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Original Article

Role of Nigella Sativa (Black Cumin Seeds) as an Adjunct Therapy in Treating Severe and Critical COVID -19 Infection Compared to Those with Standard Therapy: An Open Label Randomized Clinical Trial

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Abstract:

Background: *During recent COVID-19 pandemic (2019-2021) clinician-researchers had been looking for effective treatment of Covid-19 infection. Nigella sativa (NS), a well-known herbal medicine, has beenused asanti-viral, anti-inflammatory, immune modulatory, anti-oxidant, broncho-dilatory, anti-histaminic, anti-tussive activitiesfor patients with mild to moderate COVID-19 infection. Our study aimed to determine the efficacy of NS for treatment of severe and critically ill Covid-19 patients as an adjunct therapy with conventional treatment.*

Method: *This wasan open label randomized clinical trial conducted in severely and critically ill COVID-19 patients admitted into COVID ICU of United Hospital, Dhaka, Bangladesh. The study subjects were randomly divided into two equal groups: NS group in which subjects received NS orally in addition to the conventional treatment, and Control group, who received conventional treatment only. Primary outcome focused mainly on duration of ICU stay, use of mechanical ventilation (MV)/noninvasive ventilation (NIV)/ High-flow nasal cannula (HFNC) oxygen (HFNO) and mortality. The secondary outcomes were based on comparison of those above mentioned parameters between the groups (NS and Control).*

Results: *A total of 150 subjects were enrolled according to eligibility criteria.There were 60 deaths (29 NS + 31 Cont.) and 90 survivals (46 NS + 44 Cont.). Among the survivals 16 NS subjects as opposed to 6 Cont. subjects stayed in ICU for 8 to 14 days (P = 0.043). Twenty one subjects of NS group as opposed to 8 subjects of Cont. group stayed in ICU for less than 7 days to 14 days. Whereas among subjects who died there was no significant difference in length of stay among majority of NS and Cont. subjects. NS group required significantly lower number of O_2 delivery methods likemechanical ventilation (MV), noninvasive ventilation (NIV),High-flow nasal oxygen (HFNO) compared to their counterparts on Day 7 and Day 14 of stay in ICU.*

Conclusion: *NS as an adjunct therapy with severe and critical COVID 19 infection was associated with some reduction of duration of stay in ICU but significantly less requirement of invasive and non-invasive ventilator support, high flow nasal oxygen than standard treatment group. Establishing accurately therapeutic efficacy of NS in critically ill COVID-19 patients requires placebo controlled double blind studies.*

Key words: *Nigella Sativa; Black Cumin; COVID - 19.*

Introduction

Since it's out break at the end of December 2019 novel corona virus (2019-nCoV) or severe acute respiratory distress syndrome corona virus 2 (SARS CoV-2) was recognized to be the cause of an outbreak of respiratory illness in Wuhan city, Hubei province of China[1]. The WHO named the disease as Corona Virus 2019 (COVID -19) and finally in March 2020 announced COVID -19 outbreak as a pandemic.[2.]

This virus causes infection in the respiratory tract, nervous system, gastrointestinal tract, kidney and liver of the patients and in some cases acute respiratory distress syndrome may be developed which leads to a high mortality rate.[3, 4]

The sign and symptoms of COVID19, present at illness onset vary, but over the course of the disease many people with COVID-19 will experience the following:[5] fever or chills, cough, shortness of breath or difficulty in breathing, fatigue, muscleor bodyaches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea etc.

The disease severity was classified according to the following NIH guidelines:[6]

Asymptomatic or pre symptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test: NAAT) or an antigen test, but who have no symptoms that are consistent with COVID-19.

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Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.

Severe Illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

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The pathophysiological features of severe COVID-19 are determined by an acute pneumonic process with extensive radiologic opacity and on autopsy, diffuse alveolar damage, inflammatory infiltrates, and micro vascular thrombosis[7].

Nigella Sativa (NS) is an annual flowering plant. It grows to 20–30 cm (7.9–11.8 inch) tall and has linear lanceolate leaves. The delicate flowers have 5-10 petals and the colors are usually yellow, white, pink, pale blue or pale purple. The fruit of plant is large and inflated capsule composed of 3-7 united follicles, that each of them has numerous seeds. The black colored seeds are flattened, oblong and angular, funnel shaped, with the length of 0.2 cm and 0.1 cm wide[8].This plant is known by numerous names[9], for example black cumin or black seed (English), black caraway seeds (USA), Shonaiz (Persian) and Kalojira (Bengali) and Habbat al-Sawda (Arabic).

Since the history of mankind, herbs and their formulations have been used as a basis of traditional remedies andmodern medicines[10,11]. Being a divine panacea, NS has taken a special place in traditional medicine as well as in modern medicinal research[12]. Among various ingredients of NS seed, volatile oils and alkaloids are mostly associated with biological activities. The significant constituents of the volatile oil are nigellone, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α and β-pinened-limonene, d-citronellol, p-cymene, carvacrol, t-anethole, 4terpineol and longifolene[13, 14].

Among the alkaloids, soquinoline (nigellicimine, nigelliciminen-oxide) and pyrazol (nigellidine and nigellicine) are notable[15]. Amongst different active constituents reported so far, thymoquinone constitutes the major bioactive principle with array of therapeutic benefits[12] including antioxidant[13], anti-inflammatory[14], anti-cancer[15], antibacterial[16,17], antifungal activity[18] and anticonvulsant activity[19]. Immuno- modulatory effects of black seed have also been reported[20,21]. Also, several studies reported the antiviral effect of the black seed[22-26]. Recently, a molecular docking-based study identified nigellidine and α- hederin among the compounds of NS as novel inhibitors of SARS-CoV-2[27]. All these evidences strongly suggest the therapeutic potentials of NS seed and its active constituents against COVID-19.

Our aim is to establish the effect of NS seed on severely[6] and critically ill[6] COVID-19 patients in intensive care unit. We aim to perform prospective, randomized open label controlled study and calculate the recovery rate, oxygen and ventilator requirement, duration of ICU stay, and hospital mortality.

Materials and Methods

It was a prospective two arm randomized open label controlled study which included 150 COVID positive patients of COVID ICU (above 18 years old) as per availability. All patients with laboratory-confirmed COVID 19 positive, and subsequently admitted to the COVID ICU of United Hospital were enrolled. This study has been approved by the hospital ethical review committee before starting the trial. All study patients remained anonymous. Written informed consent was

obtained from patients' legal guardian or next of kin.

Diagnosis of COVID-19 was made based on the detection of ≥2 SARS-CoV-2 genes by reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab, throat swab, and/or any respiratory samples[28]. Data that were collected from patient included the variables like socio demographic information, clinical features, underlying illnesses, baseline laboratory parameters, chest X-ray/ CT scan of chest, antiviral therapy, oxygen support, duration of ICU stay, and outcome of treatment.

All orally fed (including nasogastric tube fed) study patients who were RT PCR positive & admitted into COVID ICU who were severely or critically ill as per NIH criteria and were 18 or > 18 years were included in the study. Patients who were Taking NS before the study, who were below 18 years of age, who were only on parenteral feed (NPO) and pregnant females were excluded from the study.

Study patients were selected randomly and every alternate patients admitted in ICU who fulfilled inclusion and exclusion criteria were given NS seeds and belonged to the NS group. Alternate admitted patients who fulfilled the inclusion and exclusion criteria and were not given NS were labeled as Control group. Total 150 subjects belonged to our study (75 in NS group and 75 in Control group).

In addition to conventional treatment each NS patient received two grams of dryNS powder (machine crushed seeds dispensed in poly bag) (Fig 1) twice daily to be taken after meal as suspension in plain water for subsequent 14 days beginning from the day of admission in ICU. Data sheet included documentation of clinical condition and laboratory investigation in details during successive fourteen (14) days from day of admission.

Fig 1

Each NS patient who were able to swallow (oral feeding not contraindicated), were given post prandial NS powder mixed with 50 CC plain drinking water to swallow. Patients who were on naso-gastric tube feeding received the NS powder (suspension made with enough plain water) through NG tube.

We documented source of admission, age of patients, clinical symptoms, laboratory parameters, co-morbidities, significant drug history, vital signs, and pattern of oxygen therapy, duration of hospital stay, weekly hospital mortality and after 28 days mortality.

NS patients who were discharged home before 14 days after admission were provided with take home NS powder in poly bags to complete the course of 14 days. In those cases data sheets were filled only on days before discharge and phone calls were made on days after discharge till the 28th day after admission to check if the patents were stillalive and well.

NS patients who were transferred to wards/cabins before 14 days continued to get NS powder to complete the course of 14 days.

All study subjects who were discharged home or transferred out of ICU before 28 days and who took NS for 14 days were followed for total 28 days (after admission) for mortality.

Patients who stayed in ICU beyond 28 days were followed in the inpatient unit till death or discharge from ICU. Patients who were transferred out of ICU beyond 28 days were followed till discharge from hospital.

This study followed WMA declaration of Helsinki – ethical principles for medical research involving humans.

Statistical analysis

Categorical variables were presented as frequency, rates, and percentages and were compared by chi-square or Fisher exact test. Continuous variables were presented as Mean ± SD. Means for continuous variables were compared using independent group t-test orANOVA when the data were normally distributed; otherwise, the Mann-Whitney test was used. Categorical variables were analyzed and presented as percentage distribution and were compared by chi-square.

Continuous variables were presented as Mean ± SD. Means for continuous variables were compared using independent group t-test or ANOVA when the data were normally distributed; otherwise, the Mann-Whitney test was used. Relative risk was calculated for some variables. Two-sided $p< 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 22.0, IBM).

RESULTS

The study duration was from August, 2020 to March, 2021.Among the 150 patient, 75 was studied in NS group and 75 were studied in Control group. Among the study subjects 66.7% were male and the rest were female (33.3%).

All study patientson admission into ICU were severely or critically illas per NIH criteria[6]. All studypatients who died in ICU were found to be critically ill before death.

Most of the study subjects were admitted through the emergency department (34%) of the hospital. Twenty percent patients were directly admitted to ICU from out of hospital and 20% of study subjects were admitted fromCOVID ward.

Fifty five percent of the study subjects were in between the age group 61 and 70 years. The mean age of the study subject was 61.40±13.40. Age of the patients ranged between 27 and 98 years.

Table I shows seven chief symptoms on admission. Table II shows the significant laboratory findings on admission.

Table I: Chief symptoms on admission (N=150)

Characteristics

symptoms	**Total**	**NS**	**Control**	**P value**
Fever	138	66	72	0.406
Dry Cough	103	42	61	0.026
Shortness of breath	101	58	43	0.721
Fatigue/malaise	15	10	5	0.503
Cough with sputum	9	8	1	0.582
Runny Nose	6	1	5	0.034
Chest pain	3	2	1	-

Table II: Laboratory findings on admission (N=150)

Parameter	**Mean ±SD : Range**		
	NS	**Contro**	**p Value**
Hemoglobin(gm/dl)	12.02±1.55	11.50±1.89	0.267
White blood cell × 10^9/ mL	14.57±7.79	14.12±6.19	0.383
Lymphocyte (%)	10.03±8.59	9.91±6.27	0.062
Platelet × 10^9/L	430004.43±9492.71	281590.21±6123.12	0.012
Activated partial thromboplastin time (second)	32.63±13.55	37.30±7.92	0.049
Prothrombin time (second)	10.71±9.68	12.52±9.64	0.437
INR	1.24±.22	1.24±.47	0.121
Sodium (mmol/L)	137.00±6.06	137.30±7.42	0.475
Potassium (mmol/L)	4.27±3.65	4.92±.48	0.166
Procalcitonin (ng/ml)	0.12±2.80	0.49±1.139	0.419
D-dimer (µg/L)	1529.71±377.31	1487.90±147.91	0.026
ALT (U/L)	49.22±26.72	50.63±23.15	0.421
Serum Creatinine (mg/dl)	1.34±.74	2.35±1.42	0.099
Lactate (mmol/L)*	1.54±.93	1.74±.91	0.503
CRP (mg/L)	102.76±72.10	104.74±71.59	0.907
Ferritin ng/mL	42.77±2.95	54.23±4.65	0.003
Interleukin-6 (pg/mL)	180.29±13.2942	168.98±21.33	0.411

*Lactate level were done on 46 and 30 subjects in NS group and Control group respectively

Fig II shows significant medication on admission. Fig III shows types of co morbidities among study subjects.

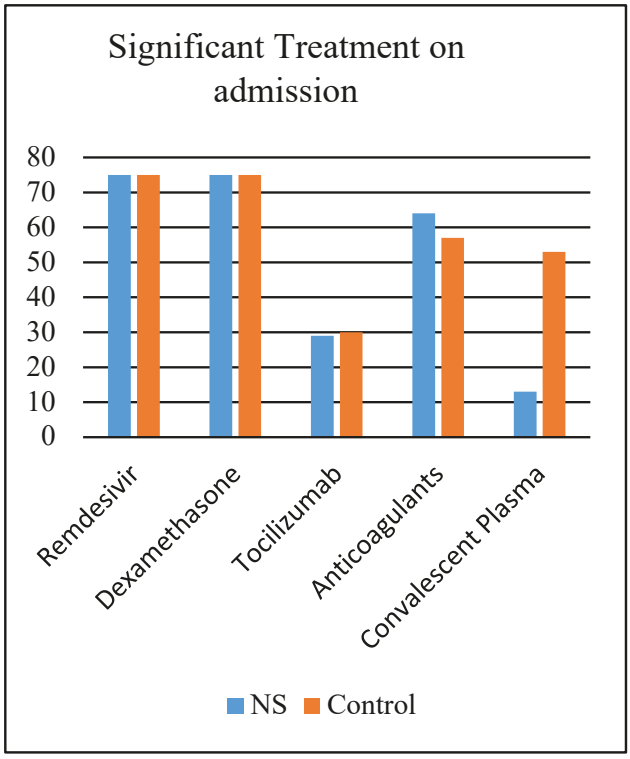

Fig II: Medications on admission

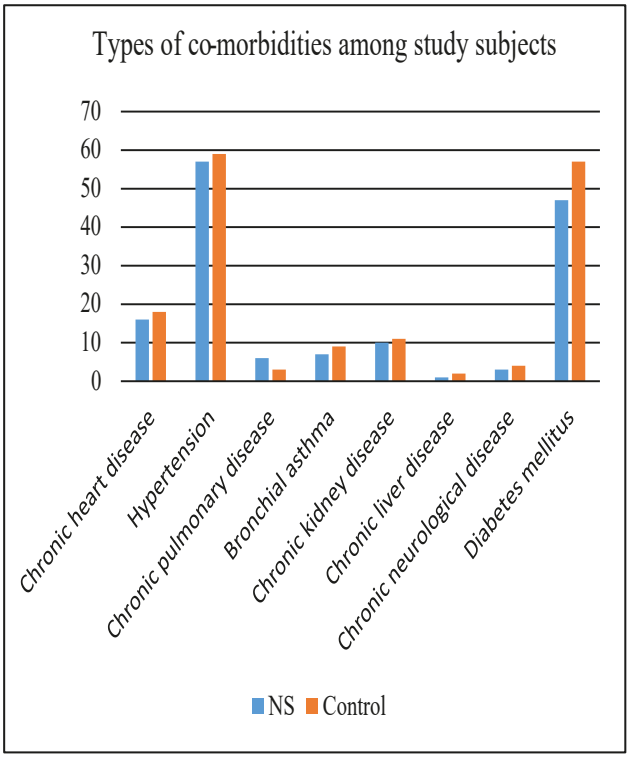

Fig III: Comorbidities

In our study irrespective of two groups, the Chest X-ray and CT scan of Chest showed various findings on all patients e.g. ground-glass opacity, bilateral patchy shadowing, unilateral patchy shadowing and interstitial abnormalities.

Table III shows oxygen therapy and ventilator care on day 7 and day 14 during ICU stay. Admission SpO_2 (Day 1) in room air on all study subjects showed no statistical difference between two groups. (83.39±6.75in NS group and 84.61±5.36 in Control group with P value 0.305).

Table III: Oxygen delivery method of two groups on day 7 & day 14 during ICU stay

Oxygen delivery method	**Frequency/ Percentage**							
	Day 7				**Day 14**			
	NS N=75 (100%)	**Control N=75 (100%)**	**Relative Risk (CI)**	**PValue**	**NS N=75 (100%)**	**Control N=75 (100%)**	**Relative Risk (CI)**	**P Value**
Nasal Cannula (1 to 4L/min)	43(57.3)	7(9.33)	1.89 (1.02-2.90)	0.003	31(41.33)	7(9.33)	2.11 (1.01-3.01)	0.001
Face mask (5 to 10 L/min)	13(17.3)	5(6.66)	1.33 (.97-1.99)	0.003	11(14.67)	6(8)	1.74 (.41-2.29)	<0.001
Non re breather mask (10 to 15 L/min)	7(9.33)	6(8)	1.02 (.41-1.56)	0.621	9(12)	6(8)	1.53 (.53-1.98)	0.413
High flow nasal oxygen 60 L/min	3(4)	7(9.34)	.81 (.23-1.06)	0.574	6(8)	12(16)	.91 (.23-1.37)	0.003
NIV /BiPAP	6(8)	32(42.7)	47 (.13-.79)	0.023	10(13.33)	23(30.7)	.34 (.003-.64)	0.004
Mechanical ventilator	3(4)	18(24)	.29 (.03-.55)	0.001	8(10.67)	21(28)	.17 (.009-.96)	0.031

Table IV shows distribution of cases: Survival and Non Survival (Death) according to length of ICU stay.

Table IV: Survival & Death in two groups

Length of Stay	Survival NS	Control	P value	Death NS	Control	P value
Within 7 days	5	2	.621	5	3	.633
8-14 days	16	6	.043*	10	9	.546
15-21 days	16	24	.573	6	7	.543
22-28 days	5	7	.539	4	7	.046*
After 28 days	4	5	.718	4	5	.652
Total	46	44		29	31	

Figure IV shows distribution of NS and Control group among survivors and non survivors of males and females.

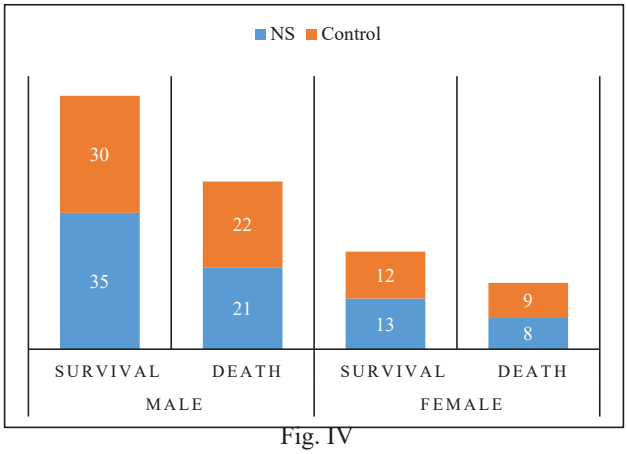

Fig. IV

Discussion

This study was a single center randomized controlled clinical trial investigating the therapeutic efficiency of NSseeds on severely as well as critically ill COVID-19 positive patients during the recent COVID -19 pandemic.

75 patients (COVID positive) received NS powder in addition to conventional treatment (NS group) and 75 COVID positive patients (Control group) received conventional treatment only.

In our study majority of subjects were admitted through Emergency Room. Only 20% patients were admitted directly into ICU from outside without going through emergency. Rest were transferred from other areas of the hospital.Age range of most of the subjects varied between 50 and 70 years and median age was 60 years.

Dry cough and runny nose were more predominant presenting symptoms of standard treatmentgroup than NS group (Table I). S ferritin and APTT were slightly higher in control group and D-dimer, Hgb and platelet count were higher in NS group.(Table I).

All study subjects equally received Remdesivir and Dexamethasone. NS group received anticoagulant in larger numbers whereas Control group received antiplatelet, blood and blood product in larger numbers. Almost equal numbers in both groups received Tocilizumab (29 vs 30) (Fig I).

Hypertension, and Diabetes mellitus were significantly present in both groups but slightly higher in control group (Fig II).

Subjects of NS group used significantly lesser number of O_2 delivery methods like MV, NIV/BIPAP, and HFNO on day 14 compared to control group during hospital stay. On day 7 of hospital stay subjects of NS group used lesser number of NIV/BIPAP than subjects of control group (Table II)

We had 60 deaths among total 150 study subjects. All of them died in the ICU. There was no mortality reported when discharged on or before 28 days from hospital. Among total deaths, 29 deaths took place in patients who received NS compared to 31 in the control group (Table IV).

21 patients of NS group as opposed to 8 patients of Control group stayed between less than 7 days and 14 days in ICU. Sixteen patients of NS group as opposed to 6 patients of Control group stayed between 8 and 14 days in ICU (P = 0.043). There was no significant difference in length of stay among patients who died and belonged to NS group and Control group (Table IV).

Fig IV shows no significant difference in survival and death between male and female population of both NS and Control groups.

A study was done by Koshaketal[28] from Saudi Arabia on adult COVID -19 patients with mild symptoms which involved patients receiving Nigella sativa oil orally post prandial. Sixty two percent recovery was noted in patients of Nigella sativa oil group compared to 36% from Control group.

Study conducted by Ashraf et al from Pakistan[29] was a multicenter, placebo controlled randomized clinical trial where ventilator patient, patient with multi organ failure and patients with chronic disease were excluded. This study involved study group comprising patient receiving honey and NS seed combinationand was compared with placebo group. Thirty day mortality in honey-nigella group was 4% as opposed to 18.77% in placebo group. Our study involved severely and critically ill ICU patients who often needed ventilator support, NIV or HFNO in ICU.

Al-Haideri et al[30] from Iraq studied 259 non- ICU patients receiving convectional treatment as control and 160 non- ICU patients receiving Nigella seeds orally in addition to conventional treatment. Authors studied 46 severe patients not requiring ICU admission (respiratory rate > 30/min, O_2 Sat < 93% in room air, PaO_2/FIO_2 300, positive lung infiltrates) out of which 44 received conventional treatment and remaining two severe patients who received Nigella seeds 40mg/day for 14 days in addition to conventional treatment. Fourteen patients died from the control group assuming they were severely infected and none died from severe patients who received Nigella.

Said et al[31] from Egypt studied 120 COVID -19 positive patients with mild to moderate symptoms and divided them into 4 groups, thirty patients each and receiving conventional treatment. In addition to conventional treatment Group 1 received 900 mg Nigella Sativa twice daily for two week, Group 2 receiving Vit D3 receiving 2000 IU once daily, Group 3 receiving Nigella and Vit. D3 combination and Group 4 (control) receiving conventional treatment only. The authors claimed that Nigella sativa andVit. D3 combination as adjunct therapy produces viral clearance in shorter time interval accompanied by reduction in severity and progression of signs and symptoms.

On literature search we can claim that our study is the first and only of its kind to observe the therapeutic efficacy of Nigella sativaseed as an adjunct therapy on severely and critically ill COVID-19 infection.

Conclusion:

Our study concludes that NS supplementation given along with conventional treatment is associated with some degree of shorter ICU stay and faster recoveryin severely and critically ill ICU patients.

Severely ill COVID -19 ICU patients receiving Nigella Sativa along with conventional treatment will significantly less likely use Mechanical Ventilator, NIV, HFNO compared to patients who receives conventional treatment only.

Our study could not conclusively prove mortality benefit in severely and critically ill COVID -19 ICU patients who received Nigella.

At the moment all COVID designated ICUs in Bangladesh are nonfunctional because of lack of critically ill COVID patients. This is also true to some extent in COVID 19 affected other countries of the world. Researcher will have to wait for another COVID-19 surge in near future to conduct confirmatory study on therapeuticuse of different biological agents like Nigella Sativa

Limitation of Study:

Our study is not without limitation. Number of study population is small. It was not a double blind placebo controlled multi-center study. Rather it was a single center, open labeled case control study.Selection bias in allocating study subjects in Nigella group and Control group could not be ruled out with certainty.

Conflict of interest: None.

Funding: Self-funded.

Author contribution:

Steering committee: MOF, AS, UKC, KS, CTH, MSN, SHN, MAR, TK, TYS

Data Collection: KS, SIO, UKC, MGH, MRH, MSS, RA, ASA

Statistical analysis: SHH, SHN

Manuscript planning and composition: MOF

Manuscript editing: MOF, SHH, SHN, MSU

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