ORIGINAL ARTICLE

Extraordinary Survival Benefits of Severe and Critical Patients with COVID-19 by Immune Modulators: The Outcome of a Clinical Trial in Bangladesh

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Abstract

Background: Coronavirus disease (COVID)-19 has devasted the healthcare delivery system as well as social establishments of almost all countries of the world. However, vaccines for containing new cases of COVID-19 are yet to be realized. Also, presently available antiviral drugs and other standard of care (SOC) management strategies could not satisfactorily control COVID-19-related mortality, which has crossed the one million mark during the last 9 months. These facts present an emergent need for developing new, novel, and evolving therapeutic strategies for the management of COVID-19.

Aim and objective: This cohort study represents a clinical trial in real-life situations in Bangladesh where two immune modulators were applied in patients with severe and critical COVID-19 patients.

Materials and methods: A total of 199 confirmed patients of COVID-19 were enrolled in this study. All of them had severe and critical COVID-19 and they were hospitalized at the intensive care unit (ICU) of the Combined Military Hospital (CMH), Dhaka, Bangladesh. All patients were positive for SARS-CoV-2 by polymerase chain reaction (PCR) of the nasal swab and they were endowed with severe pneumonia, multiple organ dysfunctions, and coagulopathy. The median percentage of lung involvement was 65%. The mean oxygen saturation was 83%. The patients received two immune modulators (tocilizumab and bevacizumab) in different combinations to retrieve broader insights about the safety and efficacy of immune modulators in COVID-19 management.

Results: Out of the total 199 patients, 122 survived and 77 expired. A single dose of tocilizumab resulted in the survival of 71.5% (73 of 102 COVID-19 patients). On the other hand, a dramatic survival benefit was found in patients receiving bevacizumab (92%).

Conclusion: The study indicates that active treatment should be started as early as possible for COVID-19 patients as moderate COVID-patients may progress to more severe illnesses with grave consequences. The safety of two immune modulators has been recorded in this cohort of severe and critical COVID-19 patients. In order to have a proper use of these immune modulators, there is a need to accomplish controlled, blinded, and large-scale prospective studies with at least two arms.

Keywords: Bangladesh, Bevacizumab, COVID-19, Immune modulators, Severe and critical COVID, Tocilizumab.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan, China, in December 2019, is the causative agent of coronavirus disease 2019 (COVID-19).[1] The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020.[2] As of the end of October 2020, about 44 million confirmed patients of COVID-19 have been detected and more than 1.16 million confirmed COVID-19 patients have died.[3] Globally, about 250,000 to 500,000 new confirmed cases of COVID-19 have been reported daily and the numbers of deaths per day due to COVID-19 have been fluctuating between 4000 and 8000.[4] And, even after embracing several preventive public health approaches (complete and partial lock-down of cities and countries, the closing of several public places including schools and restaurants and the use of protective devices and protective masks), neither the number of new and confirmed COVID-19 cases nor the frequencies of COVID-19-related deaths have been contained. Rather, a new spike in both the incidence of new COVID-19 patients and death due to COVID-19 have been reported since the 1st week of October 2020 (about 10 months after the initial reporting of COVID-19) and it is presumed that this will probably continue until the end of

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February or March 2021. The complex nature of COVID-19 infection does not allow an evidence-based kinetic of COVID-19 as these are dependent on the development of protective vaccine and their nature and quality.

Thus, there remain incredible challenges for scientists, researchers, physicians, policymakers, politicians, and mankind to get rid of the adverse effects of this incredible disease. The prime challenge is to develop a prophylactic vaccine for SARS-CoV-2 and ensure its proper and effective distribution over the whole world as soon as possible so that new infection of COVID-19 can be contained.[5,6] In line with this, extensive works have been accomplished around the world and more than 200 prophylactic vaccines have been developed and about 10 of them have entered phase III clinical trials in different countries of the world.[7] The available data indicate that the world may embrace one or more reasonably safe and moderately effective prophylactic vaccines against COVID-19 within the next 6 months.[8–10] However, localization of SARS-CoV-2 in various tissues may hinder the efficacy of the vaccine, and the half-life of the vaccine may be equally important in this respect. The nature of antibody (protective versus pathogenic) produced by vaccines will also be a critical factor in this regard.

The next challenge for mankind is to develop effective therapeutic approaches for COVID-19 patients as the total deaths have surpassed the one million mark and daily deaths are also on the rise. COVID-19 represents a highly complex pathological entity that involves several organs of the body, although it primarily infects the respiratory tree and lungs. The virus and virus-related pathologies have been traced to several vital organs such as the heart, liver, brain, kidneys, and endothelium.[11,12]

The clinical presentations of COVID-19 patients may be highly versatile and possibly represent the localization of the virus and the downstream events following viral infection. It remains almost completely asymptomatic in considerable numbers of patients, whereas the virus induces severe illnesses like pneumonia and other collateral pathologies in about 5 to 10% of patients. As of today, about 80% of the total 44 million COVID-19 patients have experienced self-limiting recoveries without or with available medications. However, about 2.5% or more than 1.16 million people with COVID-19 have died. As of the end of October 2020, about 10 million COVID-19 patients represent active patients of COVID-19 and about 80,000 COVID-19 patients are in a critical state. Most of the critical patients with COVID-19 are supposed to take downhill courses with grave consequences. Thus, elucidation of treatment or management strategies for COVID-19 patients represents a practical challenge for the scientific community. Unfortunately, neither any antiviral drug capable of containing SARS-CoV-2 has been discovered nor the standard management regimens have been optimized for COVID-19 patients. At present, the fundamentals of COVID-19 management are attributable to the alleviation of symptoms as there is a lack of understanding about evidence-based drugs and management strategies.

Bangladesh, a country of 164 million people, detected its first case of COVID-19 on March 8, 2020, and the first fatality was recorded on March 18, 2020. The numbers of new infections and mortality have shown considerable diversities within these 8 months. Initially, several patients with mild symptoms flooded the hospitals and they were treated with various drugs that have been recommended by the national authority of the country and chosen by the attending physicians. It became clear that patients with mild symptoms of COVID-19 may be managed by various types of treatment and management approaches; however, due to a lack of randomized, controlled, double-blind studies during a pandemic, proper management strategy has remained elusive in Bangladesh.[13–15] Along with the advancement of time, most of the patients with asymptomatic COVID-19 and COVID-19 with mild symptoms have rarely attending hospitals and they are managed at home. COVID-19 patients developing moderate to severe symptoms usually attend hospitals and seek proper management.

If we critically analyze the genesis of therapy and management strategies for COVID-19, a pattern is found that is more or less similar to other countries of the world. As the disease is caused by an RNA virus, SARS-CoV-2, antiviral drugs have been extensively used in COVID-19 patients. This included hydroxychloroquine, ivermectin, favipiravir, and remdesivir, although it is true that none of these drugs represent an evidence-based antiviral drug for SARS-CoV-2 and these drugs have been developed for other viruses. However, special registration was provided by most countries for the usage of these drugs during the COVID-19 pandemic. Based on symptoms, the patients of COVID-19 are also given anticoagulants (clexane or rivaroxaban), a drug for controlling wheezing and shortness of breath (montelukast), antibiotics (meropenem, moxifloxacin, doxycycline, and azithromycin), an immune suppressor (dexamethasone), analgesics, vitamins, and zinc supplements. Some patients have also received convalescent serum and other medications based on their clinical conditions. Oxygen supplementation, ventilation, and management in the intensive care unit (ICU) have also been given to several patients with COVID-19 when required (Table 1). Even with these endeavors, management of severe and critical patients of COVID-19 remains a challenge and the total death has surpassed the one million mark in the world.

Credible evidence has shown that the pathological phenomenon of COVID-19 patients is not entirely dependent on the cytopathic nature of the SARS-CoV-2 virus, implying the limited role of antiviral drugs for the treatment of COVID-19. In fact, a complex interaction among the virus, host immunity, and other unknown factors regulate the nature of pathological lesions of COVID-19 patients.[16–19] Human angiotensin-converting enzyme 2 (ACE2) acts as a receptor for viral spike protein. As 83% of the ACE2-expressing cells in humans are type II pneumonocytes, the virus is mainly localized and replicates in the lung among these particular pneumonocytes. After the entry of the virus (SARS-CoV-2) in humans, there is an inherent duty of the innate immune system to expel and contain the virus. When this can be properly accomplished, the patients may have an asymptomatic course or mild COVID-19. However, the extent and amplitude of innate immunity may be inadequate, impaired, distorted, and nonfunctional in others who develop severe forms of COVID-19. The effect of prolonged localization of virus as well as the outcome of host/virus interactions induce inflammatory cytokines and other mediators to fight the virus and as of today; this seems to be incoherent. As a matter of fact, unregulated production of cytokines induces a state of cytokine storm resulting in pneumonia and related complications of COVID-19.[20]

The scenario receives scientific support by the fact that once the downstream events related to the effects of cytokine storms are initiated in COVID-19 patients, traditional antiviral and symptomatic therapeutic regimens for COVID-19 patients may not be helpful.

Table 1: Kinetics of management strategies of COVID-19 patients

Drug regimens
Antiviral
Hydroxychloroquine
Ivermectin
Favipiravir
Remdesivir
Anticoagulant
Clexane
Rivaroxaban
Controlling wheezing and shortness of breath
Montelukast
Antibiotics
Doxycycline
Azithromycin
Meropenem
Immune suppressor
Dexamethasone
Symptomatic
Therapy of analgesics
Vitamins and zinc supplement
Novel therapy
Convalescent serum
Oxygen supplementation

However, any conclusive claim about noneffectivity or limited effectivity of antiviral drugs for the containment of COVID-19 would remain elusive due to the lack of randomized controlled trials with antiviral and other treatment regimens. In line with this, the importance of timing of commencement of antiviral therapy may have implications, and these studies cannot be formulated without proper animal models of COVID-19.

However, these observations unmasked a new and novel arena of management of severe COVID-19 patients, immune therapy. The immune status of any host is formulated by two mutually antagonistic pathways of immune responses: (1) inflammatory and (2) regulatory. As the cytokine storm is characterized by the abundance of inflammatory immune mediators, there remains an opportunity to control COVID-19 using regulatory immunity and this provides the ethical and theological basis of immune therapy of COVID-19 patients. Till now, the principle of immune therapy for COVID-19 patients has focused on containing some of the inflammatory cytokines that are exacerbated in COVID-19 patients with progressive diseases. This has been accomplished with the postulation that the reduction of proinflammatory cytokines would allow containment of cytokine storm and complications of COVID-19. Interleukin (IL)-6 is a cytokine that is upregulated in COVID-19 patients. This led to initiate several studies to block IL-6 by the administration of IL-6 receptor antagonist, tocilizumab.[18–20] This drug is used in other inflammatory conditions associated with increased IL-6 production such as rheumatoid arthritis and systemic juvenile idiopathic arthritis.[21–25]

Another immune modulator that may be used is bevacizumab. It is a human monoclonal antibody that works by attaching to a growth factor called vascular endothelial growth factor A (VEGF-A). By blocking the activity of this growth factor, the drug is able to inhibit the process of angiogenesis (formation of new blood vessels) and this may have a regulatory role in host immunity. This may endow bevacizumab with a role for containment of pulmonary complications of COVID-19 patients.[26]

It is an open question regarding the timing as well as nature of using immune modulators in COVID-19 patients: (1) should the treatment be started with immune modulators and in mild or moderate patients with COVID for blocking progression to a severe and critical state of COVID-19 or (2) should the immune modulators be used in patients with severe and critical patients of COVID-19 as the final resort.

The study presented here has assessed the implication of immune modulators in the intensive care unit (ICU) of the Combined Military Hospital (CMH), Dhaka, Bangladesh, when the patients were diagnosed to have severe or critical COVID-19 at the intensive care unit (ICU) of CMH.

Materials and Methods

Patients and Methods

Flow Chart of Patient's Entry

The study has been conducted at the Combined Military Hospital (CMH), Dhaka, Bangladesh. The Combined Military Hospital is a highly disciplined hospital and usually attributed for treatment of patients of military personnel; however, the general public also gets treatment there. A highly specific group of patients with COVID-19 have been treated by immune therapy in this observational study at CMH, Dhaka.

As per the general flowchart of management of COVID-19, patients with presumptive symptoms of COVID-19 either attend the outpatient department of CMH or contact responsible physicians by telephone (telemedicine approach during COVID-19 outbreak at Bangladesh). Based on the nature of their complaints and symptoms, they were prescribed an antiviral (ivermectin), an antibiotic (doxycycline), and symptomatic drugs such as paracetamol for control of fever with a supplement of vitamins and zinc. They were recommended to stay home and contact with hospital as and when required.

When the above-mentioned therapy could not alleviate their illness, the patients attend the hospitals and are advised to continue treatment at home or they are admitted to the general ward of the hospital, as per the observation of the attending physicians. The management strategies of the COVID-19 patients at the hospital differ considerably from patient to patient and these depend mostly on the evolving pathogenesis of COVID-19. Table 1 provides a synopsis of management style, but patients improved and were discharged earlier with minimum drugs, whereas others get almost all recorded therapeutic approaches.

This management strategy is not a uniform one for all patients. Some patients may receive initial one or two medications, whereas others get all sorts of treatment.

When COVID-19 patients pass through downhill courses and need high flow of oxygen, nasal cannula, noninvasive ventilation, mechanical ventilators, inotropic drugs, and infusion pumps are transferred to the intensive care unit (ICU) of CMH.

Study Population for Immune Therapy at ICU of CMH, Dhaka, Bangladesh

All patients enrolled in this study were admitted to the ICU units of CMH and all were diagnosed as patients with severe to critical COVID-19. Although they received most of the drugs shown in Table 1, their conditions were not improving and the attending physicians were considering accomplishing something new and novel. The patients were explained the pros and cons of immune therapy. Informed consent was also taken from the patients and/or their nearest kin. Also, the relevant authority of CMH approved the study. The clinical profiles of the patients enrolled for immune therapy are cited in Table 2.

A total of 199 patients participated in this study to have immune therapy. Out of the total of 199 patients, they exhibited four major comorbidities. Most patients (*N* = 155, 78%) had hypertension. Diabetes mellites, asthma, and chronic kidney disease were detected in 19, 2, and 7 patients, respectively. As all patients were in ICU of CMH, the presenting symptoms included pneumonia, multiple organ failure, and coagulopathy in these patients (Table 2). The extent of pneumonia and percentage of lung involvement varied from 58 to 78% at the time of preanalysis for immune therapy. It is to be mentioned that the extent of pneumonia in most patients receiving immune therapy was severe even though the patients received all sorts of management strategies while they were in the ward and ICU of CMH. In short, the patients receiving immunotherapy did not improve after receiving all sorts of management options at the ICU of CMH.

Trial Procedure

The patients were properly assessed about vital signs and physical examination was done at ICU as and when necessary, especially before the start of immune therapy. Also, all new symptoms and aggravation of preexisting symptoms were monitored. Peripheral blood was taken from each patient to check complete blood picture, levels of hemoglobulin, creatinine, bilirubin, and alanine aminotransferase (ALT) to develop insights about the condition of vital organs. X-ray of the chest revealed the conditions of the lung. The levels of oxygen saturation were monitored regularly and oxygen was given as and when necessary. Some important parameters of laboratory assessments have been shown in Table 3.

The regime of Immune Therapy for Critical Patients of COVID-19 at ICU of CMH

The study was planned to assess the implication of two immune modulators in 199 patients admitted at ICU of CMH. These immune modulators were tocilizumab and bevacizumab. These drugs were used either as an independent therapeutic approach or in combination, as shown in Table 4.

Table 2: Clinical profiles of the patients of COVID-19 receiving immune therapy

Variables	*Total (n = 199)*	*Discharged (n = 122)*	*Expired (n = 77)*	*Difference (95% CI)*	*p-value*
Characteristics of patients					
Age, median (IQR) (years)	64.0 (53.0–70.0)	60.0 (50.0–67.0)	58.0 (52.0–62.0)	6.4 (3.25–9.62)	<0.001
Age group					
18–50 – no. (%)	40 (20)	31 (25)	9 (21)		<0.05
51–70 –no. (%)	117 (59)	69 (57)	48 (74)		0.417
≥71 – no. (%)	42 (21)	22 (18)	20 (26)		0.180
Female – no. (%)	41 (21)	25 (20)	16 (21)		0.960
Male – no. (%)	158 (79)	97 (80)	61 (79)		0.960
Preexisting conditions					
Hypertension – no. (%)	155 (78)	98 (80)	57 (74)		0.298
Diabetes mellitus – no. (%)	19 (10)	13 (11)	6 (8)		0.502
Asthma – no. (%)	2 (1)	–	2 (3)		
Chronic kidney disease – no. (%)	7 (4)	4 (3)	3 (4)		0.818
Presenting symptoms					
Pneumonia – no. (%)	199 (100)	122 (100)	77 (100)		1.000
Multiple organ dysfunction syndrome – no. (%)	199 (100)	122 (100)	77 (100)		1.000
Coagulopathy – no. (%)	199 (100)	122 (110)	77 (100)		1.000
Percentage of lung involvement analyzed by HRCT, median (IQR)	65 (58–76)	58 (52–64)	74 (64–78)	11.1 (8.0–14.1)	<0.001
> 50% – no. (%)	121 (61)	65 (53)	56 (73)		
Oxygen saturation, median (IQR)	83 (82–86)	84 (82–88)	83 (81–84)	2.3 (1.4–3.1)	<0.001

The values of presenting symptoms just before the commencement of immune therapy have been cited; CI, confidence interval; IQR, interquartile range

Evaluation

The prognosis of patients was evaluated on the basis of two ultimate outcomes: survival and death.

Statistical Analysis

The data have been shown as mean and standard deviation or median and range. For statistical analysis, a paired t-test was used for normally distributed data. When the distribution was skewed, the Wilcoxon signed-rank test was used. A p-value of less than 0.05 was regarded as statistically significant.

Result

The clinical trial provided here have assessed the utility of immune therapy in severe/critical patients with COVID-19 patients with a terminal phase of clinical staging. All patients in this cohort were treated at the ICU of CMH after they experienced management at the general ward of CMH. The patients were given five regimens of immune modulators. The final evaluation was done on the basis of the survival of the patients and turning them in to the general ward from ICU versus the death of the patients.

As shown in Table 2, the median age of the patient was 64 years with a range of 21–85 years. Forty percent of patients were below the age of 50 years and the remaining patients were more than 50 years of age, indicating mostly patients with higher age groups enrolled in this study. Out of the 199 patients, 158 were male, and the remaining 41 were female. As mentioned, all patients had severe levels of COVID-19 with pneumonia, multiple organ failure, and coagulopathy. Hypertension was the most common comorbidity with some patients with diabetes mellitus and chronic kidney failure.

Out of the total of 199 COVID-19 patients receiving different regimens of immune therapy, 122 survived and shifted to the general ward, whereas 77 died. Patients with hypertension had poor survival. The levels of lymphocytes were significantly higher in patients those expired compared to those who survived. The levels of lactate dehydrogenase and C-reactive protein were not significantly different between survived and dead patients.

In order to critically analyze the role of different regimens of immune therapeutic agents, survival and death were checked in each group (Table 3). Seventy-two percent of patients receiving a single dose of tocilizumab survived, whereas survival reduced to 21% when two doses of tocilizumab were given. Only 3 patients received 3 doses of tocilizumab and 2 of them survived. Inspiring survival was noted in critical COVID-19 patients receiving only bevacizumab (92%). However, when a single dose of tocilizumab and bevacizumab were combinedly given to 21 patients, the survival was recorded in 14 patients (66%) (Table 4).

We analyzed the duration of ICU staying of the severe and critical COVID-19 patients receiving immune modulators. Patients receiving a single dose of bevacizumab had the least hospital staying, whereas ICU staying was maximum for the patients receiving 3 doses of tocilizumab (Table 5).

Discussion

COVID-19 has emerged as an incredible pandemic, causing hundreds of thousands of new SARS-CoV-2 infections and several thousands of deaths each day. The infection with this new type of coronavirus started in late December 2019 and neither the incidence of SARS-CoV-2 infection nor COVID-19-related deaths have shown any convincing signs of containment over the last

Table 3: Laboratory data of the patients prior to starting of immune therapy

Variables	*Total (n = 199)*	*Discharged (n = 122)*	*Expired (n = 77)*	*Difference (95% CI)*	*p-value*
Baseline hemato-biochemical profiles [#]					
Percentage of neutrophils, median (IQR)	87 (82–90)	87 (82–90)	85 (80–90)	3.06 (0.10–6.6.01)	<0.05
Percentage of lymphocytes, median (IQR)	9 (6–13)	9 (6–12)	10 (6–16)	3.11 (0.46–5.76)	<0.05
D-dimer (µg/mL), median (IQR)	0.72 (0.48–0.95)	0.74 (0.48–1.08)	0.68 (0.49–0.84)	0.23 (0.03–0.43)	<0.05
Lactate dehydrogenase (U/L), median (IQR)	986 (786–1352)	980 (831–1224)	986 (768–1568)	50.26 (–69.8 to 170.3)	0.409
C-reactive protein (mg/L), median (IQR)	12.0 (6.0–12.0)	12.0 (12.0–12.0)	12.0 (6.0–24.0)	0.94 (–0.81 to 2.69)	0.297

The values are shown based on available data; [#]neutrophil normal range 40 to 70% of WBC; lymphocyte normal range 20 to 40% of WBC; D-dimer normal value ≤ 0.05 µg/mL; lactate dehydrogenase normal range 135 to 480 U/L; C-reactive protein normal value ≤ 10.0 mg/L; CI, confidence interval; IQR, interquartile range

Table 4: Treatment approaches of patients with COVID-19

Variables	*Total (n = 199)*	*Discharged (n = 122)*	*Expired (n = 77)*	*p-value*
Treatments approaches				
Tocilizumab single dose – no. (%)	102	73 (72)	29 (28)	<0.01
Tocilizumab double doses – no. (%)	48	10 (21)	38 (79)	<0.001
Tocilizumab triple doses – no. (%)	3	2 (66)	1 (33)	0.849
Bevacizumab – no. (%)	25	23 (92)	2 (8)	<0.001
Tocilizumab plus Bevacizumab – no. (%)	21	14 (66)	7 (34)	0.596

Table 5: Clinical outcomes of COVID-19 patients treated with immunosuppressive drugs

Variables	*Total (n = 199)*	*Discharged (n = 122)*	*Expired (n = 77)*	*Tocilizumab single doses (n = 102)*	*Tocilizumab double doses (n = 48)*	*Tocilizumab triple doses (n = 3)*	*Bevacizumab alone (n = 25)*	*Tocilizumab plus Bevacizumab (n = 21)*
Duration of ICU stay, mean ± SD – day	6.54 ± 5.49	5.71 ± 4.93	7.89 ± 6.08	6.10 ± 5.54	7.93 ± 5.89	7.00 ± 5.57	4.57 ± 3.60	7.43 ± 5.40
Discharged – no. (%)	122 (61)	–	–	73 (72)	10 (21)	2 (67)	23 (92)	14 (67)
Expired – no. (%)	77 (39)	–	–	29 (28)	38 (79)	1 (33)	2 (8)	7 (33)

10 months. Rather, it seems that the peak is yet to emerge and some countries or regions have already entered into devastating sequences of COVID-19.

When patients with COVID-19 follow progressive downhill courses, most of these severe and critical patients of COVID-19 are admitted to the ICU, if available. At the same time, aggressive management strategies including the usage of antiviral drugs, antibiotics, steroids, anticoagulants, and oxygen supplementation are given to these patients. This is the most unpleasant period for the attending physicians with such a HANDS UP, EYE CLOSED reality.

Here, we have shown that there may remain comparatively new, novel, and evidence-based therapeutic approaches for the management of these serious and intractable COVID-19 patients. In this study, a total of 199 patients with severe and critical forms of COVID-19 were enrolled at the ICU of CMH, Dhaka, Bangladesh. The patients mostly received treatment in the general ward before being referred to ICU. All patients had pneumonia and the median percentage of lung involvement was 65%. More than two-thirds of the patients had comorbidities like hypertension. Features of multiple organ dysfunction and coagulopathy were evident in all patients.

As shown in Table 3, the patients received different regimens of immune modulators as the last resort of evolving therapy. Immune therapy of these critical patients with COVID exhibited a survival benefit in 122 patients (61.3%). After subjective and biochemical improvement of these patients, the survived patients were transferred to the general ward and ultimately, they were discharged. Seventy-seven COVID-19 patients in this cohort expired and a comparison was made to find out the factors associated with fatal outcome. Age of the patients, the percentage of lung involvement, and levels of oxygen saturation prior to the start of immune therapy emerged as significant factors related to prognosis (survival vs death) (Table 2).

We are not the first to claim the usage of immune therapy for COVID-19 patients. However, there are some notable points of this study: (1) this study enrolled quite considerable numbers of severe and critical patients of COVID-19 (N-199), (2) different regimens of immune therapies were tested in COVID-19 patients to get some insights into the most appropriate design, (3) combination of two immune modulators were used, and (4) this is possibly one of the pioneering studies on immune therapy in COVID-19 patients from developing countries.

Tocilizumab has been used by others in different types of COVID-19 patients and our data are mostly supportive of their outcome. On the other hand, usage of bevacizumab in COVID patients has not been reported in peer-reviewed journals. However, this drug has been recommended for COVID-19 patients in non-peered publications and general communications.

One of the notable findings of our trial indicates that a single dose of bevacizumab exhibited 92% survival benefit. However, the numbers of enrolled patients were only 25 and we are not providing any conclusive comment about the magical survival benefit of this drug.

Now, the critical query is about the role and position of immune therapeutic agents for the management of COVID-19. If the immune therapy is capable of handling so many severe and critical patients of COVID-19, then why there is a need to use other therapeutic regimens, especially antiviral drugs.

As in other countries of the world, the traditional antiviral drugs could not stand the test of time in Bangladesh as well as in other countries of the world. Initially, hydroxychloroquine emerged as a therapeutic choice for COVID-19; however, adverse effects and low efficacy in severe COVID-19 patients did not allow its wide usage.[13,14] Also, this drug was used in mostly mild patients of COVID-19. Ivermectin has been reported as an agent inducing negativity of SARS-CoV-2 in a short time. In fact, we reported the excellent antiviral potential of ivermectin in mild and moderate patients of COVID-19 in Bangladesh.[15] However, almost all patients in this cohort received ivermectin at some point in their disease, and intake of ivermectin did not block progression to critical forms of COVID-19. We are not sure if these patients had SARS-Cov-2 negative due to the use of ivermectin. Also, the timing of ivermectin usage could not be properly confirmed as most patients with COVID-19 in Bangladesh usually use this drug. The timing of intake of ivermectin or other antiviral drugs may be one limiting factor and if the pathological processes of SARS-CoV-2 progress to the lower part of the lung, it seems that antiviral drugs may have minimal impact on these patients. What needs to be exposed if the usage of antiviral drugs is related to the downhill prognosis of any of these patients. A meta-analysis of two groups was carried out: one receiving standard care plus favipiravir and the other receiving standard care plus other regimen indicating no specific treatment benefit of favipiravir.[27] Another meta-analysis with 76 articles using remdesivir revealed that further randomized controlled trials with larger sample sizes are required to identify the best candidate components that should comprise combined treatments for COVID-19.[28]

Thus, complete eradication of SARS-CoV-2 by available antiviral drugs has not been achieved, and supportive therapy with antiviral drugs has shown some promise in some, but in all patients with COVID-19. Regarding dexamethasone, several studies have documented favorable outcome of this drug in hospitalized patients. However, a meta-analysis by Juul et al.[29] has concluded that the certainty of the evidence was low to very low, so more trials are needed.

In this pretext, the study presented here is endowed with a direction provider for new and novel therapy with innovative approaches. What would happen if we start or initiate treatment of moderate to severe patients of COVID-19 by immune modulators

with the support of antibiotics, dexamethasone, and other supportive management strategies without antiviral drugs. Also, there might be logical evidence of proper action of immune modulators in presence of antiviral medications.

This is a single-arm study and randomization of this type of study during a pandemic and with critical patients of COVID-19 is not a realistic option at this moment. Thus, a direct comparison of our therapeutic approach with other treatment approaches is not possible and viable. When there is a pandemic and patients with COVID-19 present with pneumonia and related complications, all sorts of drugs are used. However, this study has clearly shown that usage of immune modulators was related to considerable survival benefit. The outcome has initiated several alternative therapeutic approaches for COVID-19. As of today, it seems that too many drugs have been used for the management of COVID-19. If further well-designed studies provide a similar outcome of immune modulators, it might be possible to provide a realistic and evidence-based treatment option for COVID-19. This is an important issue as COVID-19 would not behave like other pandemics with a finite duration. Rather, evidence suggests that COVID-19 may remain for years or even for decades. Thus, well-planned, well-designed, and evidence-based therapeutic strategies should be formulated by conducting future studies.

Conclusion

In conclusion, the role of aberrant immunity has been found in patients with COVID-19 and this seems to be critical for the development of cytokine storm and other complications. The present study unmasks a situation for using new and novel immune modulators for the management of COVID-19 patients, however, more studies and trials with new and novel immune modulators will be required to optimize the treatment regimen. The overall trials with immune modulators should be randomized, double-blinded, and placebo-controlled in a well-planned sample size. Although this may not be possible just now among pandemics, this is an urgent challenge regarding COVID-19 management. In addition, if the limitations of presently available antiviral drugs for treating COVID-19 become clear in controlled trials, complete new therapeutic recommendations may surface for the management of COVID-19. However, all these are dependent on the nature of the clinical trials and retrieved outcomes.

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