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Original Article

C-Reactive Protein, Ferritin and D-dimer as Predictors of Covid-19 Severity

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Abstract

***Background**: Coronavirus Disease 2019 (COVID 19) is a novel infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It emerged in Wuhan and has quickly spread across the world. In Bangladesh, the mortality rate in critically ill patients with COVID-19 is high. This study compares biochemical parameters between mild/moderate and severe patients, helping to identify severe or critical patients early. **Objective**: To identify severe or critical covid-19 patients early by analysis of biochemical parameters. **Materials and Methods**: This cross-sectional study was done in Intensive Care Unit (ICU) of Enam Medical College Hospital from April 2021 to August 2021. Total 60 Covid positive patients were enrolled. Among them 30 were severe (ICU) patients and 30 were mild/moderate (non–ICU) patients. **Results**: A comparison of the hematological parameters between the mild/moderate and severe groups showed significant differences in lymphocyte, neutrophil, ferritin, D-dimer and C-reactive protein (CRP) levels. **Conclusion**: The findings suggest that ferritin, D-dimer and CRP levels can be used to detect the severity of COVID-19 patients.*

***Key words**: COVID-19; Ferritin; D-dimer; C-reactive protein*

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Introduction

A novel coronavirus, designated as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China in December 2019.[1] SARS-CoV-2 is highly infectious and asymptomatic patients may also become the source of infection. World Health Organization (WHO) announced that the disease caused by SARS-CoV-2 was Corona Virus Disease 2019 (COVID–19) on 11 February 2020. A lot of severe or critical patients had been admitted into the intensive care unit (ICU). As the number of COVID-19 patients is dramatically increasing worldwide and treatment in ICU has become a major challenge, early recognition of severe forms of COVID-19 is absolutely essential for timely

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recovery of patients.[2] Although most patients with COVID-19 were mild in the early days, some patients progressed rapidly to metabolic acidosis, septic shock, ARDS (acute respiratory distress syndrome) or death. Early identification of risk factors for critical patients could facilitate appropriate supportive care and thus reduce the mortality.[3] A study of the first 138 laboratory-confirmed cases with COVID-19 showed the changes of neutrophil count, lymphocyte counts, and D–dimer levels.[4] Increased inflammation-related indicators were found in patients with COVID–19, including erythrocyte sedimentation rate (ESR), interleukin-6 and C–reactive protein (CRP).[5] Vargas–Vargas et al[6] says that ferritin is a key mediator of immune dysregulation and hyperferritinemia may contribute to cytokine storm. They suggested patients with elevated serum ferritin level will experience severe complication from COVID-19.[6] However, little is known about the relationship between disease severity and clinical and biochemical features in patients with COVID-19.

Bangladesh, a lower-middle-income country and one of the world's most densely populated areas, is struggling to combat the spread of the disease. With almost every country adopting aggressive non–therapeutic measures to control the spread of nCoV-2, Bangladesh in Southeastern Asia has followed the same trend; however, there is an ongoing debate as to whether measures have been adopted adequately and implemented efficiently. The country confirmed the first COVID-19 case in its territory on 7 March 2020, though many experts speculated that nCoV–2 may have entered the country earlier than that but had not been detected due to inadequate monitoring.[7] With regard to the clinical outcomes of COVID-19 and its association with various pathophysiological factors, no comprehensive study has been conducted in Bangladesh. Some of the studies did not include a large sample size.[8-10]

We aimed to perform a comprehensive evaluation of characteristics of patients with COVID-19 admitted to Enam Medical College Hospital, Savar. This study analyzed biochemical parameters between mild/moderate and severe patients, which may help to identify critical cases and perform appropriate clinical intervention early.

Materials and Methods

In this cross-sectional study, 60 patients were included and divided into mild/moderate and severe groups.

Study procedure

This is a cross-sectional study and all consecutive patients with confirmed COVID-19 who were admitted in Enam Medical College Hospital, Savar, Dhaka from April to August 2021 were enrolled.

The clinical classification are as follows: i) mild, minor symptoms and imaging shows no pneumonia. ii) moderate, with fever, respiratory tract symptoms and imaging shows pneumonia. iii) severe, meet any of the following−a) respiratory distress, respiratory rate ≥ 30 beats/min; b) in resting state, mean oxygen staturation ≤ 93%; c) arterial blood oxygen partial pressure/oxygen concentration ≤300 mm Hg; d) pulmonary imaging showed that the lesion progressed more than 50% within 24−48 hours. iv) critical, one of the following conditions−a) respiratory failure occurs and requires mechanical ventilation; b) shock; c) ICU admission is required for combined organ failure[1].

In this study, patients with mild or moderate symptoms were classified as mild/moderate group, and patients with severe or critical symptoms were as severe/critical group.

Upper respiratory throat swab samples of all suspected infectious patients were taken at admission and then shipped to designated authoritative laboratories to detect the SARS-CoV-2. Bacterial and fungal detections of sputum or respiratory secretions and other laboratory tests were completed in the biochemistry laboratory in Enam Medical College & Hospital, Savar. C-reactive protein (CRP) and ferritin were detected by immunoturbidimetry method. D-dimer was measured by Enzyme Linked Immunosorbent Assay. Patients with positive polymerase chain reaction (PCR) test result of SARS-CoV-2 were included in the study. Patients aged below 18 years, patients with history

of liver malignancy, liver failure, cirrhosis, hepatitis, receiving medical treatment leading to impairment of liver functions, pregnant women, individuals with cancer were excluded.[11] Deceased patients and those who were not interested in participating or did not give consent were also excluded.

Categorical variables were given as frequency rates and percentages; continuous variables were defined using mean values. The independent sample t test was used for the continuous variables and the chi-square test for categorical variables. Statistical analyses were performed using PSPP. A 2-tailed $p<0.05$ was considered as statistically significant.

Results

The study population included 60 patients with confirmed COVID-19. The mean age of mild/moderate group is 52.57 years and severe group is 59.75 years. Among patients, diabetes (14 in mild, 27 in severe), hypertension (15 in mild, 25 in severe) and cardiovascular disease (11 in mild, 20 in severe) were the most common coexisting conditions (Table I).

Table II shows the comparison of biomarkers between mild/moderate and severe COVID-19 patients. There were significant differences in lymphocytes, neutrophils, D-dimer, ferritin and CRP levels between two groups.

Discussion

We reported here 60 patients with laboratory-confirmed COVID-19. The clinical presentations were very similar to SARS-CoV. Coronaviruses, a large family of single-stranded RNA viruses, can infect a wide varieties of animals, including humans, causing respiratory, enteric, hepatic and neurological diseases.[12]

Human Covid is one of the main pathogens of respiratory infections.[5] Most patients have mild symptoms and a good prognosis. So far, a few patients with SARS-CoV-2 have developed severe pneumonia, pulmonary edema, ARDS or multiple organ failure and died. Patients with severe illness developed ARDS and requied ICU admission.[13] Lymphopenia and elevated serum levels of CRP were the most common initial laboratory findings. Clinical severity of disease varied from mild to severe.[14]

This study reported the results of blood biochemistry, coagulation function and infection-related biomarkers of the adult patients with COVID-19. We found that lymphocyte and neutrophil counts were significantly different between mild/moderate and severe group, which is similar with the findings of Huang et al[13], who have also found low lymphocyte count in most patients. But Gao et al[15] found no significant difference

Table I: Baseline characteristics of study subjects (n=60)

Variables	Mild/Moderate	Severe (ICU)	p values
Age (years)	52.57	59.75	0.092
Diabetes	14	27	0.073
Hypertension	15	25	0.063
Cardiovascular disease	11	20	0.042

Data are expressed in mean ± SD. p values < 0.05 were statistically significant.

Table II: Biomarkers in mild/moderate and severe COVID-19 patients (n=60)

Markers	Mild/Moderate	Severe (ICU)	p values
Lymphocytes ($\times 10^9$/L)	22.41	10.83	0.001
Neutrophils ($\times 10^9$/L)	65.94	84.44	0.000
D-dimer (µg/L)	50.21	1124.27	0.012
Ferritin	10.6	1159.31	0.027
CRP (mg/L)	10.14	134.74	0.000

Data are expressed in mean ± SD. p values < 0.05 were statistically significant.

in cell counts (WBC, lymphocyte, neutrophil) between two groups.

We found that ferritin, D-dimer and CRP levels significantly increased in severe group. Similarly Herold et al[16] found maximal CRP level before intubation and showed strongest association with the need for mechanical ventilation. They found increased CRP levels (>32.5 mg/L at presentation and rising maximal value >97 mg/L) in the evaluation of 40 patients.[16] Wang et al[4] found a difference in laboratory findings between patients admitted into ICU (414 mg/L) and those not admitted into the ICU (166 mg/L), including higher levels of D-dimer. The results showed that patients with severe conditions would have abnormal coagulation. Coagulation activation could have been related to the sustained inflammatory response. Infection-related biomarkers appeared to differ between the two groups.

Paliogianis et al[17] found by their review of 13 studies that the serum D-dimer concentrations in patients with severe forms of the disease were significantly higher than those in patients with milder forms. Velavan & Meyer[2] found elevated serum ferritin levels due to secondary hemophagocytic lymphohistiocytosis and cytokine storm syndrome have been reported in severe COVID-19 patients. They also showed that CRP levels are increased in COVID-19 patients and it has been shown that survivors had median 40 mg/L while non-survivors had median values of 125 mg/L, indicating a strong correlation with desease severity and prognosis. In that study, non-survivors have shown significantly higher levels of plasma D-dimers compared to survivors.

In conclusion, the findings suggest that ferritin, D-dimer and CRP levels can be used to estimate the severity of COVID-19. If necessary, the levels should be measured as they can help diagnose the severity of adult COVID-19.

This study has several limitations. Firstly, the sample size was relatively small, which may have some impact on the results. Secondly, due to the large-scale outbreak of the epidemic restricting the flow of people, data on healthy patients are lacking as blank controls.

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