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Original article

Evaluation of Serum Interleukin-6 Level Among Hospital Admitted COVID-19 Patients and Correlation with Their Disease Severity in a Tertiary Care Hospital

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Abstract

Background:The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the cause of Coronavirus Disease 2019 (COVID-19). Excessive and heightened release of pro-inflammatory cytokines (IL-6) is observed in COVID-19 patients, which can lead to several severe symptoms. Elevated levels of interleukin-6 in patients with COVID-19 indicate cytokine storm and are thought to be a significant factor in identifying the most severe forms of the illness. ***Objectives:*** The study is aimed to assess IL-6 levels among hospital-admitted COVID-19 patients and evaluate their relationship with disease severity. ***Materials and Methods:*** A total of 136 Rapid antigen test positive or RT-PCR positive COVID-19 patients from the Department of Medicine of Sylhet MAG Osmani Medical College and Shahid Shamsuddin Ahmed Hospital, Sylhet from January 2021 to December 2021 were enrolled in this study by convenient sampling technique. With all aseptic precautions 4ml of venous blood was collected from ante-cubital vein and the serum was separated by centrifuge process at 4000 rpm for 10 minutes and stored in the laboratory at -20ºC. Serum IL-6 level was assayed by solid-phase chemiluminescent immunoassay, according to the manufacturer's instructions. (ADVIA Centaur CP IL-6 immunoassay system, SIEMENS, Berlin, Germany, Lot no: 145032). ***Result:*** In this study among 136 patients, 66 (48.5%) were aged between 51-70 years and the mean age was 49.59 ± 18.03 years. There were 65 (47.8%) male and 71 (52.2%) female patients. Out of 136 patients, 76 (55.9%) were moderate cases, 43 (31.6%) were severe cases and 17 (12.5%) were critical cases. The mean age of moderate cases was 44.36 ± 18.53 years, severe cases were 52.36 ±14.34 years and critical cases were 64.65 ± 13.90 years. Interleukin-6 level was 6.06 ± 3.69 pg/mL in moderate cases, 44.71 ± 4.49 pg/mL in severe cases and 242.97± 21.48 pg/mL in critical cases and it was higher in critical cases than severe and moderate cases. ***Conclusion:*** This study showed that IL-6 level is significantly associated with the severity of illness. So, it can serve as an effective marker for the severity of the disease and can help physicians to correctly allocate the hospital-admitted COVID-19 patients at an early stage and to identify critically ill COVID-19 patients.

Keywords: Serum interleukin-6 level, Moderate, severe and critical COVID-19 patients.

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Introduction:

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the cause of the worldwide health disaster known as the Corona Virus Disease of 2019 (COVID-19). The coronavirus, which is a member of the Coronoviridae family, was initially discovered and named in the 1960s. This virus is zoonotic, meaning it may infect both people and animals. The virus is encased and has a helical nucleocapsid.It has a non-segmented, single-stranded RNA genome. The spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein (E) are the four normal viral structural proteins.[1- 4]

The novel coronavirus (SARS-CoV-2) first emerged on December 31, 2019 in Wuhan, China. On January 30, 2020, the World Health Organization classified the COVID-19 outbreak as a worldwide public health emergency; the pandemic was announced on March 11, 2020. On March 8, 2020, the first case of patients suffering from COVID-19 disease caused by the SARS-CoV-2 virus was confirmed in Bangladesh. As of January 2022, there were 364,191,494 confirmed cases of COVID-19; including 5,631,457 deaths were reported to WHO. Among them, Bangladesh has confirmed a total of 1,798,833 cases and 28,394 deaths.[5]
Coronavirus initially undergoes viral replication in the respiratory tract and then spreads to other organs and tissues. Then it enters the pulmonary alveolar epithelial cells through angiotensin-converting enzyme receptor 2 (ACER-2). The main mechanism for inflammation and organ damage is cytokine storm, especially in pulmonary vascular endothelial cells with increased inflammatory cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and interferon- γ (IFN-γ). Exaggerated and excessive synthesized cytokines like IL-6, and IL-10 can lead to cytokine storm which is associated with the disease severity of COVID-19 patients.[6-10]

The clinical manifestations of COVID-19 are wide-ranging, from asymptomatic, mild, moderate to severe viral pneumonia such as acute respiratory distress syndrome (ARDS).COVID-19 patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia (SpO2≥ 90% on room air) are categorized as moderate case,adults with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: severe respiratory distress, respiratory rate> 30 breaths/min or SpO2< 90% on room air categorized as severe case (Severe Pneumonia) and severe COVID-19 case with any of the following criteria: respiratory failure and requiring mechanical ventilation, sepsis, septic shock, ARDS, any organ failure that requires ICU care categorized asCritical cases (Cases requiring ICU care).[11] But some COVID-19 patients experience respiratory deterioration over a short period during their clinical course. Thus, it is essential to identify patients who are likely to develop severe conditions as early as possible.[12,13] Several blood markers could predict respiratory failure in COVID-19 patients. Some inflammatory cytokines could distinguish disease severity in COVID-19. In some patients, the general condition dramatically worsens within a couple of days with severe respiratory failure. Therefore, it is of high priority to identify reliable blood markers that could predict respiratory illness in the short term in clinical settings. In COVID-19 patients with cytokine release syndrome (CRS), interleukin-6 (IL-6), IL-10, and interferon (IFN)-γ are consistently elevated. In COVID-19 patients IL-6 contributes to many of the symptoms, such as the production of acute phase reactants by hepatocytes, activation of the extrinsic coagulation pathway, and production of vascular endothelial growth factor (VEGF), leading to endothelial inflammation. IL-6 plays a pivotal role in the pathophysiology of lung damage in COVID-19 patients.High levels of serum IL-6 have been observed in many patients with cytokine storm in severe COVID-19. COVID-19 patients with comorbidities with high IL-6 levels at admission are at increased risk of developing a severe form of the disease, requiring mechanical ventilation and ICU and progressing to respiratory distress syndrome and multiorgan failure.[14-18] In a meta-analysis including nine studies reported that mean IL-6 levels were more than three times higher in patients with complicated COVID-19 compared with mild or moderate diseases. The concentration of IL-6> 24pg/ml at initial assessment predicted the development of hypoxemia requiring hospitalization.[19] So, by this study we can evaluate serum IL-6 levels among hospital-admitted COVID-19 patients and can make an association of IL-6 with the severity of the diseases in hospital-admitted COVID-19 patients and can help in further management of patients.

Materials and Methods

From January to December 2021, the Department of Microbiology and Virology at Sylhet MAG Osmani Medical College and Shahid Shamsuddin Ahmed Hospital, Sylhet, collaborated with the Department of Medicine to undertake this cross-sectional observational study. After obtaining ethical clearance, a total of 136 Rapid antigen test-positive or RT-PCR-positive COVID-19 patients were enrolled in this study by convenient sampling technique. With all aseptic precautions 4ml of venous blood was collected from ante-cubital vein and the serum was separated by centrifuge process at 4000 rpm for 10 minutes and stored in the laboratory at -20ºC. Serum IL-6 level was assayed by solid-phase chemiluminescent immunoassay, according to the manufacturer's instructions. (ADVIA Centaur CP IL-6 immunoassay system, SIEMENS, Berlin, Germany, Lot no:145032). Data were recorded in a pre-designed structured data collection form. One-way ANOVA and unpaired t-test were applied to analyze the data by using SPSS version 26.

According to National Guidelines on Clinical Management of COVID-19, 9th edition:

Moderate case: Adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia (SpO2≥ 90% on room air).

Severe case (Severe Pneumonia): Adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: severe respiratory distress, respiratory rate> 30 breaths/min or SpO2< 90% on room air.

Critical cases (Cases requiring ICU care): Severe COVID-19 case meeting any of the following criteria: respiratory failure and requiring mechanical ventilation, Sepsis, Septic shock, ARDS or any organ failure that requires ICU care.

Results

The patients in this study were between the ages of 18 and 90. The patient's average age was 49.59 (SD± 18.03) years.

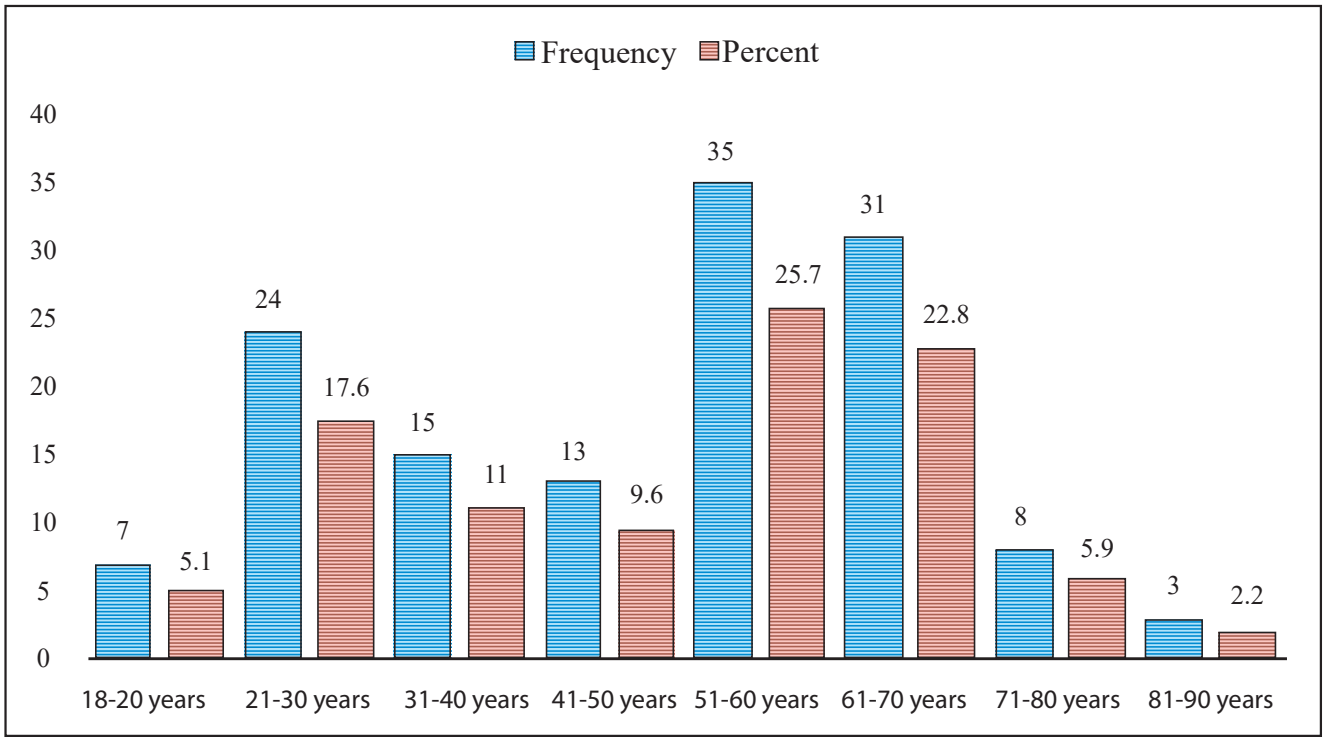

Figure 1: Distribution of the patients according to age group (n=136)

Figure 1: Shows out of 136 patients, the majority 35(25.7%) were aged between 51-60 years followed by 31 (22.8%) were in the age group of 61-70years.

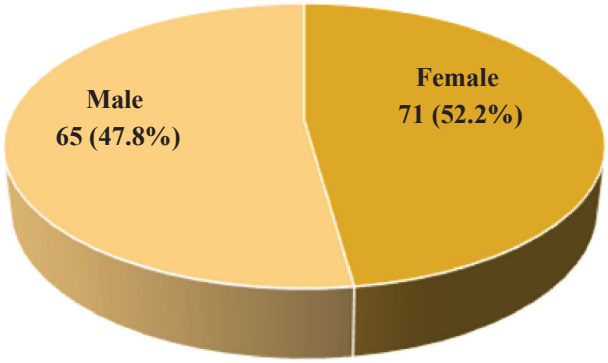

Figure 2: Distribution of the patients according to gender (n=136)

Figure 2: Shows out of 136 COVID-19 patients, male patients were 65 (47.8%) and female patients were 71 (52.2%).

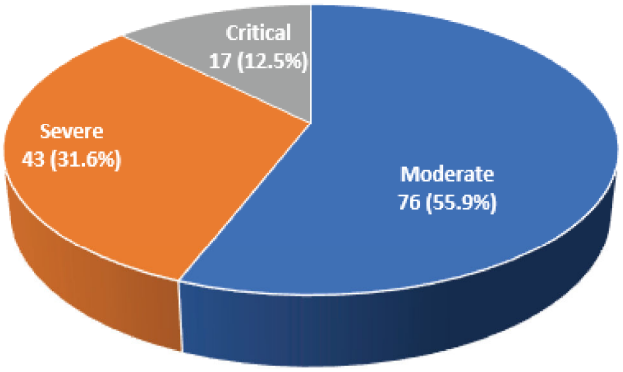

Figure 3: Distribution of the COVID-19 patients according to disease severity

Figure 3: Shows out of 136 patients, moderate cases were 76 (55.9%), severe cases were 43 (31.6%) and critical cases were 17 (12.5%).

Table 1: Distribution of age of the COVID-19 patients according to disease severity

Age(year)	Severity			*p -value
	Moderate	Severe	Critical	
Mean	44.36	52.36	64.65	p<0.001
± SD	± 18.53	±14.34	± 13.90	

*One-way ANOVA was applied to analyze the data

Table 1: Shows the mean age of moderate cases was 44.36 ± 18.53 years, severe cases was 52.36 ±14.34 years and critical cases were 64.65 ± 13.90 years and the difference in the age of the patients of the different groups was statistically significant (F=11.360; p<0.001).

Table 2: Distribution of COVID-19 patients according to co-morbidity

Co -morbidity	**Frequency**	**Percentage**
Hypertension	20	14.7
Diabetes mellitus	15	11.0
Bronchial asthma	5	3.7
Chronic kidney disease	4	2.9

Table 2: Out of 136 participants, 14.7% were hypertensive, 11.0% were diabetic, 3.7% were asthmatic and 2.9% with chronic kidney disease.

Table 3: Comparison of IL-6 levels among moderate, severe and critical COVID-19 patients:

Interleukin-6 level (pg/mL)	Severity			*p -value
	Moderate(76)	Severe(43)	Critical(17)	
Mean	6.06	44.71	242.97	p<0.001
± SD	± 3.69	±4.49	± 21.48	

*One-way ANOVA was applied to analyze the data

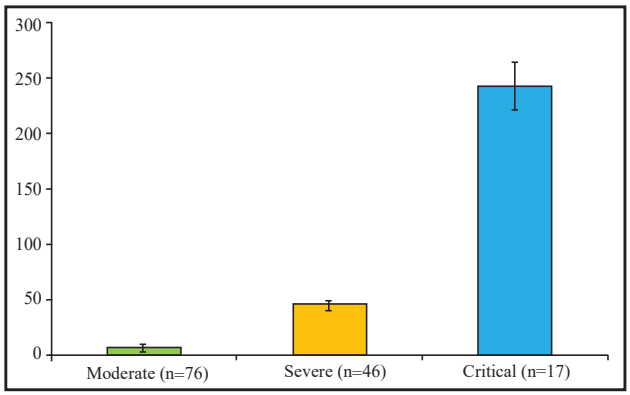

Figure 4: Comparison of interleukin-6 level among severity of COVID-19 patients

Table 3 and Figure 4: Show IL-6 levels were 6.06 (SD± 3.69) pg/mL, 44.71 (SD± 4.49) pg/mL, and 242.97(SD± 21.48) pg/mL in moderate, severe and critical cases of COVID 19 patients respectively. IL-6 level significantly differed among the severity of cases (F=318.641; p<0.001) and the difference was statistically significant.

Discussion:

The present study was undertaken for the assessment of IL-6 levels of moderate, severe and critical COVID-19 patients. In this study the age of the patients ranged from 18 years to 90 years and the mean age was 49.59± 18.03 (SD) years. In Cruz et al. mean age was 45.24±13.97 (SD) years and in Vultaggio et al.[20] The mean age was 63±15 (SD) years. The majority 66(48.5%) of the patients were aged between 51-70 years.

There were 65 (47.8%) male and 71 (52.2%) female cases with a ratio of male and female 1:1.1 in this study. Gender distribution was reported by Liu et al. in China, where 46.98% were male and 53.02% female and in Cruz et al. where male patients were 52%, and female patients were 48%.The gender ratio of the study subjects was almost the same. Men and women had the same prevalence of COVID-19 in Jiang et al.

In the present study out of 136 patients, 76 (55.9%) were moderate cases, 43 (31.6%) were severe cases and 17 (12.5%) were critical cases of COVID-19. (Patient's categorization: moderate, severe, and critical case according to national guideline 9th edition: pages 1 & 2). The case distribution was reported by Azmy et al., 2021 in New Haven, USA where the moderate case was 48%, the severe case was 30% and the critical case was 22%.

In this study the mean age of moderate cases was 44.36 ± 18.53 years, severe cases were 52.36 ±14.34 years and critical cases was 64.65 ± 13.90 years. A similar observation was recorded in China where the mean age of moderate cases was 45.29± 13.08 years, severe cases was 60.41 ± 9.80 years and critical cases was 65.88 ± 13.61 years. So, the mean age of patients was higher in critical cases, than in severe and moderate cases.

In this study out of 136 patients, 20 (14.7%) patients had hypertension, 15 (11.0%) patients had diabetes mellitus, 5 (3.7%) patients had bronchial asthma and 4 (2.9%) patients had chronic kidney disease. A total of 32.3% of patients had at least one comorbidity. A study conducted in China by Liu et al., 2019 also showed a total of 36.23% of COVID-19 patients had at least one comorbidity.

In the present study interleukin-6 level was 6.06 ± 3.69 pg/mL in moderate cases, 44.71 ± 4.49 pg/mL in severe cases and 242.97± 21.48 pg/mL in critical cases of COVID-19 patients respectively. The mean value of IL-6 was higher in critical cases than in severe and moderate cases. A study by Vultaggio[21] in China showed the mean interleukin-6 level was 15.7 ± 15.60 pg/mL in moderate cases and 53.63± 63.8 pg/mL in severe and critical cases, 27 ± 40.9 pg/mL in all cases of COVID 19 patients respectively. Another study in New Haven, USA showed interleukin-6 level was 19.5 pg/mL in moderate cases and 21.20 pg/mL in severe cases of COVID-19 patients respectively. IL-6 value in critically ill COVID-19 patients admitted to the ICU was 336 pg/mL in Gorham, California. So, IL-6 level was significantly higher in critical cases compared to moderate and severe cases.

Conclusion:

COVID-19 was caused by a new strain of beta coronavirus, SARS-CoV-2. Worldwide it is emerging as a huge threat to human health and the mortality rate is higher among severe and critical cases. Cytokine storm causes systemic inflammation, ARDS and multi-organ dysfunction in COVID-19 patients. The current study indicates that high IL-6 levels suggest a cytokine storm which may play a major role in the pathophysiology of this disease and are considered as a relevant parameter in predicting most severe cases of disease. In this study, IL-6 level was significantly higher in critical cases compared to moderate and severe cases who needed more intensive care and treatment due to severe lung damage. IL-6 levels significantly differed among the moderate, severe and critical COVID-19 patients. Therefore, IL-6 could be a potential marker for disease monitoring in hospital-admitted COVID-19 patients. Anti-cytokine therapies that target IL-6 may be useful in treating inflammatory cytokine storms as the illness worsens. Gaining further insight into the role of IL-6 in the pathophysiology of COVID-19, particularly in severe instances, might potentially improve disease management.

Limitations of the study

1. This study did not examine correlations or associations with other inflammatory markers.

2. To eliminate this uncertainty, IL-6 and its upstream and downstream characteristics should be recorded in greater detail.

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