with the license number-AUS782. All the herbs which constituted NF2 were subjected to quality control. All the ingredients were blended with excipients followed by granulation, drying and compression. Once the tablets passed the QC tests, they were packed in bottles following standard procedure.

2.3.2. NF2 group
Participants enrolled in the NF2 arm were provided the NF2 tablets in a sealed bottle. The dosage for NF2 arm was 2 tablets (500 mg each) thrice a day after food for 10 days.

2.3.3. Comparator Group

The placebo control group was provided with the placebo tablets, which were packed in bottles identical to the NF2 tablets by Sri Sri Tattva. The dosage for the placebo arm was also 2 tablets (500 mg each) thrice a day after food for 10 days. The placebo was made of starch.

2.3.4. Standard treatment

In addition to receiving NF2 or placebo, both groups received the standard of care treatment as prescribed by the government guidelines. Symptomatic treatment for fever, cough and cold was given. The standard treatment included tablet Vitamin C (500 mg BD), tablet Zinc (50 mg OD), tablet Doxycycline (100 mg BD), tablet Ivermectin (12 mg OD) for 5 days. Routine medicines were given for cold or cough. Patients with fever were given Paracetamol when required.

2.4 Outcomes

Clinical history was obtained from each participant, followed by a clinical examination and baseline investigations.

2.4.1. Primary Outcomes

The primary outcome of the study was to measure the recovery from COVID-19 through RT-PCR analysis. The percentage of population turning RT-PCR negative by day 3, day 7 and day 10 in both arms was measured as the primary outcome. One nasal and one throat swab were taken from each patient and subjected to PCR analysis to identify the viral load in patients at the assessment time points.

2.4.2. Secondary Outcomes

The secondary outcome was to assess the clinical improvement among study subjects using blood biomarkers. Cytokine levels (IL-6), inflammatory markers (CRP) and antithrombotic activity (D- Dimer) were measured. The blood parameters and immune markers were measured at baseline, day 3 and day 7 to observe any significant changes. Observation of adverse events or side effects of the drugs were also included in secondary outcomes.

2.4 Sample size calculation

Sample size per group was estimated to be 50, based on the thumb rule for pilot studies\textsuperscript{[28]}. There was a sharp decline in COVID cases at site towards the end of the study, so enrollment was stopped at 95 patients.

2.5 Randomization and blinding

The study participants were allocated into different study arms, in a 1:1 ratio, with the help of a computer-generated randomization sequence. The allocation was sequentially distributed. Since both NF2 and placebo were
packaged in identical bottles, the participants were blinded to their intervention. The participants, data collector and the laboratory technician were also blinded to the study group allocation.

2.6 Statistical analysis

An Intention to Treat (ITT) approach was used for the analysis. Data was compiled and analyzed using Microsoft Excel 2019 (16.0.12026.20334) 32-bit. Data was tested for normality using Kolmogorov-Smirnov test.

The baseline characteristics of both study groups were reported as proportion/ mean (SD). Association between quantitative variables was tested using the paired T test wherever appropriate at 95% confidence interval. Blood parameters were evaluated by descriptive statistics. Qualitative tests were analyzed using Fisher’s exact test. A p value of less than 0.05 was considered statistically significant.

3.0 Results

A total of 92 IPD participants were enrolled in the study, 41 in the arm and 43 NF2 in the placebo arm. Those who did not adhere to the protocol or could not comply were excluded from the data analysis. No significant difference was found in the age and gender distribution between the two groups (Table 1).

![Table 1](image)

### Demographic Characteristics of the study population.

| Demographic characteristics | NOQ19 (n=41) | Placebo (n=43) | Total | p value |
|-----------------------------|--------------|---------------|-------|---------|
| IPD (n)                     | 47           | 45            | 92    | NA      |
| Age Range (yrs)             | 21-66        | 19-69         | 19-69 |         |
| Age Mean (SD)               | 39.7 (11)    | 38.7 (13.7)   | 39.2 (12.3) | 0.692   |
| Female (n, %)               | 14 (30%)     | 20 (44%)      | 34 (37%) | 0.1953  |
| Male (n, %)                 | 33 (70%)     | 25 (56%)      | 58 (63%) |         |
| No. of days of Admission Mean (SD) | 11.0 (2.9) | 10.8 (1.7)    | 10.9 (2.4) | 0.672   |

Table 1 shows no significant difference in the age and gender distribution, and duration of hospital stay between the two groups.

**Primary Outcome - % Population with RT-PCR Negativity**

As depicted in Table 2, a significantly higher percentage of population was found to be RT-PCR negative in the NF2 arm, at all assessment time points. The NF2 arm showed a significant increase in negative patients in 3 days (19%, pvalue 0.012) while the placebo arm had no improvement on Day 3. On the 7th day, 41% of patients in the NF2 arm had a negative RT-PCR compared to 18% of patients in the placebo arm. By Day 10, 73% of patients in the NF2 arm had turned negative compared to 44% in the placebo arm (p value 0.035). The intra group p values were found to be significant among both the groups. Overall, the NF2 arm showed a faster recovery
Table 2
Percentage of population turning of RT-PCR negativity at Day 3, Day 7 and Day 10

|          | NF2 (n = 41) | Placebo (n = 43) | Inter group p value |
|----------|--------------|------------------|---------------------|
|          | % (n)        | % (n)            |                     |
| Day 1    | 0            | 0                |                     |
| Day 3    | 19% (6)      | 0% (0)           | 0.012*              |
| Intragroup p value | 0.012* | –                |
| Day 7    | 41% (11)     | 18% (5)          | 0.077               |
| Intragroup p value | 0.0003** | 0.022*           |
| D10      | 73% (19)     | 44% (12)         | 0.035*              |
| Intragroup p value | 0.000** | 0.000**          |

*<0.05-significant

**<0.001-very significant

Secondary Outcome - Blood markers

No significant differences were found in the CBC count, Creatinine, D-Dimer and CRP levels between the two study arms at baseline or at Day 3 or 7. There was an improvement in both arms, but it was not statistically significant (Supplementary Table 1). No adverse events or side effects in the population taking NF2 during the study duration.

4.0 Discussion

The indigenous medicinal plants have been extensively used since the dawn of civilization to treat various health ailments [29,30]. According to an estimate, more than 80,000 plant species have been identified and used as medicinal herbs globally [31]. One of the key observations of the present study is the improvement in the rate of recovery as measured by the RT-PCR. Patients in the NF2 arm reported a significant improvement and recovery by the 3rd Day of enrollment. However, no improvement was noted in the placebo arm. One probable explanation for the result could be the presence of Yashtimadhu (Glycyrrhiza glabra) in the formulation. Glycyrrhizin, the chief component of Yashtimadhu, is known to inhibit viral replication by attaching to the viral proteins [32]. In an in vitro study on Glycyrrhizin and SARS-CoV, Glycyrrhizin eliminated the virus completely at a concentration of 4000mg/ml [33]. A combination of Ashwagandha (Withania somnifera) and Guduchi (Tinospora cordifolia) can also help inhibit viral replication by attaching to RNA dependent RNA polymerase enzyme, as noted in a polyherbal formulation in-silico study [34].

To the best of our knowledge this is the first study on therapeutic efficacy of NF2 in rural patients in India. According to a previous epidemiological study in India, a similar prevalence of COVID-19 cases was noted in both rural and urban areas of Karnataka [35]. However, towards the end of the second wave, the cases remained predominantly higher in the rural areas, probably due to the lack of treatment [36]. The results of this study are on
par with results from earlier preclinical studies. NF2 demonstrated a 100% antiviral efficacy at a concentration of 0.9mg/ml in an in vitro study [25] and showed a decrease of 78.2% in lung viral load in an in vivo study [26]. Another pilot feasibility study on NF2 showed early recovery of patients, as measured by RT PCR, which is in congruence with the results of this study [27]. The results of our study correlate with previous studies conducted on individual components. Withania somnifera (Ashwagandha) has anti-inflammatory, anti-microbial, adaptogenic, neuroprotective, cardioprotective, hepatoprotective and immunomodulatory properties which help reduce the clinical severity of the disease, resulting in faster clinical improvement and recovery among COVID-19 patients [37]. Ayurvedic formulations have been studied for both prophylactic and therapeutic management of COVID-19 [38]. A pragmatic study suggests Ayurveda as a supportive treatment for COVID patients with mild and moderate symptoms [39].

Alkaloidal properties of Adhatoda vasica (Vasaka) can also contribute towards the antimicrobial activity of NF2 [40]. This herb is used to treat chronic fever, cough, and asthma since ancient times because of its antitussive activity. Although our study did not capture the improvement in oxygen levels and absence of breathlessness, the presence of Vasaka in NF2 can play an important role in the symptomatic relief from COVID-19 [41]. Vasaka’s antispasmodic and expectorant properties can help alleviate the respiratory problems faced by elder patients suffering from COVID-19 [42].

Curcuma longa (Tumeric, commonly used in Indian kitchens as a culinary spice, is beneficial for inflammatory conditions and pain management [43]. Cytokine storms caused by inflammatory markers can be potentially reduced by the presence of turmeric in NF2. Ocimum sanctum (Tulsi or holy basil), another common plant found in Indian households, is one of the most extensively used medicines in Ayurveda. It is considered a potent adaptogen that promotes wellbeing and resilience. It is antimicrobial, antioxidant, anti-inflammatory, neuro-protective, cardio-protective, analgesic, antipyretic and immunomodulatory in nature [44].

This study has certain limitations. First, the study site was in a rural area and a few patients did not come for follow-up once they started feeling better, possibly due to lack of transport or to avoid missing work. Some took early discharge against medical advice as well. Secondly, during the study period, there was a decline in the number of COVID 19 cases around the country; hence the sample size ended up being smaller than projected. Lastly, the non-inclusion of patients with comorbidities was another limitation of the study. Future scope of work includes larger studies and including patients from multiple geographical areas.

5.0 Conclusion

Populations in several countries around the world have explored natural plant based herbal solutions for management of COVID-19. This study spotlights the efficacy of a 19-ingredient Ayurvedic formulation called NF2 in early recovery of COVID-19 patients. Patients in both the study arms received the standard of care treatment. The arm which received NF2 in addition to SOC displayed a faster recovery, as evident by the higher percentage of population that was RT-PCR negative at Day 3, 7 and 10. An integrated approach including NF2 has the potential to emerge as a cost-effective treatment that can reduce the burden on healthcare systems, in both rural and urban areas.

Declarations
**Data Availability:** The individual patient level data can be accessed at the following link https://docs.google.com/spreadsheets/d/1keaMxG6JblvyGV1n7EMbK8Yo_WaJbAiPeDj_KTHvpiQ/edit#gid=0

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**Statement of Ethics**

**Study approval statement:**

The study was conducted at the Community Care Center, Konnanuru, Hassan, Karnataka. The study was approved by the Doctors for You (DFY) Ethics Committee (Ref. Number- DFY/ DELHI/R/ B407/2021-22). The protocol of the study was in compliance with Helsinki ethical standards and Good Clinical Practice.

**Consent to participate statement:**

A total of 92 IPD Patients from Community Care Center, Konnanuru, Hassan, Karnataka were enrolled in the study after receiving their written consent.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

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**Author Contribution:**

Conceptualization: Divya Kanchibhotla; Methodology / Study design: Divya Kanchibhotla, Dr Akhilesh Mohan Wodeyar, Rohini Wadhawan.; Validation: Divya Kanchibhotla, Rohini Wadhawan; Formal analysis: Divya Kanchibhotla, Saumya Subramanian;Investigation: Dr. K P Bharath Chandra, Dr. Alefia Zakir Marfatia;Resources: Divya Kanchibhotla, Rohini Wadhawan;Data curation: Dr. K P Bharath Chandra, Saumya Subramanian; Writing – original draft: Dr. Jeetu Pathak, Divya Kanchibhotla; Writing – review and editing: Saumya Subramanian, Divya Kanchibhotla; Visualization: Divya Kanchibhotla; Supervision: Divya Kanchibhotla, Rohini Wadhawan.

**Data availability**

The data that support the findings of this study is available from the corresponding author upon reasonable request.

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**Supplementary Table**
|                     | NOQ19 (n=41) | Placebo (n=43) | Intergroup value |
|---------------------|--------------|----------------|-----------------|
| **D-Dimer (mg/dl)** |              |                |                 |
| Day 1 Mean (SD)     | 0.5 (0.4)    | 0.3 (0.2)      | 0.042*          |
| Day 3 Mean (SD)     | 0.5 (0.5)    | 1.0 (3.0)      | 0.236           |
| **Intragroup p value Day 1 vs Day 3** | 0.95 | 0.134 |
| Day 7 Mean (SD)     | 0.6 (0.8)    | 0.3 (0.2)      | 0.041*          |
| **Intragroup p value Day 1 vs Day 7** | 0.289 | 0.81 |
| **CRP (mg/dl)**     |              |                |                 |
| Day 1 Mean (SD)     | 0.8 (0.6)    | 0.7 (0.4)      | 0.213           |
| Day 3 Mean (SD)     | 0.8 (0.4)    | 0.7 (0.4)      | 0.248           |
| **Intragroup p value Day 1 vs Day 3** | 0.719 | 0.956 |
| Day 7 Mean (SD)     | 0.8 (0.6)    | 0.6 (0.2)      | 0.064           |
| **Intragroup p value Day 1 vs Day 7** | 0.786 | 0.117 |
| **Creatinine (mg/dl)** |            |                |                 |
| Day 1 Mean (SD)     | 0.9 (0.1)    | 0.9 (0.1)      | 0.37            |
| Day 3 Mean (SD)     | 0.9 (0.1)    | 0.9 (0.1)      | 0.335           |
| **Intragroup p value Day 1 vs Day 3** | 0.282 | 0.446 |
| Day 7 Mean (SD)     | 0.9 (0.19)   | 0.9 (0.1)      | 0.174           |
| **Intragroup p value Day 1 vs Day 7** | 0.063 | 0.811 |

*p<0.05-significant

**Figures**
Figure 1

Legend not included with this version