

Clinical Manifestations of Hospitalized COVID-19 Patients in Bangladesh: A 14-day Observational Study

Modhusudon Shaha^{1,6}, Md A Islam², Faizul Huq³, Bithi Roy⁴, Md A Kabir⁵, Md Salimullah⁶, Mamun Al Mahtab⁷, Sheikh MF Akbar⁸

ABSTRACT

Objectives: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is currently a significant public health concern and causing a pandemic in the world. Despite immense attention to the coronavirus disease 2019 (COVID-19), very little attention has been given to the kinetics of disease progression in infected patients. Therefore, in this study, we present a 14-day clinical observation of hospital-admitted COVID-19 patients.

Methods: After recording the demography of 42 COVID-19 patients on day 1, we observed the clinical progression for 14 days by investigating the hematological and biochemical responses of patients' blood and serum, respectively.

Results: Approximately, 62% of the hospital-admitted COVID-19 patients presented cough, followed by fever (~52%). The top comorbidities of these patients were hypertension (30%) and diabetes mellitus (19%). The average blood hemoglobin (Hb) level was slightly low among the patients in the early days of infection and went up to the normal level on the later days. A substantial increase in the level of ALT or SGPT [up to 106 IU/L; standard error of the mean (SEM): 12.64] and AST or SGOT (up to 64.35 IU/L; SEM: 5.013) in COVID-19 patients was observed, which may suggest that infection with coronavirus is associated with the functionality of other organs of COVID-19 patients.

Conclusion: This 14-day observational study may help clinicians to decide the choice of treatment for COVID-19 patients.

Keywords: Blood hemoglobin, Clinical manifestations, Comorbidity, COVID-19, Liver functionality, Pneumonia.

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INTRODUCTION

Coronaviruses have been causing significant disease outbreaks globally over the past two decades. In 2002, severe acute respiratory syndrome (SARS) emerged in East Asia,¹ and later on, the Middle east respiratory system (MERS) was associated with an outbreak in the Middle East in 2012.² Recently, a novel coronavirus, Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged in late 2019 in China and posed a threat to global health, causing coronavirus disease 2019 (COVID-19).³ This virus is currently causing a pandemic in the world. The novel SARS-CoV-2 was first reported in Wuhan, China, on December 12, 2019.⁴ Globally, health workers are currently making tremendous attempts to control the ongoing disease outbreaks caused by this virus.

Newly emerged SARS-CoV-2 poses a threat to the current public health worldwide. The source of infection of this third coronavirus outbreak in humans is not identified yet. After appearing in Wuhan, this virus has spread rapidly throughout the country and, eventually, to other countries. Due to the rapidly spreading nature of this virus on a global scale and the severity of the ongoing outbreak, the World Health Organization announced a Public Health Emergency of International Concern on January 31, 2020.⁵ Later on March 11, 2020, they declared the situation a pandemic. At the latest, new variants of this virus have emerged in some countries, including Bangladesh.⁶⁻¹¹ After developing an infection in the host, the virus exploits the immune system of the respective host in a very rapid time and poses threats to the hosts' life. However, the clinical manifestations of how the infection progresses to the severe disease and/or subsequently recovers are yet to be understood. Here, in this study, we present the kinetics of clinical manifestations of the hospital-admitted COVID-19 patients for 14 days and patients' comorbidity with the COVID-19 disease.

¹Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

²Directorate General of Medical Services, Bangladesh Army Medical Corps, Dhaka, Bangladesh

³Department of Medicine, Combined Military Hospital, Dhaka, Bangladesh

⁴Department of Agronomy, Bangladesh Agricultural University, Mymensingh, Bangladesh.

⁵Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

⁶National Institute of Biotechnology, Dhaka, Bangladesh

⁷Department of Hepatology, Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka, Bangladesh

⁸Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan

Address reprint requests to: Mamun-Al-Mahtab, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka, Bangladesh, e-mail: shwapnil@agni.com

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MATERIALS AND METHODS

Selection of Patients and Sample Collection

The study was conducted between April and May 2020 at Combined Military Hospital, Dhaka, Bangladesh. Forty-two patients were

included in this study who tested COVID-19 positive and were admitted to the hospital. The mean age of these patients was 40.02 years, with SEM of 1.911. Of these patients, female (mean age: 32.13; SEM: 5.313) and male (mean age: 41.88; SEM: 1.91) patients were approximately 19% and 81%, respectively. The demographic of these patients was collected on the day of hospital admission. The enrolled patients were in observation for 14 days (unless otherwise stated), and their blood samples were collected each day at the same time during the course of observation. For hematological analyses, blood samples of the COVID-19 patients were collected in tubes containing anticoagulant ethylenediaminetetraacetic acid. For performing serum biochemistry, blood samples were collected without anticoagulant and were centrifuged at 500 g for 10 minutes to separate serum (Eppendorf 5702, Hamburg, Germany). The separated serum was then stored at -20°C until use. This study was approved by the Institutional Ethics Committee (approval number: FGH/2020/01).

Hematological and Biochemical Analyses

A complete blood count using the COVID-19 patients' blood samples was performed using the commercial kit (Promega Corporation, Fitchburg, Wisconsin, USA) using ADVIA 2120 Hematology System (Siemens Diagnostics, Erlangen, Germany) according to the manufacturer's instructions. Blood oxygen was measured using a pulse oximeter (Thermo Fisher Scientific, Waltham, Massachusetts, USA) as per the protocol given by the supplier.

Biochemical analyses of serum components, such as albumin, bilirubin, creatinine, chloride, sodium, and potassium, were performed using standard routine techniques. Serum AST and ALT levels were determined by the standard colorimetric method of Reitman and Frankel. Enzyme activities were determined at 37°C . Serum biochemistry was performed using a standard autoanalyzer (ABX Diagnostics, Tokyo, Japan).

Other Relevant Observations and Statistical Analysis

Body temperature, respiratory rate, blood pressure, and heart rate of the COVID-19 patients were measured as routine procedures in

the laboratory. Chest X-ray reports were kindly provided by the imaging unit of the hospital on day 1. Glasgow Coma Scale (GCS) score was determined as per the standard protocol.¹² All statistical analysis was performed using GraphPad Prism v9.

RESULTS

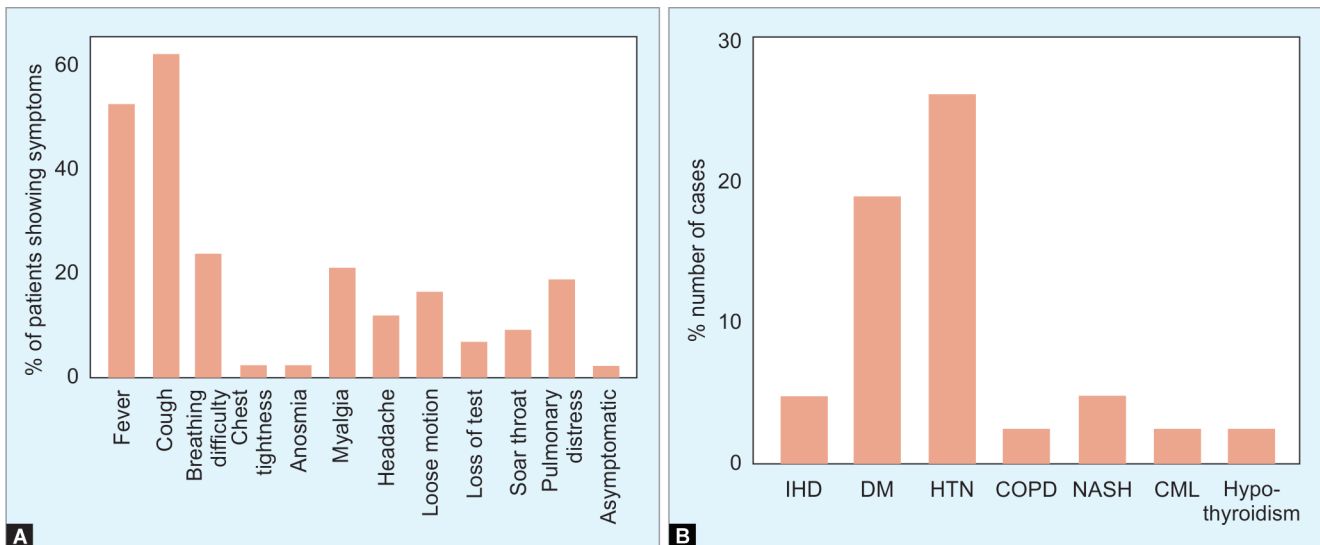
Differential Clinical Symptoms and Comorbidities were Presented by the COVID-19 Patients

Of the 42 hospital-admitted COVID-19 patients, approximately 62% were affected by cough, followed by fever (~52%), breathing difficulty (~24%), myalgia (~22%), loose motion (~17%), and others (Fig. 1A). Of these patients, approximately 19% got pneumonia, and only about 2% were asymptomatic. These results indicate that in addition to fever and cough, COVID-19-infected patients presented a wide range of other clinical symptoms.

Chronic conditions were reported as common comorbidities among the COVID-19 patients. Data revealed that nearly 30% of the included patients were affected with hypertension. Diabetes mellitus was the second comorbid condition, as reported by 19%. Ischemic heart disease (5%), nonalcoholic steatohepatitis (6%), and hypothyroidism (<5%) were the other common comorbid conditions among the patients (Fig. 1B). At that time of COVID-19 pandemic, the patients were treated with Favipiravir plus standard of care (SoC) (~19%), Hydroxychloroquine plus azithromycin plus SoC (~38.1%), and Hydroxychloroquine plus doxycycline plus SoC (54.8%). Approximately, 14.3% of the patients were given a combination of Favipiravir and hydroxychloroquine plus doxycycline plus SoC therapy at that time. Only 1 (2.4%) patient needed oxygen during the course of observation.

Increased Respiratory Rate of COVID-19 Patients

As the COVID-19 patients present a wide range of clinical symptoms and comorbidities related to both respiratory and heart organs, we determined the respiratory rate as well as the heart rate of these patients from day 1 to day 14. We observed a higher mean respiratory rate (25.07 breaths/minute; SEM: 0.6652; normal range,



Figs. 1A and b: Clinical symptoms (A) and comorbidity (B) presented by the hospital-admitted COVID-19 patients. The bar chart was prepared using GraphPad Prism v9 software package. Data are presented as the percentage (%) of the total included patients. IHD, ischemic heart disease; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; NASH, nonalcoholic steatohepatitis; CML, chronic myelogenous leukemia

12 to 16 breaths/minute) among the COVID-19 patients on day 1. The respiratory rate of these patients fluctuated slightly during the course of observation but remained higher than the normal range, as shown in Figure 2. However, the heart rate of these patients was in the normal range during the course of observation.

We also measured the body temperature of the COVID-19 patients in the course of observation. Analysis of data revealed that the mean body temperature of the patients gradually decreased from the hospital's day 1 (99.42°F; SEM: 0.3614) to the day 11 (96.71°F; SEM: 0.3555). There was an increase on day 12 (97.43°F; SEM: 0.321). The mean temperature was recorded on day 14 as 96.69°F (SEM: 0.4606) (data not shown).

Irregular Level of Blood Components in COVID-19 Patients

After observing a differential level of respiratory rate and body temperature of the COVID-19 patients in different days of hospital stay, we hypothesized that the level of blood components would vary in patients in the course of the disease. Therefore, we considered four observation periods (days 1, 3, 7, and 14) for each patient in this course of COVID-19 infection. We collected blood samples from these patients on respective days and measured the level of blood hemoglobin (Hb), red blood cell (RBC), white blood cell (WBC), platelet, neutrophil, and blood oxygen (SpO₂).

On day 1, we observed a downregulated Hb level (approximately 11.5 gm/dL; SEM: 0.4008) among the female COVID-19 patients, where the normal range of Hb level is 12.1 to 15.1 gm/dL. The Hb level among them was then found to be gradually increased to the normal level by day 3 with a slight decrease to approximately 12.1 (SEM: 0.621) on day 7. In regard to the male COVID-19 patients, the Hb level goes down to approximately 13.6 gm/dL (SEM: 0.3602) from 14.0 gm/dL on day 7 and then went up to the normal level (13.8–17.2 gm/dL) again on day 14 (Figs 3A and B). This result suggests that blood Hb level is slightly downregulated among male and female COVID-19 patients in the early days of disease progression.

We observed an increased level of RBC from day 1 to day 7 in both male (normal range is $4.5\text{--}5.9 \times 10^{12}/\text{L}$) and female (normal range is $4.1\text{--}5.1 \times 10^{12}/\text{L}$) COVID-19 patients compared to the normal

range as shown in Figure 3C and D. However, after 7 days of disease symptoms, RBC level went down to the normal range.

Infection with coronavirus may not alter the level of SpO₂, neutrophil, blood platelet, and WBC. However, the level of blood platelet and WBC was observed gradually upregulated within the normal range from day 3 to day 14 (data not shown).

Level of Serum Components in COVID-19 Patients

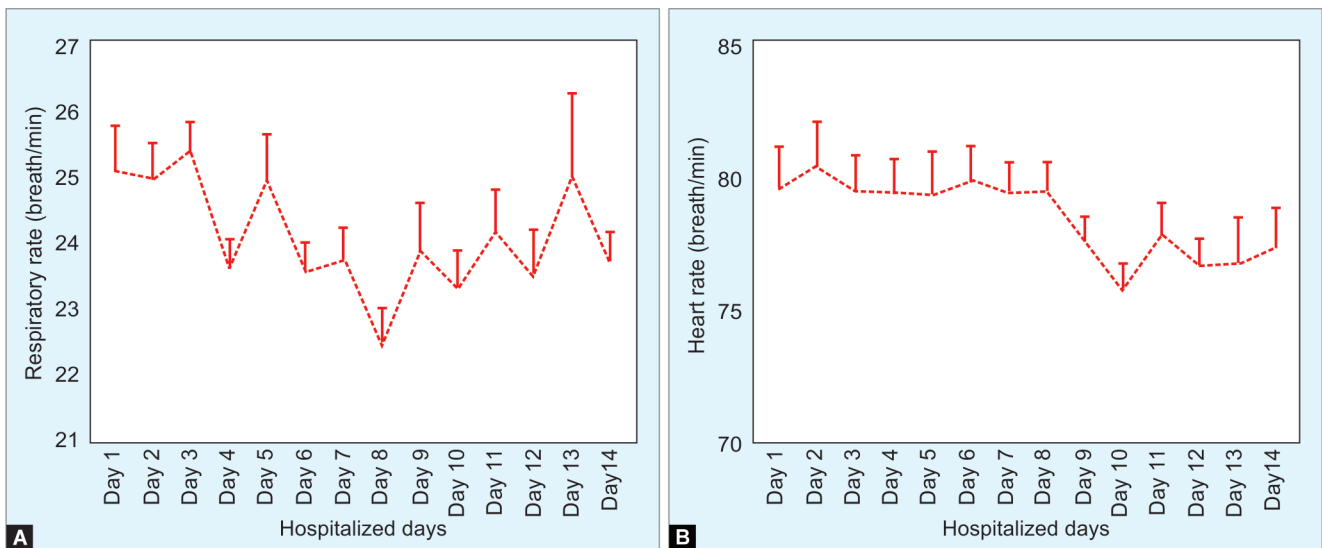
As the level of some of the blood components was differentially influenced by COVID-19, we tried to analyze the effect of this disease on the level of serum components in the hospital-admitted patients during the course of the disease. Therefore, we measured the level of serum albumin, bilirubin, creatinine, sodium, potassium, and chloride from the prepared serum samples of the COVID-19 patients.

We observed the average serum chloride level is downregulated to approximately 95 mEq/L (SEM: 0.7997) below the normal range (96–106 mEq/L) on day 14. However, infection with coronavirus does not significantly affect the level of serum albumin, bilirubin, creatinine, sodium, and potassium Figure 4.

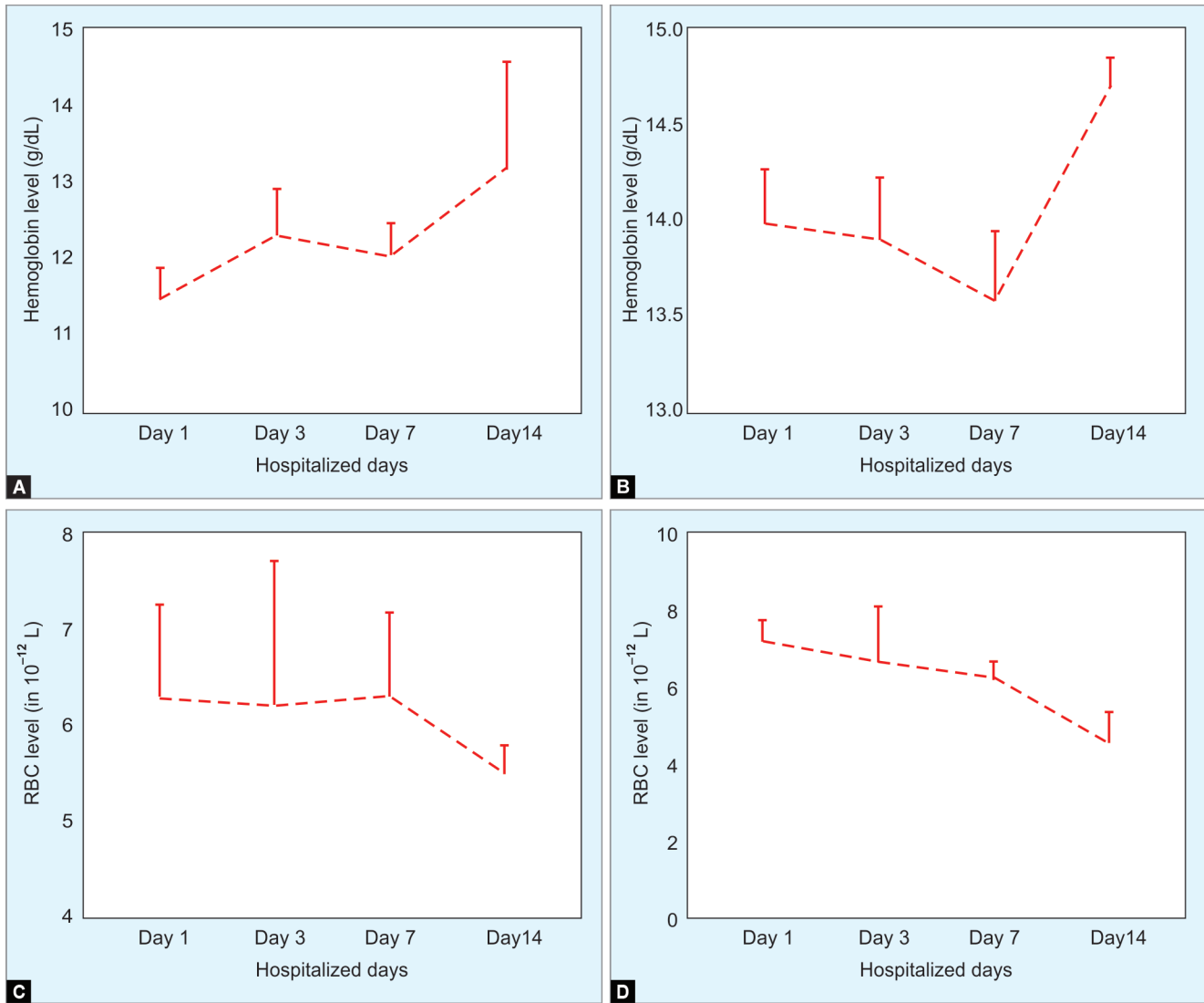
High and Sustained Serum ALT Level in COVID-19 Patients

After observing the effect of COVID-19 on blood and serum components of the coronavirus-infected patients, we hypothesized that COVID-19 influences the functionality of other organs of COVID-19 patients. Therefore, we analyzed the level of ALT or SGPT, AST or SGOT, and GCS scores in these patients during the course of the disease. ALT or SGPT is an enzyme, which is synthesized mainly by the liver, whereas the AST or SGOT is synthesized by multiple organs, including the liver, heart, etc.

Importantly, we observed a substantial increase in the level of ALT or SGPT (approximately 70 IU/L; SEM: 13.56; normal range is 7–56 IU/L) in COVID-19 patients on day 7, and it was increased further to approximately 106 IU/L (SEM: 12.64) on day 14. Likewise, we observed a significant increase in the level of AST or SGOT in COVID-19 patients even from day 1 (approximately 64.35 IU/L; SEM: 5.013; normal range is 5–40 IU/L). The level of AST or SGOT remained high in the duration of our 14-day observations



Figs. 2A and B: A 14-day observation of respiratory rate (A) and heart rate (B) of the COVID-19 patients. The graph was prepared using GraphPad Prism v9 software package. The represented data denote mean ± SEM



Figs. 3A to D: Determination of the level of blood Hb and RBCs in COVID-19 patients. Hb level was analyzed in both female (A) and male (B) patients. RBC level was also analyzed in both female (C) and male (D) patients. The graph was prepared using GraphPad Prism v9 software package. The represented data denote mean \pm SEM

and fluctuated, as shown in Figure 5. These results indicate that infection with coronavirus may affect the functionality of other organs of COVID-19 patients. Regarding the GCS score, only one patient was observed to present a score of 11 on day 4, and that patient sadly died on that day.

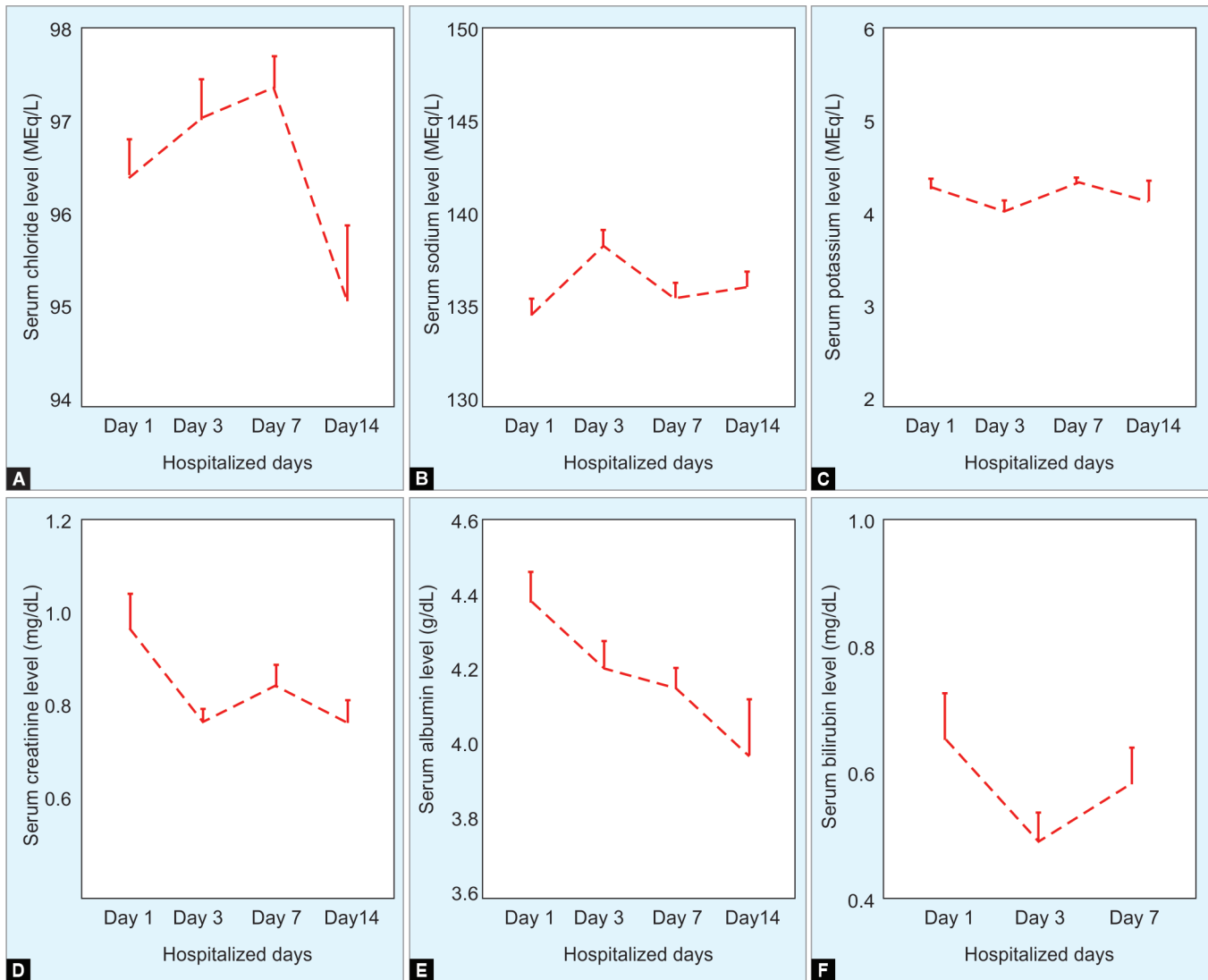
DISCUSSION

The severity of COVID-19 exceeds other respiratory viral infections regarding infectiousness as well as global mortality. Although there has been a tremendous increase in COVID-19 research since the commencement of the pandemic, some major research gaps still need to be addressed to better understand the nature of infection and the subsequent diseases contributed by coronavirus. One of the critical research gaps seems to be the observation of the infected patients' daily clinical manifestations. Therefore, in this study, we analyzed the clinical progression of the COVID-19 disease through

regular observation of biological parameters among the hospital-admitted COVID-19 patients over 14 days.

On day 1, approximately 19% of the patients developed pneumonia. Also, the overall respiratory rate of the patients was higher than the normal range on day 1, which is consistent with other studies with COVID-19 patients.¹³ The increase in respiratory rate was observed heightened during the course of disease till day 14. Though the patients were not tested for chest X-ray in the subsequent days, the gradual increase in the respiratory rates may suggest that the disease was still influencing the patient's lung over time.

Our findings noted hypertension and diabetes were the most common comorbid conditions among the cases admitted to hospitals in Bangladesh and elsewhere.¹⁴⁻¹⁶ This finding reaffirmed observations reported in previous studies. One study with a sample of 100 admitted cases in Dhaka Medical College Hospital, the largest teaching hospital in Bangladesh, reported the prevalence



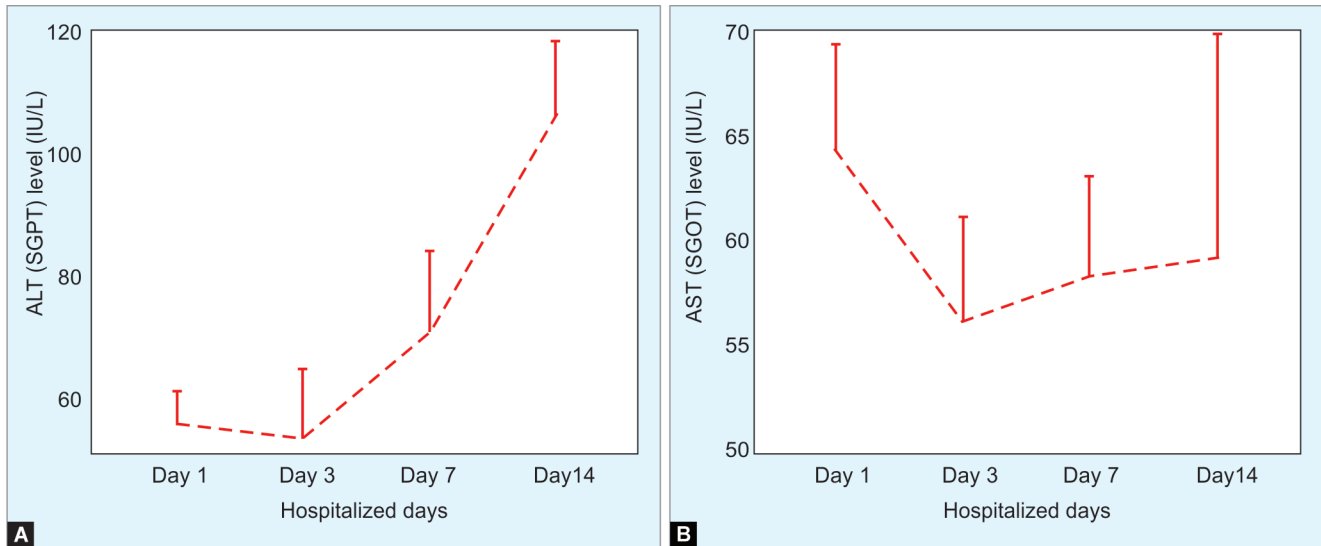
Figs. 4A to F: A 14-day observation of the level of serum components chloride (A), sodium (B), potassium (C), creatinine (D), albumin (E), and bilirubin (F) synthesized in COVID-19 patients. The graph was prepared using GraphPad Prism v9 software package. The represented data denote mean \pm SEM

of hypertension (21%), diabetes mellitus (16%), and ischemic heart disease (8%) among the admitted cases.¹⁶ However, a single-center retrospective study with a sample of 157 hospitalized patients reported diabetes mellitus (24.8%) as the highest comorbid condition followed by hypertension (23.2%). This study's inclusion criteria might be explained by the relatively higher prevalence of diabetes mellitus, as this study included patients with at least one comorbid condition.¹⁴ Another study with a nearly similar sample size ($n = 33$) reported diabetes mellitus (15%) and hypertension (27%) with the hospitalized patients.¹⁷ Studies conducted in similar settings reported hypertension and diabetes as the commonly comorbid conditions among the hospitalized patients; for example, a nationwide analysis in China¹⁸ reported hypertension (19.9%) and diabetes (8.2%). In addition to the single study, systematic reviews^{19,20} and meta-analysis reported hypertension and diabetes as the common comorbid conditions among people infected with the virus.

The COVID-19 patients were observed to have a reduced Hb level than the normal range on day 1, which is aligned with a study

conducted with COVID-19 intensive care unit patients.²¹ This is a unique feature of coronavirus infection, which may indicate that the virus is acquiring the iron from the patient's body for their survival and replication, though more research is needed to confirm this. Hb is essential to transfer oxygen from the lung to the tissues through the blood. Interestingly, though there is a lower Hb level in the patients' blood, the level of oxygen was not altered enough.

COVID-19 was observed to influence the functionality of other body organs. Serum ALT or SGPT level of the patients was found enormously heightened after 7 days of disease progression than the normal range and sustained upregulated till day 14. Serum ALT is a potential marker of liver functionality.²² The normal range of this enzyme is 7 to 56 units/L of serum. On day 14 of our observation, we found that the level of ALT went significantly up by more than twice (108 units/L) than the normal range. Likewise, the level of AST was observed strongly high (approximately 64 units/L) on day 1 among the COVID-19 patients than its normal range 5 to 40 units/L and remained heightened during the course of observation. A high



Figs. 5: Analysis of the ALT (A) and AST (B) levels in the serum of COVID-19 patients. The graph was prepared using GraphPad Prism v9 software package. The represented data denote mean ± SEM

level of ALT and AST indicates the abnormality of liver function in the patients’ bodies, and it provokes a risk of liver damage.²² Heightened AST level further denotes a risk of heart failure. Therefore, these results suggest that infection with coronavirus poses threat to not only the respiratory tract organ but also to the liver as well as the heart.

In this study, we found one patient who sadly died of COVID-19 on day 4 after hospital admission. That patient was a male patient of 56 years old who had the comorbidity of hypertension and presented symptoms of fever and breathing difficulties from day 1 of hospital admission. The respiratory rate was consistently high (average of 42.4 breaths/minute) and slightly low blood pressure (110/70 on day 3 and 80/50 on day 4). The GCS rate was regular (GCS 15) in the first 2 days of observation. However, on days 3 and 4, the GCS rate went much lower to 12 and 11, respectively. Notably, the patient had already developed pneumonia on day 1 of hospital admission.

CONCLUSION

This study presents a novel 14-day clinical observation of COVID-19 patients and is significant for three main reasons. Firstly, we present the potential comorbidities and wide ranges of symptoms shown by the COVID-19 patients. Secondly, the COVID-19 patients were essentially in our observation for approximately 14 days, and the clinical manifestations during the observations were analyzed. Thirdly and most importantly, the association of COVID-19 with subsequent liver and heart functionalities was identified by assessing the level of ALT and AST. We believe that the data of this study will help clinicians to decide the appropriate management of COVID-19 patients and take necessary actions to prevent the failure of other organs of the affected patients.

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