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Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study

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Abstract

Background and objectives: Various existing non-antiviral drugs are being used to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based mostly on existing data from previous coronavirus outbreaks. Ivermectin is one of such agents being widely used to treat early-stage of COVID-19. This study evaluated the outcome of ivermectin treated mild to moderate COVID-19 cases compared to usual care.

Methods: This open-label randomised controlled study was conducted at a sub-district (Upazila) health complex from 1st May 2020 to the end of July 2020. Consecutive RT-PCR positive eligible COVID-19 patients were randomised into control and intervention arms. In the intervention arm, ivermectin 200 micrograms/kg single dose was administered orally in addition to usual care and was followed up till recovery. Repeat RT-PCR was done on day ten since the first positive result. The end point with regard to treatment outcome was time required for the resolution of symptoms from the onset of the symptoms and following enrollement in the study.

Results: A total of 62 mild to moderate COVID-19 patients were enrolled in the study. There were 30 patients in the control arm and 32 patients in the intervention arm. Total recovery time from the onset of symptoms to complete resolution of symptoms of the patients in the intervention arm was 10.09 ± 3.236 days, compared to 11.50 ± 5.32 days in the control arm (95% CI -0.860,3.627, $p > .05$) and was not significantly different. The mean recovery time after enrolment in the intervention arm was 5.31 ± 2.48 days, which also did not differ significantly from the control arm of 6.33 ± 4.23 days (95% CI $- 0.766, 2.808$, $p > 0.05$). Results of negative repeat RT- PCR were not significantly different between control and intervention arms (control 90% vs intervention 95%, $p > .05$).

Conclusion: Ivermectin had no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases.

Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified during an outbreak of a respiratory illness in Wuhan City, Hubei Province, China, in December 2019 [1]. On March 11, WHO declared COVID-19 a global pandemic [2]. To date (August 11, 2020), approximately 20 million people worldwide have been infected, and about 0.75 million patients died of COVID-19. Currently, no drug is clearly found effective in the treatment of COVID-19. Based on experience from previous coronavirus outbreak, some antiviral agents namely remdesivir and

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favipiravir, have shown some promise in the treatment of COVID-19. However, these are very expensive and are reserved for severe cases only [3,4]. Treatment for patients with mild to moderate disease is not well established [5,6]. Several national and international observational studies have reported encouraging results of ivermectin in the treatment of COVID-19 patients with a mild degree of severity [7].

Ivermectin has been a popular anti-parasitic drug since the late 1970s. This drug stimulates gamma-aminobutyric acid-controlled chloride channels, which leads to hyperpolarisation and paralysis of the affected organism. The antiviral function of ivermectin has been discovered in recent years and is fascinating. This drug has a wide range of antiviral activities, both in vivo and in vitro, against various RNA and DNA viruses [8,9]. Efficacy against specific flaviviruses (dengue, Japanese encephalitis, and tick-borne encephalitis virus) and the chikungunya virus have been demonstrated *in-vitro* [10,11]. In a study by Caly et al has demonstrated that Vero/hSLAM cells infected with SARS-CoV-2 when treated with ivermectin resulted in a 5,000-fold reduction in viral RNA after 48 hours [12]. The exact mechanism of this effect is not yet known. However, the possible mechanism is inhibition of importin α / β1 mediated transport of viral proteins in and out of the nucleus [13].

The promising result of the *in-vitro* study mentioned above has led clinicians in many countries to use ivermectin to treat COVID-19 patients. A retrospective cohort study in hospitalised patients with confirmed SARS-CoV-2 infection in four hospitals in Florida showed significantly lower mortality rates among those who received ivermectin compared to the usual treatment [14]. The mortality rate was also significantly lower in ivermectin-treated patients with severe lung disease, although the rate of successful extubation was not significantly different [14]. In an observational study in Bangladesh, involving 100 COVID-19 patients treated with a combination of ivermectin and doxycycline showed adequate viral clearance in mild and moderately ill patients [7]. A recently published randomised controlled trial in Bangladesh found that a combination of ivermectin and doxycycline was safe and effective in patients

infected with SARS-CoV-2, and showed no significant adverse events and had an improved tolerance compared to a combination of 'hydroxychloroquine and azithromycin [15]. However, there was no control (usual care) group in this study. The available pharmacokinetic data suggest that plasma concentrations of ivermectin with significant activity against SARS-CoV-2 could not be achieved without potentially toxic doses of ivermectin in humans [13].

Therefore, use of ivermectin warrants rapid implementation of controlled clinical trials to assess the efficacy against SARS-CoV-2 [16]. Although observational data suggest a beneficial effect of ivermectin in the treatment of COVID-19, there has been no randomised controlled trial (RCT) with ivermectin compared to the usual care in patients with mild to moderate COVID-19. Therefore, it is essential to conduct a clinical trial with ivermectin in patients with COVID-19 to evaluate the effectiveness of this drug in treating mild to moderate COVID-19 patients. This study was designed to evaluate the benefit of, if any, adding ivermectin to usual care, compared to usual care alone in the treatment of COVID-19 cases at a semi-rural settings.

Methods

Study design, randomisation and intervention

This study was an intention to treat prospective randomised controlled trial conducted at Debidwar Upazila (sub-district) Health Complex, Debidwar, Comilla. Patients were enrolled from the outpatient department of the health center from the beginning of May 2020 to the end of July 2020. All COVID-19 suspected cases were advised for RT-PCR test. Consecutive RT-PCR positive eligible mild to moderate COVID-19 cases of more than 18 years of age, of both sexes, were enrolled and randomised into control and intervention arms and followed till recovery. Randomisation was done using an odd-even methodology applied to registration numbers, in a consecutive fashion of 1:1 ratio. Patients with known pre-existing hypersensitivity to Ivermectin, pregnant and lactating mothers, and patients taking other antimicrobials or hydroxychloroquine were excluded from the study.

Mild to moderate diseases were defined according to WHO COVID-19 disease severity classification. Symptomatic patients without evidence of viral pneumonia or hypoxia (SpO2 >93% on room air) were considered as a mild disease and patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2≥ 90% on room air were considered as a moderate disease [6]. Upon enrollment, all COVID-19 cases received symptomatic treatment which included antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days) to treat possible community-acquired pneumonia as part of the local working protocol and this treatment schedule was termed as 'usual care'. The control arm continued to receive the 'usual care', and the intervention arm in addition to usual care, received single dose of ivermectin 200 micrograms/kg on the day 1 of randomisation. Procedure for enrollment of cases is shown in Figure-1. The selected cases were treated on an OPD basis.

Repeat RT-PCR was performed on day 10 after the first positive test result. Data were collected in a semi-structured questionnaire devised for the study by the research team. Both face-to-face and telephonic communication were used for follow-up and data collection.

Outcome measures

The outcome end point was the time needed for resolution of fever, cough, shortness of breath and finally, full recovery from all symptoms and the negative result of repeat RT-PCR on day 10. Recovery time was defined as time required for the resolution of symptom(s) from the date of enrolment in the study as well as from the onset of initial illness.

Ethics and statistical analysis

Permission was taken from the head of the health centre. Informed written consent from the patients was obtained before enrolment.
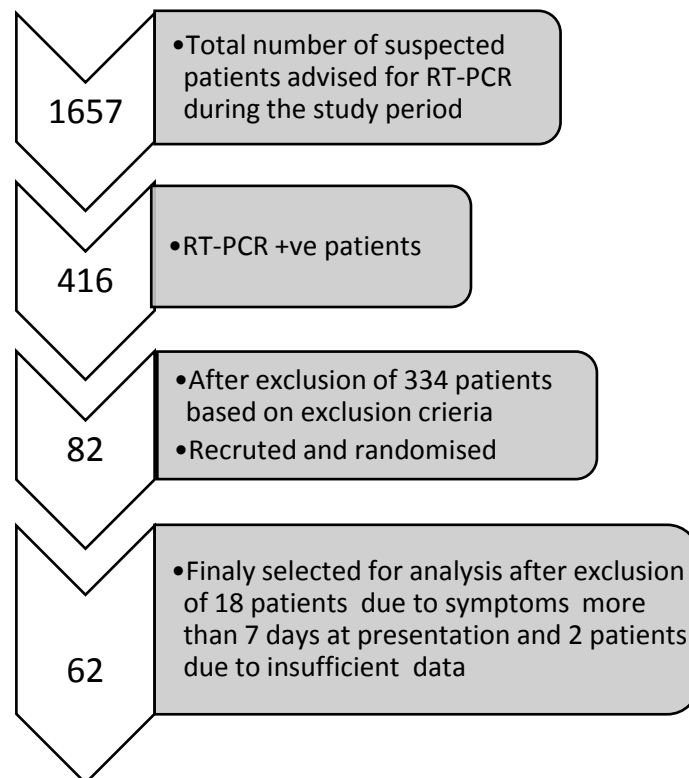

Fig-1: *Sample selection flow chart*

After collection, data editing and clearing were done manually and prepared for data entry and analysis by using SPSS version 20. The data was checked for any omissions, irrelevance, and inconsistencies. The omissions were corrected by repeating history. Irrelevant and inconsistent data were discarded. Finally, 62 patients were included in the intention-to-treat analysis. The unpaired t-test was used to compare the means between control and intervention arms. Crosstab and chi-square tests were used to compare demographic parameters between control and intervention arms. P-value of less than 0.05 was taken as significant.

Results

Initially, 82 patients were recruited; of these, 62 patients who presented within seven days of onset of symptoms were finally selected for analysis. Twenty patients were excluded as 18 had symptoms for more than seven days at the time of enrollment and two other patients had insufficient data. There were 30 patients in the control arm, and 32 patients were in the intervention arm. The mean age of the all enrolled cases was 39.16±12.07 years. The mean age of cases in control and intervention arms were not significantly different (39.97±13.24 *versus* 38.41±11.02 years; p>0.05). Out of 62 cases, 44 (71.0%) were male and 18 (29.0%) were female. With regard to category, 50 (80.6%) and 12 (19.4%) were mild and moderate COVID-19 cases respectively. The predominant symptoms of the study population were fever (50, 80.6%), followed by cough (42, 67.7%). There was no statistically significant differences in baseline demographic and clinical parameters between control and intervention arms except sore throat (Table-1).

Table-2 shows the duration of different symptoms of the study participants at the time of enrolment. Mean duration of different symptoms of the cases in both control and intervention arm was not significantly different (p>0.05) at the time of enrolment.

Table-1: *Demographic and clinical characteristics of the patients at the time of enrolment in the study (n=62)*

Characteristics	Total N=62 n (%)	Control arm (N=30) n (%)	Intervention arm (N = 32) n (%)	p value
Male	44 (71.0)	21 (70.0)	23 (71.9)	>.05
Female	18 (29.0)	9 (30.0)	9(28.1)	
Presenting symptoms				
Fever	50 (80.6)	23 (76.7)	27 (84.4)	>.05
Cough	42 (67.7)	21 (70.0)	21 (65.6)	>.05
Shortness of breath)	12 (19.4)	6 (20)	6 (18.8)	>.05
Sore throat	14 (22.6)	11 (36.7)	3 (9.4)	<.05
Anosmia	14 (22.6)	5 (16.7)	9 (28.1)	>.05
Dysgeusia	3 (4.8)	2 (6.7)	1 (3.1)	>.05
Diarrhoea	6 (9.7)	2 (6.7)	4 (12.5)	>.05
Myalgia	22 (35.5)	8 (26.7)	14 (43.8)	>.05
Fatigue	12 (19.4)	7 (23.3)	5 (15.6)	>.05
Headache	7 (11.3)	5 (16.7)	2 (6.3)	>.05
Rhinorrhoea	8 (12.9)	4 (13.3)	4 (12.5)	>.05
Severity of illness				
Mild	50 (80.6)	24 (80.0)	26 (81.3)	>.05
Moderate	12 (19.4)	6 (20)	6 (18.8)	

Note: p value calculated by comparing between control and intervention arm.

Table-2: *Duration of symptoms of patients in intervention and control arms at the time of enrolment (n=62).*

Symptoms	Mean (± SD) duration in days			
	All patients	Control arm	Intervention arm	p[a]
Fever	3.92±2.12	4.00±2.17	3.85±2.11	>.05
Cough	3.76±2.07	3.62±2.27	3.90±1.89	>.05
Shortness of breath	2.42±1.31	3.00±1.27	1.83±1.17	>.05
Fatigue	4.00±2.13	4.71±2.36	3.00±1.41	>.05
Myalgia	3.67±1.86	4.50±3.54	3.25±.96	>.05

Note: a=Compared between control and intervention arm by student's t test

Table-3: *Time required for the resolution of symptoms of cases in control and intervention arms from the date of enrolment in the study*

Symptoms	Recovery time following enrolment in the study			95% Confidence Interval of the difference of means	
	Control group Mean ±SD (days)	Intervention group Mean ±SD (days)	p value	Lower	Upper
Complete recovery[a]	6.33±4.23	5.31±2.48	>.05	-0.766	2.808
Fever	3.18±2.61	3.33±2.18	>.05	-1.729	1.415
Shortness of breath	6.33±3.67	4.83±1.72	>.05	-2.187	5.187
Fatigue	5.67±3.62	6.00±4.85	>.05	-6.097	5.430

Note: [a]Resolution of all symptoms. Some parameters are excluded from the analysis due to inadequate data

Table-4: *Time required for the resolution of symptoms of cases in control and intervention arms from the date of onset of illness*

Symptoms	Recovery time from the onset of initial symptoms			95% Confidence Interval of the difference of means	
	Control group Mean ±SD (days)	Intervention group Mean ±SD (days)	p	Lower	Upper
Complete recovery[a]	11.50±5.32	10.09±3.24	>.05	-.860	3.672
Fever	6.43±2.45	6.48±3.39	>.05	-1.755	1.662
Cough	10.45±3.70	9.23±3.22	>.05	-.883	3.338
Shortness of breath	8.86±4.74	6.67±1.86	>.05	-2.294	6.675
Fatigue	9.57±3.65	9.00±3.61	>.05	-4.164	5.306

*[a]Resolution of all symptoms; *Some parameters are excluded from the analysis due to inadequate data*

There were no significant differences with regard to recovery time for fever, cough, shortness of breath and complete resolution of all symptoms between control and intervention arms either from the date of enrolement or from the onset of illness (Table-3 and Table-4). Therefore, the duration of the illness from onset to recovery was not significantly different among the of COVID-19 cases in two study arms.

Repeat RT-PCR was done in 40 patients on day ten since the first positive RT-PCR. Repeat RT-PCR for SARS-CoV-2 was negative in 37 (92.5%) patients.

Results of repeat RT- PCR were not significantly different between control and intervention arms (Table-5).

Table-5: *Result of repeat RT-PCR on 10th day (n=40)*

Repeat RT-PCR test	Intervention arm n (%)	Control arm n (%)	Sig
Positive	2 (10)	1(5)	p>.05
Negative	18 (90)	19 (95)	
Total	20	20	

Discussion

In this open-label, single-centre, intention-to-treat randomised controlled study involving mild to moderate RT-PCR confirmed COVID-19 patients, a 200 micrograms/kg single dose of ivermectin added to usual care did not provide better clinical outcomes in terms of duration of symptomatic recovery and rate of repeat RT-PCR negativity.

The COVID-19 pandemic has caused a tremendous burden on healthcare facilities around the world, due to its rapid spread with devastating consequences. Currently, no medication is recommended for mild to moderate COVID-19. The development of a whole new molecule takes time, so researchers are also trying to explore the effectiveness of existing drugs against SARS-CoV-2, which have already been shown to be effective in treating similar viruses. Several of these drugs are currently in use without having apparent benefits. Hydroxychloroquine and chloroquine were the most widely used drugs. Initial observational studies showed significant benefit of these drugs against COVID-19 [17,18]. However, later in RCTs, these presumed benefits were negated [19,20]. Ivermectin is also one of these drugs, widely used as a treatment for the early stage of COVID-19. This drug has shown its *in-vitro* activities against SARS-CoV-2 [12]. Initial observational studies have also shown benefits, but no RCTs have been published yet to prove its benefit over usual care in the management of mild to moderate COVID-19 cases.

In this study most of the patients were men; also, in other Bangladeshi studies, men were found more affected than women [7,15,21,22] though internationally, no gender difference was found in COVID-19 [23]. The predominant symptoms found in the study was fever followed by cough were typical of the presentation of COVID-19 [15,24]. There was no significant difference in age, sex, and disease severity at presentation between the cases of control and intervention arms and thus eliminated the selection bias. However, one of the limitation of our study was that we could not perform detail biochemical and hemotological investigations of the study participants. It was due the fact that the study was carried out at a primary health care center at a semi-rural settings. Thus, we were unable to determine the effect of ivermectin (if any) on the biochemical and haematological parameters of the COVID-19 cases. However, the study emphasis was on the clinical outcome following ivermectin treatment.

A recent RCT in Bangladesh, reported ivermectin-doxycycline combination superior to hydroxychloroquine-azithromycin combination therapy in mild to moderate COVID-19 cases [21]. However, the time difference to become symptom-free and the time difference for negative RT-PCR were not statistically significant (consecutively p=0.071 and p= 0.2314). The mean duration of symptomatic recovery was 5.93 days (5 to 10 days) in the ivermectin group and 6.99 days (4 to12 days) in the hydroxychloroquine group. In our study, the mean duration of symptomatic recovery was not different between the control and intervention arms.

Another study compared the viral clearance by ivermectin+doxycycline with hydroxychloroquine plus azithromycin in patients with COVID-19 [15]. In this study, Rahman M et al. compared the benefits of viral clearance between the groups mentioned above and found better viral clearance in the ivermectin group. However, the results of the two groups were assessed at different time frames, making comparisons disputed and was criticised in an editorial comment in the same issue of the journal [25].

The ineffectiveness of ivermectin on the overall COVID-19 outcome is not unexpected. Available pharmacokinetic data from clinically relevant and excessive dose studies suggest that the ivermectin concentration required to inhibit SARS-CoV-2 in humans is unlikely to be attainable in serum and

tissue with known dosing regimens [13]. In a brief review of ivermectin and COVID-19, Chaccour et al. concluded that ivermectin is incorrectly used to treat COVID-19 without scientific evidence of demonstrable efficacy and safety [16].

In conclusion, adding ivermectin to usual care in the management of mild to moderate COVID-19 patients did not show any benefit. However, since the sample size was small, future multicentre studies with a larger sample size could be conducted to confirm the outcome.

Author's contributions

CSP was involved in study planning, patient recruitment and data collection; NC was involved in patient recruitment, data collection, data entry; MIS did patient recruitment, data entry; WMMH did study planning, data analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

Funding

References

1. Zheng J. SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. *Int J Biol Sci*. 2020; **16**(10): 1678-85.

2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta bio-medica: Atenei Parmensis [Internet]. 2020; **91**(1): 157-160.

3. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*. 2020; **19**(3): 149-50.

4. De Clercq E. Potential antivirals and antiviral strategies against SARS coronavirus infections. *Expert Rev Anti Infect Ther*. 2006; **4**(2): 291-302.

5. Disease Control Division. Directorate General of Health Services. Ministry of Health & Family Welfare. Government of the People's Republic of Bangladesh. National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19). Version 7.0. Published, 28 May 2020.

6. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization; 2020.

7. Alom M, Murshed R, Bhiuyan E, Saber S, Alam R, Robin R. A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *J Bangladesh Coll Phys Surg*. 2020; **38**(Supplement Issue): 10-15.

8. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Ann Clin Microbiol Antimicrob*. 2020; **19**(1): 23.

9. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot (Tokyo)*. 2020; **73**(9): 593-602.

10. Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob Chemother*. 2012; **67**(8): 1884-1894.

11. Varghese FS, Kaukinen P, Gläsker S, Bespalov M, Hanski L, Wennerberg K, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Res*. 2016; **126**: 117-124.

12. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020; **178**: 104787.

13. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. *Biotechnol Biotechnol Equip*. 2020; **34**(1): 469-74.

14. Rajter JC, Sherman M, Fatteh N, Vogel F, Sacks J, Rajter J-J. ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19. *medRxiv*. 2020:2020.06.06.20124461.

15. Rahman M, Iqbal S, Islam M, Niaz M, Hussain T, Siddiquee T. Comparison of Viral Clearance

between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients. *J Bangladesh Coll Phys Surg*. 2020; **38**(Supplement Issue): 5-9.

16. Chaccour C, Hammann F, Ramón-García S, Rabinovich NR. Ivermectin and COVID-19: Keeping Rigor in Times of Urgency. *Am J Trop Med Hyg*. 2020; **102**(6): 1156-7.

17. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020; **56**(1): 105949-.

18. Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020; **97**: 396-403.

19. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020; **3**(4): e208857-e.

20. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med*. 2020.

21. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. Research Square; 2020.

22. Bhuyan MA, Al Mahtab M, Ashab E, Haque MJ, Hoque SMM, Faizul Huq A, et al. Treatment of COVID-19 Patients at a Medical College Hospital in Bangladesh. *Euroasian J Hepatogastroenterol*. 2020; **10**(1): 27-30.

23. Spagnolo PA, Manson JE, Joffe H. Sex and Gender Differences in Health: What the COVID-19 Pandemic Can Teach Us. *Ann Intern Med*. 2020.

24. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *J Med Virol*. 2020.

25. Rahim M, Mostafi M. Re-purposive Use of Drugs in COVID-19: A Wake-up Call. *J Bangladesh Coll Phys Surg*. 2020; **38**(Supplement Issue): 3-4.