Therapeutic efficacy of Honey and Nigella sativa against COVID-19: A multi-center randomized controlled clinical trial (HNS-COVID-PK)

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BACKGROUND

Coronavirus Disease 2019 (COVID-19) is causing havoc across the globe. Since no effective treatment exists for the disease, there is a dire need to find one. Honey and *Nigella sativa* (HNS) are two natural food ingredients with anti-inflammatory, anti-viral, anti-microbial and immune modulating properties. We investigated whether they could be beneficial in COVID-19 patients.

METHODS

We conducted an add-on, randomized, open label, placebo-controlled clinical trial using parallel group design. This was a multi-center study with superiority framework conducted in RT-PCR confirmed COVID-19 adults showing moderate or severe disease. A study period of three months was defined. Patients presenting with multi-organ failure, ventilator support and chronic diseases (except diabetes mellitus and hypertension) were excluded. All patients receiving standard care were randomized into treatment and control groups. In the treatment group, patients received HNS in predefined doses for up to 13 days. Outcome measures (time taken for alleviation of symptoms, viral clearance, clinical status improvement and mortality etc) were assessed along the course of the trial.

RESULTS

Of 1046 patients testing positive for the SARS-CoV-2, 210 with moderate and 103 with severe disease were randomized into treatment and control groups. For the moderate cases, 107 were assigned to the HNS group and 103 to the control group, whereas for the severe cases, 50 were assigned to the HNS group and 53 to the control group. In both the moderate and severe cases, HNS treatment was associated with an earlier alleviation of disease symptoms, by 3 and 7 days (HR: 6.11; 95% CI: 4.23-8.84, P<0.0001 and HR: 4.04; 95% CI, 2.46-6.64, P<0.0001) respectively. The treatment was also associated with significant earlier viral clearance in both the moderate and severe disease groups (4 days earlier reduction in median viral clearance time (moderate HR: 5.53; 95% CI: 3.76-8.14, P<0.0001 and severe HR: 4.32; 95% CI: 2.62-7.13, P<0.0001)). Also, a higher %age of patients cleared virus in the HNS group. Moreover, in the intention-to-treat analysis, the HNS groups led to a lower (better) clinical score on day 6 with resumption of normal activity among 63.6% of the moderate (OR: 0.07; 95% CI: 0.03-0.13, P<0.0001) and 28% of severe cases (OR: 0.03; 95% CI: 0.01-0.09, P<0.0001). Furthermore, a significant reduction in mortality among severe patients was observed in the HNS arm (4% versus 18.87%, OR: 0.18; 95% CI: 0.02-0.92, P=0.029). No HNS-related adverse effects were noted.
CONCLUSIONS

The HNS treatment resulted in a significant reduction in the severity of clinical symptoms, earlier viral clearance and reduced mortality in COVID-19 patients. In the current study, it represents a safe, effective, over the counter and affordable therapy for this disease and could potentially lower burden on health care systems across the World. It can be used alone or in combination with other treatments to achieve potentiating effects. (Funded by Smile Welfare Organization, Shaikh Zayed Medical Complex and Services Institute of Medical Sciences; NIH Clinical Trial Register number: NCT04347382.)

KEY WORDS

COVID-19, SARS-CoV-2, Honey, Nigella sativa, Randomized Controlled Trial
The COVID-19 pandemic, caused by the novel coronavirus named SARS-CoV-2, has infected more than forty million people and has resulted in more than a million deaths in the world\(^1\). In the absence of an effective prophylactic vaccine, there is an urgent need for finding effective treatments for COVID-19 patients. At a minimum, an ideal treatment should expedite recovery from the disease, decrease viral transmission in the community by earlier viral clearance from the infected patients and reduce morality. In this context, certain treatments including hydroxychloroquine/azithromycin, lopinavir-ritonavir, remdesivir, dexamethasone, convalescent plasma and antibody therapies have shown some efficacy\(^2-8\). However, there is still a long way to go before we have an effective treatment regimen for severe COVID-19 patients. Towards this end, we have conducted a clinical trial in which we have investigated the potential efficacy of a combination of honey and *Nigella sativa* (HNS) in treating COVID-19 patients.

Both components of HNS have anti-viral, anti-microbial, anti-inflammatory and immune stimulating effects with proven safety profiles\(^9-13\). Beneficial effects of honey against different viruses including rubella virus, Herpes Simplex virus, Hepatitis virus, and Varicella Zoster virus have been reported earlier\(^14, 15\). Moreover, in silico molecular docking studies have shown that six flavonoid compounds from honey might inhibit SARS-CoV-2 replication by binding to the viral 3-chymotrypsin-like-cysteine protease\(^16\). Honey has also shown efficacy against several multidrug resistant bacteria, especially in synergism with antibiotics\(^17, 18\). Honey also exhibits immunity-boosting effects mainly via its polyphenolic components, which stimulate both innate and adaptive immune responses\(^19\). Its use has been shown to be beneficial in upper respiratory tract infections\(^20\).

*Nigella sativa* (NS), a widely used medicinal plant of the family Ranunculaceae and commonly known as Black Cumin or Kalonji, has been shown to exert antiviral effects against a variety of viruses such as Mouse Cytomegalovirus and HCV\(^21-23\). It has also been shown to decrease replication of SARS-CoV in vitro in cell cultures\(^24\). Moreover, molecular docking studies have shown that some of its components such as nigelledine, α-hederin and thymoquinone, etc., have high affinity with several SARS-CoV-2 enzymes and proteins. In fact, they exhibit an energy complex score better than that of chloroquine, hydroxychloroquine and favipiravir, the drugs that
have shown some anti-SARS-CoV-2 effects\(^{25}\). The components’ antimicrobial properties against various microbes as well as their anti-inflammatory and immunomodulatory effects have also been established\(^{13, 26, 27}\).

As honey and \textit{Nigella sativa} show similar pharmacological profiles, we reasoned that the combination could be more effective in attenuating severity of the disease, controlling viral replication and curing COVID-19 patients. In fact the combination has been used successfully in a variety of disease conditions\(^{28-32}\). We report here that the HNS treatment results in earlier recovery and viral clearance in COVID-19 patients.

**METHODOLOGY:**

**PATIENTS**

2523 suspected COVID-19 presenting within three months of study duration in four health care facilities were tested for SARS-CoV-2 by RT-PCR of their nasopharyngeal swabs in International Organization for Standardization (ISO) certified designated laboratories of Pakistan. The test positive, adult males and non-pregnant females, who presented to seek medical care within 96 h of ailment underwent randomization. Exclusion criteria included having no or mild clinical symptoms, inability to give written consent, multi-organ dysfunction, ventilator support, septic shock, known hypersensitivity to HNS and chronic illness other than hypertension and diabetes mellitus.

**TRIAL DESIGN AND OVERSIGHT**

This was an investigator-initiated, open-label-placebo and randomized controlled trial conducted from April 30 to July 29, 2020 in four medical care facilities in Pakistan (Shaikh Zayed Medical Complex, Services Institute of Medical Sciences, Doctor’s Lounge and Ali Clinic; all located in Lahore). Written informed consent was obtained from each participant. Eligible patients were stratified based upon the severity of their clinical symptoms into two groups: mild to moderate (cough, fever, sore throat, nasal congestion, malaise and/or shortness of breath), and severe cases (fever and/or cough along with pneumonia, severe dyspnea, respiratory distress, tachypnea (>30 breaths/min) or hypoxia (SpO2 <90\% on room air)\(^{33}\)). The severity of the disease was defined as outlined in the Clinical Management Guidelines for COVID-19 by the Ministry of National Health Services, Pakistan. Within each of these two groups, patients were randomized (by lottery) into treatment and control groups. The HNS group received honey (1 mg) plus \textit{Nigella sativa} seeds (80
mg) per kg body weight orally in 2-3 divided doses daily for up-to 13 days while the control group received placebo (empty capsules). Additionally, each patient in the trial received standard care therapy (SCT) as advised by the treating physician, following the clinical management guidelines for COVID-19 established by the Ministry of National Health Services of Pakistan. SCT primarily comprised of anti-pyretic drugs, antibiotics, supplemental oxygen and mechanical ventilation. The trial was approved by the institutional review boards of Shaikh Zayed Medical Complex and Services Institute of Medical Sciences. It was supervised by an independent trial steering committee. The trial’s executive committee vouched for accuracy, anonymity of the data and for compliance (Supplementary Appendix 1). The trial was conducted as an urgent study during peak of the COVID-19 outbreak in Pakistan (May-July 2020), and in accordance with principles of Good Clinical Practice Guidelines of the International Conference on Harmonization.

**CLINICAL AND LABORATORY MONITORING**

The study participants were assessed for clinical symptoms daily by an on-site investigator (nurse/doctor) for 13 days. During the study, when a patient recovered and remained asymptomatic for 48 h, he/she underwent a second SARS-CoV-2 RT-PCR test within the next 48 h (Figure 1). If the patient tested negative, he/she was deemed to have cleared the infection and his/her treatment was stopped. In case of a positive test, a third PCR test was performed on day 14 with no further follow-up. A clinical grading score (CGS) was recorded for each patient on day 0, 4, 6, 8, 10 and 12. It was based on a seven-point ordinal scale: grade 1 (not hospitalized, no evidence of infection and resumption of normal activities), grade 2 (not hospitalized, but unable to resume normal activities), grade 3 (hospitalized, not requiring supplemental oxygen), grade 4 (hospitalized, requiring supplemental oxygen), grade 5 (hospitalized, requiring nasal high-flow oxygen therapy and/or noninvasive mechanical ventilation), grade 6 (hospitalized, requiring ECMO and/or invasive mechanical ventilation) and grade 7 (death). This scale has previously been used as end point in clinical trials in COVID-19 patients\(^3\). Body temperature was measured, and fever was graded as no fever (0; 98-99 °F), mild (1; >99-<100 °F), moderate (2; 100-101.9 °F) and severe (3; ≤102°F). Serum C-reactive Protein (CRP) levels were measured by ELISA kit (Invitrogen, USA).

Safety outcomes including adverse events were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Laboratory investigations were assessed as a part of the protocol as per recommendations of the treating
physician. Trial safety was monitored by the trial steering committee. For the patients who were discharged before day 13 or were home-quarantined, the follow-up was done by telemedicine.

OUTCOME MEASURES

The primary outcomes were viral clearance (negative RT-PCR for the SARS-CoV-2 RNA), alleviation of clinical symptoms and the lowering of CGS on day 6. Secondary outcomes included reduction in fever degree (day 4), CRP levels (day 6), severity of symptoms (day 8), CGS score (day 10) and mortality on day 30.

STATISTICAL ANALYSIS

In univariate analyses, we used a log-rank test to compare time taken for viral clearance, alleviation of symptoms, time to improvement in severity of clinical symptoms, degree of fever, cough, shortness of breath, myalgia and how sick do you feel. Kaplan Meier method was applied to estimate survival curves for time for alleviation of symptoms and viral clearance. The Fisher’s Exact test was used to compare 30-day mortality. In multivariate analyses, we used a multivariate regression models to adjust for the effects of age (<40 or ≥40), gender, baseline clinical status grade, history of diabetes/hypertension and oxygen use. In the multivariate analyses of ordinal outcomes, we used ordinal logistic regression models assuming proportional odds. We also used a linear regression model to analyze the continuous outcome CRP and Cox proportional hazards models to analyze time to symptom alleviation and the time to viral clearance. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for these analyses.

RESULTS:

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

Initial COVID-19 screening was done on 2523 patients of which 1046 patients tested positive for the SARS-CoV-2 nucleic acid. From these patients, 313 met the inclusion criteria (Figure 1). Based upon the spectrum of their clinical symptoms, they were stratified into two groups: moderate and severe. The two groups comprised 210 and 103 patients, respectively. The patients within each of the two groups were randomly assigned to the treatment and control groups. The number of patients in moderate control, moderate HNS, severe control and severe HNS were 103, 107, 53 and 50, respectively. Their baseline demographics with clinical and laboratory parameters are
shown in Table 1. Paracetamol and azithromycin were the top two prescribed drugs as part of the SCT. Two patients opted for home quarantine despite needing oxygen therapy.

**PRIMARY OUTCOMES**

Primary outcomes are shown in Table 2. Alleviation of COVID-19 symptoms for patients in the HNS groups occurred earlier than control groups: 4 versus 7 days for the moderate patients (HR: 6.11; 95% CI: 4.23-8.84; P<0.0001) and 6 versus 13 days for the severe disease patients (HR: 4.04; 95% CI: 1.53-3.58; P<0.0001). Viral clearance (being negative for the SARS-CoV-2 RT-PCR test) occurred 4 days sooner in the HNS group for both moderate (HR: 5.53; 95% CI: 3.76-8.14; P<0.0001) and severe cases (HR: 4.32; 95% CI: 2.62-7.13; P<0.0001). The Kaplan-Meier curves for these variables are shown in Figure 2. In moderate patients, the HNS group resumed while control group was unable to resume activities of daily life as evident by the lower median CGS at day 6 (odds ratio: 0.07; 95% CI: 0.03-0.13; P<0.0001). Meanwhile, in severe groups, the HNS cases were discharged whereas the control cases were hospitalized on supplemental oxygen as per median CGS at day 6 (Odds Ratio: 0.03; 95% CI: 0.01-0.09; P<0.0001).

**SECONDARY OUTCOMES**

There were significant differences in all secondary outcomes between the treatment and control groups (see Table 2 for secondary outcomes). In moderate COVID-19 patients, degree of fever (median) was 100-101.9°F (moderate) in the control group while HNS arm participants were afebrile on day 4 (OR: 0.05; 95% CI: 0.03-0.1; P <0.0001). A significant reduction in degree of fever was observed in the severe cases on day 4 (OR: 0.21; 95% CI: 0.09-0.46; P=0.0001). CRP levels decreased significantly (P<0.0001) on day 6 in both the HNS groups compared with their respective control groups. As per median degree of symptom severity on day 8, 98.13% patients were asymptomatic in HNS treated moderate cases in comparison to 56.31% in the control group (OR: 0.009; 95% CI: 0.001-0.08; P<0.0001). In severe cases, more patients were asymptomatic in the HNS group while more had moderate symptoms (median) in the control arm (OR: 0.1; 95% CI: 0.04-0.24). By day 10, 96.26% of the moderate cases patients fully resumed normal activities with HNS compared to 68.93% in control group (OR: 0.07; 95% CI: 0.02-0.21). For the severe group, the median CGS at day 10 revealed that HNS cases resumed normal activities while control patients were still hospitalized requiring oxygen therapy (OR:0.05; 95% CI: 0.02-0.15). The distribution of patients in the ordinal-scale categories over time is shown in Figure 3. Thirty-day morality was 18.87% in control group and 4% with HNS therapy (OR: 0.18 95% CI: 0.02-0.92).
ADDITIONAL OUTCOMES

In HNS group, median day achievement of normal status on ordinal scale was earlier in severity of symptoms (moderate, 5 versus 8, HR; 4.49 (3.15-6.38), P<0.0001 and severe, 7 versus 13 HR; 2.74 (1.68-4.49), P<0.0001), degree of fever [4 versus 8, HR; 4.17 (2.98-5.84), P<0.0001 and severe 6 versus 10, HR; 2.64 (1.74-4.11), P<0.0001]), degree of cough [moderate 5 versus 7, HR; 2.67 (1.73-4.12), P<0.0001 and severe 6 versus 9, HR; 2.04 (1.26-3.31), P=0.0001]), degree of shortness of breath (severe 6 versus 13 HR; 2.39 (1.48-3.87), P<0.0001), degree of myalgia (moderate 4 versus 6 HR; 3.34 (2.14-5.25), P<0.0001) severe 5 versus 9, HR; 2.75 (1.62-4.69), P<0.0001) and how sick do you feel (moderate 5 versus 8 HR (3.55 (2.55-4.93), P<0.0001 and severe 7 versus 13 HR; 2.87 (1.75-4.69), P<0.0001) (Table 2). Distribution on degree of fever, cough, myalgia, feeling of sickness, emotional status, shortness of breath, oxygen saturation, oxygen requirement and severity of symptoms over 13 days is given in supplementary Tables S2-S10. No evident adverse effects were noted with HNS.

DISCUSSION

The study was a multicenter open-label, randomized, placebo-controlled clinical trial investigating the therapeutic efficacy of HNS against COVID-19. To the best of our knowledge, this trial is the first of its kind in which a combination of two natural substances was investigated. Current study showed superior efficacy of HNS for COVID-19 in all studied outcomes. About half of the patients in the control groups required double time to become asymptomatic compared with those in the HNS group (Figure 2). In severe cases, HNS group had a significantly lower recovery time compared with the control group (6 days versus 13 days, P<0.0001). In comparison to this, the recovery time reported for remdesivir was 10 days versus 15 days for the control (P<0.001)\(^{(5)}\) whereas lopinavir-ritonavir resulted in no decrease in the recovery time (16 days versus 16 days; P=0.09)\(^{(3)}\). In our study, in ~50% of cases, SARS-CoV-2 RT-PCR became negative 4 days sooner in HNS than in control groups. Mortality among severe cases in comparison to control group was 27.0% (versus 25.0%) for hydroxychloroquine\(^{(2)}\), 19.2% (versus 25.0%) for lopinavir-ritonavir\(^{(3)}\), 15.7% (versus 24.0%) for convalescent plasma\(^{(34)}\), 11.4% (versus 15.2%) for remdesivir\(^{(5)}\), 22.9% (versus 25.7%) for dexamethasone\(^{(8)}\) and only 4% (versus 18.87%) for HNS. Thus, HNS provided clinical superiority in reducing mortality in COVID-19 patients. Of note, combined mortality data provided by Solidarity and ACTT-1 for remdesivir and by Solidarity and Recovery trial for
lopinavir-ritonavir failed to provide statistical improvement in mortality \(^{(35)}\). In contrast to these drugs, HNS represents a safer and more affordable option that can be used as an in-house remedy.

The trial results show that the use of HNS in COVID-19 patients promotes viral clearance and reduces severity of the disease. The beneficial effects of the treatment are particularly encouraging as our inclusion criteria were very stringent: excluding asymptomatic patients as well as patients with mild symptoms. The trial results are in line with anti-viral, anti-microbial, anti-inflammatory and immune stimulating effects of honey and *Nigella sativa* \(^{(9-13)}\). Anti-diabetic, anti-hypertensive, cardio-protective and broncho-dilatory properties of HNS make it even more beneficial in diabetic, hypertensive, cardiac and asthmatic patients which have a higher COVID-19 associated mortality \(^{(36, 37)}\). Furthermore, anti-platelet and anti-coagulant effects of HNS also shield COVID-19 patients from thromboembolic complications, which are main cause of morbidity and death in this disease \(^{(38)}\). Hepato- and reno-protective nature of HNS gives added advantage over other drugs in limiting COVID-19 related hepatic and renal injuries \(^{(36, 37)}\). Anti-pyretic, analgesic and antitussive properties of HNS also provide symptomatic relief \(^{(39, 40)}\). Furthermore, HNS’s antimicrobial properties and synergism with other antibiotics against superadded infections prevent sepsis related deaths \(^{(17, 18)}\). These findings strengthen the use of HNS as a potential candidate for combating SARS-CoV-2 worldwide.

Our study has some limitations including the fact that it was an open label study. Honey and NS were not administered as individual treatments to the patients. Hence, the effects of each of the two components of HNS (i.e., honey and NS) as well as their additive or synergistic effects, if any, remain unknown. Patients on ventilator support were not enrolled in this study. Also, we cannot exclude any favorable psychological effect of HNS on its users due to their religious beliefs. A multinational study with larger sample size is required to investigate potential variations in responses to the treatment in COVID-19 patients from different racial and ethnic origins.

**CONCLUSIONS**

HNS is a safe and effective therapy for COVID-19 patients and promotes viral clearance, quicker recovery and survival. Its affordability (< $5 for the whole treatment course), over the counter availability and ease of administration (as an easily practicable home-based remedy) will make
this treatment very attractive. Furthermore, as an inexpensive nutraceutical, HNS could be used alone or in combination with other drugs for additive effects. The treatment is very likely to reduce burden on health care systems in a significant manner.

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AUTHORS’ CONTRIBUTIONS:
SA, ShA, MoA and MAI contributed equally to this paper and share joint first authorship. SA, ShA, AA, MA, QAS and MI share joint corresponding authorship. LK, UNS, and MG were co-chief authors of this draft. SA, MAI, AA and MA contributed to conception, designing, acquisition of data, manuscript drafting and intellectual input. SA and MoA proposed the hypothesis and study design and obtained the funding. RA, KH, HR and ABA added the research delivery to the study centers. MA, MoA, SiA and MFN contributed biochemical, pharmacological and pharmaceutical inputs along with dosimetry. MKA, SuA, MAz and HZ led the development of data cleaning and analysis and took responsibility for the results in this draft and future analysis. SA, MoA, RA and AH drafted the first version of the manuscript. NM, IF, SR, AbH, ZA, AK, ZH, ShaA, HR, ABA, KH and AAr represented the conduction and validation of the data compilation and analysis in the manuscript. KN, MSu, SZ, IA, AH, AM, TM, SS, MeA, AA, MA, QAS and MI has overlooked the conduction and validity of the trial along with contributed to intellectual inputs in study protocol and methodology along with final manuscript write up. MeA and MI made sure validity of the data collection, data analysis and ethical considerations in their institutes. All authors are responsible for their contributions, providing critical edits and final authorization of the article. The corresponding authors attest the authenticity of that all listed authors meet authorship criteria.
Figure 1: Study Flow Chart. Team A: Responsible for the recruitment and SARS-CoV-2 RT-PCR testing; Team B: Daily evaluated degree of fever, cough, myalgia, shortness of breath, oxygen therapy, how sick do you feel and rate emotional status; Team C: Reported clinical grading scale (CGS) on seven-point ordinal scale assessment as 0, 4, 6, 8, 10 and 12 days; Team D conducted follow-up PCR and CRP determinations.
| Parameter                                           | Total (n=313) | Control (n=156) | Honey-Nigella Sativa (n=157) | P-Value |
|-----------------------------------------------------|---------------|-----------------|-------------------------------|---------|
| **Age (Years)**                                     |               |                 |                               |         |
| ≤40                                                 | 156 (49.84)   | 80 (51.28)      | 76 (48.4)                     | 0.48    |
| 40-59                                               | 93 (29.71)    | 45 (28.85)      | 48 (30.57)                    |         |
| 60-79                                               | 52 (16.61)    | 26 (16.67)      | 26 (16.56)                    |         |
| ≥80                                                 | 12 (3.83)     | 5 (3.2)         | 7 (4.45)                      |         |
| **Sex**                                             |               |                 |                               |         |
| Male                                                | 178 (56.87)   | 88 (56.41)      | 90 (57.32)                    | 0.87    |
| Female                                              | 135 (43.13)   | 68 (43.59)      | 67 (42.68)                    |         |
| **Profession**                                      |               |                 |                               |         |
| Health care†                                        | 71 (22.68)    | 38 (24.36)      | 33 (21.02)                    | 0.48    |
| Non-Health care                                     | 242 (77.32)   | 118 (75.64)     | 124 (78.98)                   |         |
| **Co-Morbidities**                                  |               |                 |                               |         |
| Hypertension                                        | 99 (31.63)    | 51 (32.69)      | 48 (30.57)                    | 0.69    |
| Diabetes Mellitus                                   | 115 (36.74)   | 60 (38.46)      | 55 (35.03)                    | 0.53    |
| **Onset of symptoms before admission**              |               |                 |                               |         |
| 48 hours                                            | 88 (38.1)     | 49 (41.53)      | 39 (34.51)                    | 0.22    |
| 72 hours                                            | 143 (61.9)    | 69 (58.47)      | 74 (65.49)                    |         |
| 96 hours                                            | 82 (36.44)    | 38 (35.51)      | 44 (37.29)                    |         |
| **Severity of Symptoms**                            |               |                 |                               |         |
| Moderate                                            | 210 (67.09)   | 103 (66.03)     | 107 (68.15)                   | 0.69    |
| Severe                                              | 103 (32.91)   | 53 (33.97)      | 50 (31.85)                    |         |
| **ARDS**                                            | 57 (17.38)    | 28 (17.95)      | 29 (16.86)                    | 0.9     |
| **Chest X-Ray**                                     |               |                 |                               |         |
| Normal                                              | 217 (66.16)   | 101 (64.74)     | 116 (73.88)                   | 0.71    |
| Pneumonic Patch                                     | 12 (3.66)     | 8 (5.13)        | 4 (2.54)                      |         |
| Unilateral Infiltrates                              | 40 (12.2)     | 19 (12.18)      | 21 (13.38)                    |         |
| Bilateral Infiltrates                               | 59 (17.99)    | 28 (17.94)      | 31 (19.74)                    |         |
| **Clinical Grading Score at day 0**                  |               |                 |                               |         |
| Median Grade Score (IQR)                            | 3 (2-4)       | 3 (2-4)         | 3 (2-4)                       |         |
| 2- Not hospitalized with unable to resume normal activities | 139 (44.41)  | 68 (43.59)      | 71 (45.22)                    | 0.73    |
| 3- Hospitalized, not requiring supplemental oxygen  | 71 (22.68)    | 35 (22.44)      | 36 (22.93)                    |         |
| 4- Hospitalized, requiring low flow supplemental oxygen | 44 (14.06) | 23 (14.74)      | 21 (13.38)                    |         |
| 5- Hospitalized, requiring high flow supplemental oxygen | 59 (18.85)  | 30 (19.23)      | 29 (18.47)                    |         |
| **Patients hospitalized in**                        |               |                 |                               |         |
| Shaikh Zayed Hospital                               | 78 (25.66)    | 39 (25.83)      | 39 (25.49)                    | 0.56    |
| Services Institute of Medical Sciences              | 91 (29.93)    | 48 (31.79)      | 43 (28.1)                     |         |
| Doctors Lounge                                      | 52 (17.11)    | 27 (17.88)      | 25 (16.34)                    |         |
| Patients showing symptoms |       |       |       |
|---------------------------|-------|-------|-------|
| Fever                     | 303 (96.81) | 152 (97.44) | 151 (96.17) |
| SOB                       | 106 (33.87) | 56 (35.9) | 50 (31.85) |
| Cough                     | 192 (61.34) | 90 (57.69) | 102 (64.97) |
| Myalgia                   | 169 (53.99) | 89 (57.05) | 80 (50.96) |

| Patients receiving |       |       |       |
|-------------------|-------|-------|-------|
| Panadol           | 297 (94.89) | 147 (94.23) | 150 (97.54) |
| Azithromycin      | 231 (73.8) | 120 (76.92) | 111 (70.7) |
| Montelukast       | 106 (33.87) | 56 (35.9) | 50 (31.85) |
| Supplemental Oxygen | 105 (33.55) | 55 (35.25) | 50 (31.85) |
| Low Molecular Weight Heparin | 72 (23) | 38 (24.36) | 34 (21.66) |
| Hydrocortisone    | 83 (26.52) | 45 (28.85) | 38 (24.2) |
| Multivitamins     | 147 (46.96) | 73 (46.8) | 74 (47.13) |
| Tanzobactam + Piperacillin | 73 (23.32) | 42 (26.92) | 31 (19.74) |
| Ivermectin        | 114 (36.42) | 60 (38.46) | 54 (34.39) |
| Meropenem         | 62 (19.81) | 35 (22.43) | 27 (17.2) |

* Data are presented as no. (%) unless indicated. The Intention-to-Treat analysis was performed on all the patients who had undergone randomization. ECMO: Extracorporeal membrane oxygenation; CRP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; ECG: Electrocardiography; ARDS: Acute respiratory distress syndrome; SOB: Shortness of breath.

¶ P < 0.05 was determined significant

Medical doctors, nurses and pharmacists.

These medications were part of standard care therapy as per decision of treating physician and clinical Management Guidelines for COVID-19 by Ministry of National Health Services, Pakistan.
| PRIMARY OUTCOME | Moderate COVID-19 Cases | Severe COVID-19 Cases | PRIMARY OUTCOME | Moderate COVID-19 Cases | Severe COVID-19 Cases |
|-----------------|-------------------------|-----------------------|-----------------|-------------------------|-----------------------|
| Time Taken (days) For alleviation of symptoms in days (IQR) | 7 (7-8) | 4 (3-4) | 6.11 (4.23-8.84) | <0.0001 | 13 (9-15) | 6 (5-7) | 4.04 (2.46-6.64) | <0.0001 |
| Time Taken (days) for SARS-CoV-2 RT-PCR clearance (IQR) | 10 (9-12) | 6 (6-7) | 5.53 (3.76-8.14) | <0.0001 | 12 (11-17) | 8.5 (8-9) | 4.32 (2.62-7.13) | <0.0001 |
| Clinical Grading Score at day 6 | | | | | | | |
| Median CGS (IQR) | 1 (1-2) | 0 (0-1) | 0.07 (0.03-0.13) | <0.0001 | 3 (3-4) | 1.5 (0-2) | 0.03 (0.01-0.09) | <0.0001 |
| 1= Not hospitalized with resumption of normal activities - n (%) | 11 (10.68) | 68 (63.55) | 2 (1-3) | 2 (1-2) | 2 (3.77) | 11 (22) | 0.21 (0.09-0.46) | 0.0001 |
| 2= Not hospitalized, but unable to resume normal activities - n (%) | 51 (49.51) | 35 (32.71) | 23 (31.5) | 10 (20) | 13 (17.8) | 2 (4) |
| 3= Hospitalized, not requiring supplemental oxygen- n (%) | 35 (33.98) | 3 (2.8) | 13 (17.8) | 2 (4) | 10 (13.7) | 13 (26) | 0.03 (0.01-0.09) | <0.0001 |
| 4= Hospitalized, requiring low flow supplemental oxygen- n (%) | 4 (3.88) | 1 (0.93) | 23 (31.5) | 10 (20) | 13 (17.8) | 2 (4) |
| 5= Hospitalized, requiring high flow nasal oxygen- n (%) | 2 (1.94) | 0 (0) | 23 (31.5) | 10 (20) | 13 (17.8) | 2 (4) |
| 6= Hospitalized, requiring mechanical ventilation- n (%) | 0 (0) | 0 (0) | 23 (31.5) | 10 (20) | 13 (17.8) | 2 (4) |
| 7= Death- n (%) | 0 (0) | 0 (0) | 23 (31.5) | 10 (20) | 13 (17.8) | 2 (4) |
| SECONDARY OUTCOMES | | | | | | | |
| Degree of Fever at Day | | | | | | | |
| Median Degree Score (IQR) | 2 (1-2) | 0 (0-1) | 0.05 (0.03-0.1) | <0.0001 | 2 (1-3) | 2 (1-2) | 0.21 (0.09-0.46) | 0.0001 |
| 0= No Fever- n (%) | 4 (3.88) | 63 (58.88) | 2 (3.77) | 11 (22) | | | |
| 1= Mild Fever- n (%) | 30 (29.13) | 31 (28.97) | 12 (22.64) | 13 (26) | | | |
| 2= Moderate Fever- n (%) | 60 (58.25) | 12 (11.21) | 23 (43.4) | 24 (48) | | | |
| 3= Severe Fever- n (%) | 9 (8.74) | 1 (0.93) | 16 (30.19) | 2 (4) | | | |
| Mean CRP Level at Day 6 (mg/l) ± SD | 9.44 ± 4.94 (n=67) | 6.15 ± 2.45 (n=61) | -3.16 (-4.52 - -1.81) | <0.0001 | 23.32 ± 8.73 (n=44) | 15.83 ± 7.17 (n=36) | -8.48 (-11.82 - -5.13) | <0.0001 |
|----|------------------|------------------|---------------------|---------|-------------------|-------------------|---------------------|---------|

**Severity of Symptoms at Day 8**

| Median Score (IQR) | 0 (0-2) | 0 (0-0) | 0.009 (0.001-0.08) | <0.0001 | 2(1-3) | 0(0-1) | 0.1 (0.04-0.24) | <0.0001 |
|-------------------|---------|---------|---------------------|---------|-------|-------|----------------|---------|
| 0= Asymptomatic- n (%) | 58 (56.31) | 105 (98.13) | 10 (19.61) | 35 (70) | 0.009 (0.001-0.08) | 2(1-3) | 0(0-1) | 0.1 (0.04-0.24) | <0.0001 |
| 1= Mild Symptoms- n (%) | 18 (17.48) | 2 (1.87) | 15 (29.41) | 7 (14) | 10 (19.61) | 35 (70) | 0.009 (0.001-0.08) | 2(1-3) | 0(0-1) | 0.1 (0.04-0.24) | <0.0001 |
| 2= Moderate Symptoms- n (%) | 21 (20.39) | 0 (0) | 4 (7.84) | 2 (4) | 15 (29.41) | 7 (14) | 10 (19.61) | 35 (70) | 0.009 (0.001-0.08) | 2(1-3) | 0(0-1) | 0.1 (0.04-0.24) | <0.0001 |
| 3= Severe Symptoms- n (%) | 6 (5.83) | 0 (0) | 22 (43.14) | 6 (12) | 21 (20.39) | 0 (0) | 15 (29.41) | 7 (14) | 10 (19.61) | 35 (70) | 0.009 (0.001-0.08) | 2(1-3) | 0(0-1) | 0.1 (0.04-0.24) | <0.0001 |

**Clinical Grading Score at day 10**

| Median Score (IQR) | 1 (1-2) | 1 (1-2) | 4 (2-4) | 1 (1-1) | 10 (18.87) | 39 (78) | 0.05 (0.02-0.15) | <0.0001 |
|-------------------|---------|---------|---------|---------|-----------|--------|----------------|---------|
| 1= Not hospitalized with resumption of normal activities- n (%) | 71 (68.93) | 103 (96.26) | 10 (18.87) | 39 (78) | 0.05 (0.02-0.15) | <0.0001 |
| 2= Not hospitalized, but unable to resume normal activities- n (%) | 26 (25.24) | 3 (2.8) | 13 (24.53) | 2 (4) | 0.05 (0.02-0.15) | <0.0001 |
| 3= Hospitalized, not requiring supplemental oxygen- n (%) | 2 (1.94) | 0 | 2 (3.77) | 3 (6) | 0.05 (0.02-0.15) | <0.0001 |
| 4= Hospitalized, requiring low flow supplemental oxygen- n (%) | 1 (0.97) | 0 | 1 (0.93) | 0 | 0.05 (0.02-0.15) | <0.0001 |
| 5= Hospitalized, requiring high flow nasal oxygen- n (%) | 1 (0.97) | 0 | 4 (7.55) | 1 (2) | 0.05 (0.02-0.15) | <0.0001 |
| 6= Hospitalized, requiring mechanical ventilation- n (%) | 1 (0.97) | 0 | 4 (7.55) | 1 (2) | 0.05 (0.02-0.15) | <0.0001 |
| 7=Death- n (%) | 0 (0) | 0 | 4 (7.55) | 0 (0) | 0.05 (0.02-0.15) | <0.0001 |

**30 Day Mortality**

| Median Score (IQR) | 1 (1.37) | 0 | 0 (0-0) | 0.49 | 10 (18.87) | 2 (4) | 0.18 (0.02-0.92) | 0.029 |
|-------------------|---------|---------|---------|------|-----------|--------|----------------|-------|

**ADDITIONAL OUTCOMES**

| Median time to clinical improvement of severity of symptoms (95% CI) — days |
|------------------|---------|---------|---------|------|-----------|--------|----------------|-------|
| Improvement of one category on ordinal scale | 5 (5-6) | 3 (3-4) | 2.88 (2.10-3.94) | <0.0001 | 5 (5-7) | 3 (3-4) | 2.26 (1.48-3.45) | <0.0001 |
| Improvement of two category on ordinal scale | 8 (7-9) | 5 (4-5) | 4.18 (2.97-5.89) | <0.0001 | 12 (7-non-estimable) | 5 (5-6) | 2.59 (1.6-4.14) | <0.0001 |
| Achievement of normal status on ordinal scale | 8 (8-9) | 5 (4-6) | 4.49 (3.15-6.38) | <0.0001 | 13 (10-non-estimable) | 7 (6-8) | 2.74 (1.68-4.49) | <0.0001 |
|                          | Improvement of one category on ordinal scale | Improvement of two category on ordinal scale | Achievement of normal status on ordinal scale |
|--------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| **Median time to clinical improvement of degree of fever** (95% CI) | 5 (4-5)                                      | 7.5 (7-8)                                    | 8 (7-8)                                    |
|                          | 3 (non-estimable)                           | 4 (4-5)                                     | 4 (4-5)                                    |
|                          | 2.54 (1.87-3.46)                           | 3.96 (2.84-5.52)                            | 4.17 (2.98-5.84)                           |
|                          | <0.0001                                     | <0.0001                                     | <0.0001                                    |
|                          | 3 (3-4)                                     | 7 (6-8)                                     | 10 (8-11)                                  |
|                          | 3 (2-3)                                     | 5 (4-5)                                     | 6 (6-7)                                    |
|                          | 1.80 (1.18-2.75)                            | 2.23 (1.45-3.43)                            | 2.64 (1.7-4.11)                            |
|                          | 0.0003                                      | <0.0001                                     | <0.0001                                    |

| **Median time to clinical improvement of cough** (95% CI) | 4 (4-6)                                      | 6 (5-6)                                     | 7 (6-8)                                    |
|                                                        | 3 (non-estimable)                           | 5 (4-5)                                     | 5 (4-6)                                    |
|                                                        | 2.32 (1.53-3.53)                            | 2.27 (1.46-3.55)                            | 2.67 (1.73-4.12)                           |
|                                                        | <0.0001                                     | <0.0001                                     | <0.0001                                    |
|                                                        | 4 (3-4)                                     | 7 (6-8)                                     | 9 (8-10)                                  |
|                                                        | 3 (3-4)                                     | 5 (5-6)                                     | 6 (6-7)                                    |
|                                                        | 1.04 (0.66-1.63)                            | 1.59 (0.98-2.59)                            | 2.04 (1.26-3.31)                           |
|                                                        | 0.82                                        | 0.03                                        | 0.01                                       |

| **Median time to clinical improvement of shortness of breath** (95% CI) | 2 (2-non-estimable)                         | 2 (2-non-estimable)                         | 2 (2-non-estimable)                         |
|                                                                      | 2 (non-estimable)                           | 2 (non-estimable)                           | 2 (non-estimable)                           |
|                                                                      | 1.33 (0.14-12.82)                           | 1.33 (0.14-12.82)                           | 1.33 (0.14-12.82)                           |
|                                                                      | 0.617                                       | 0.617                                       | 0.617                                       |
|                                                                      | 6 (4-11)                                    | 13 (8-non-estimable)                        | 6 (4-6)                                    |
|                                                                      | 3 (3-4)                                     | 6 (4-6)                                     | 2.39 (1.48-3.87)                            |
|                                                                      | 2.65 (1.7-4.14)                             | 0.0001                                      | 0.0001                                      |

| **Median time to clinical improvement of myalgia** (95% CI) | 4 (3-4)                                      | 6 (5-7)                                     | 6 (6-7)                                    |
|                                                           | 3 (non-estimable)                           | 4 (4-5)                                     | 4 (4-5)                                    |
|                                                           | 2.3 (1.52-3.46)                             | 3.09 (1.92-4.98)                            | 3.34 (2.14-5.23)                           |
|                                                           | <0.0001                                     | <0.0001                                     | <0.0001                                    |
|                                                           | 4 (3-7)                                     | 8 (6-11)                                    | 9 (7-11)                                  |
|                                                           | 3 (3-4)                                     | 5 (4-5)                                     | 5 (4-6)                                    |
|                                                           | 1.83 (1.1-3.05)                             | 2.64 (1.53-4.54)                            | 2.75 (1.62-4.69)                           |
|                                                           | 0.0033                                      | <0.0001                                     | <0.0001                                    |

| **Median time to clinical improvement of “how sick do you feel”** (95% CI) | 5 (4-5)                                      | 7 (7-8)                                     | 8 (7-9)                                    |
|                                                                           | 3 (non-estimable)                           | 5 (4-5)                                     | 5 (4-6)                                    |
|                                                                           | 2.58 (1.9-3.51)                             | 3.27 (2.37-4.51)                            | 3.55 (2.55-4.93)                           |
|                                                                           | <0.0001                                     | <0.0001                                     | <0.0001                                    |
|                                                                           | 5 (4-9)                                     | 8 (7-non-estimable)                         | 13 (10-non-estimable)                      |
|                                                                           | 4 (3-4)                                     | 5 (5-6)                                     | 7 (6-8)                                    |
|                                                                           | 1.82 (1.12-2.77)                            | 2.18 (1.37-3.48)                            | 2.87 (1.75-4.69)                           |
|                                                                           | 0.0012                                      | 0.0002                                      | 0.0001                                     |
The Intention-to-Treat analysis was performed on all the patients who had undergone randomization. n=number of patients, IQR: Interquartile Range, ECMO: Extracorporeal membrane oxygenation; CRP: C-reactive protein. The effect estimate for time to symptom alleviation, viral clearance and median time to clinical improvements are hazard ratios, for CRP are mean differences, and for ordinal variables are odds ratios. Median number of days (95% confidence interval) with hazard ratio estimation using log-rank test. Ordinal logistic regression models assuming proportional odds applied (multivariable regression models to adjust for the effects of patient age, gender, baseline clinical status grade, and history of diabetes/hypertension.) Time taken for the alleviation of symptoms was the difference between date of enrollment and becoming clinically asymptomatic. Viral load clearance was the difference between date of first positive and next negative SARS-CoV-2 RT-PCR. Clinical status grading was assessed on 6th and 10th day using the seven-level ordinal scale representing effect estimate as odds ratio (95% confidence interval). Fever is classified as mild, moderate and severe. None (0) 98-99 °F, mild (1) <100 °F, moderate (2) 100-101.9 °F, severe (3) ≤ 102°F. Severity of symptoms is classified as mild, moderate and severe. Mild denotes symptoms of upper respiratory tract viral infection i.e. low grade fever, dry cough, sore throat, nasal congestion, malaise, Moderate are respiratory symptoms (fever, cough and shortness of breath) without signs of severe pneumonia and severe is classified as fever associated with severe dyspnoea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). Fischer exact P value (2-tail), significant if <0.05. Cough is categorized from 0 to 3; None (0), Mild (1) occasional, transient cough, Moderate (2) frequent cough, slightly influencing day time activities, Severe (3): frequent cough, significantly influencing daytime activities. Shortness of Breath is grouped as Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5. Grade 1=Not troubled by breathlessness except on strenuous exercise, Grade 2=Short of breath when hurrying on the level or walking up a slight hill, Grade 3=Walks slower than most people on the level, stops after a mile or so, or stop after 15 minutes walking at own pace, Grade 4=Stops for breath after walking about 100 yds or a few minutes on level ground and Grade 5=Too breathless to breathless when undressing. Myalgia is graded as none (0), mild (1), moderate (2), and severe (3) on subjective basis. How Sick Do You Feel is categorized as none (0), mild (1), moderate (2), and severe (3) on subjective basis.
Figure 2. Kinetic changes in outcomes. A. Mean oxygen saturation spO2 over time in severe cases; Kaplan-Meier probability curves for time taken (in days) for alleviation of symptoms in moderate (B) and severe cases (C); Kaplan-Meier probability curves for time taken (in days) for vial clearance in moderate (D) and severe cases (E). ns = non-significant, *= P<0.05, **=P<0.001, ***=P<0.0001
Figure 3. Kinetics of clinical status grading in Ordinal-Scale in COVID-19 patients. The figure shows kinetic changes in clinical grade score (in 7-point ordinal-scale) in COVID-19 patient receiving the treatment (HNS) or placebo (Control). Note increases numbers of patients within scale 1 in the HNS group both for the moderate and severe cases.
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