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Study of Serum Interleukin-6 in COVID-19 Patients in Tertiary Care Hospital, Jharkhand

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Abstract
Aims: This study was aimed to measure and evaluate the serum interleukin-6 level in diagnosed cases of COVID-19 Patients.
Study design: An observational study.
Place and Duration of Study: Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, between 28th March 2021 and 27th April 2021.
Methodology: We included 110 patients (68 men, 42 women; age range 18-99 years) with documented COVID-19 were reviewed. The subjects were divided into two groups: severe and non-severe COVID-19. The details were recorded on a pre-structured performa. Between groups, differences were tested using the t test and Mann-Whitney's U-test. The receiver operating characteristic curve was plotted for C-reactive protein with severity. A binary logistic regression was used to identify variables independently associated with severity. The data was analyzed using Statistical Package for the Social Sciences (SPSS).
Results: Out of 110 patients, 72 patients were included in the non-severe group and 38 patients in the sever group. Patients with increased serum interleukin levels were significantly higher ($p<0.05$) in severe cases [mean 44±70ng/ml] than in non-severe patients[mean10 ±21ng/ml]. Binary logistic regression showed ferritin to be an independent predictor of all-cause mortality supplemented with an AUC of 0.78 on ROC analysis.
Conclusions*: Serum interleukin-6 levels are an indicator of disease severity and prognosis of disease. Those patients who have higher serum interleukin-6 level have poor prognosis so CRP level must be monitored during the course of disease.*
Keywords: *[covid-19, serum interleukin level, severe, prognosis]*

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I. Introduction

The novel coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the World Health Organization (WHO), was first observed in Wuhan, China, in December 2019 [1]. By March 30, 2021, 127,349,248 confirmed cases of COVID-19, including 2,787,593 deaths, were reported to the World Health Organization (WHO) [2]. Even though the rapidly evolving clinical course and presentation continue to amaze the medical fraternity, cases infected with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), often present with severe pneumonia and organ targeted injuries involving the liver, heart, and kidneys [3]. Many patients with severe COVID-19 experience acute respiratory distress, whereas critically ill patients experience respiratory failure. Although most cases are mild to moderate and can heal spontaneously, some patients develop critical illness, characterized by respiratory dysfunction and/or multiple organ failure. Identifying patients at high risk of critical illness is important, as it can provide these patients with more active treatment and reduce morbidity and mortality rates. At present, the relationships among COVID-19 disease progression, prognosis, and immune status are unclear, and no effectively predictive biomarkers have been proposed. The progression of novel coronavirus-associated pneumonia to a critical and life-threatening illness is thought to be associated with the cytokine storm, defined as the unregulated and excessive release of pro-inflammatory factors in the body [4,5]. The serum concentrations of interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) [6–8], and other cytokines have been found to be significantly increased in patients with severe infections of viruses such as SARS-CoV and H1N1 influenza virus [9,10]. These inflammatory factors can recruit and activate immune cells in the lungs. Many immune system cells and tissue fluids accumulate in the lungs of these patients, blocking gas exchange between the alveoli and capillaries and leading to ARDS. Induction of a cytokine storm results in the immune system destroying large numbers of healthy lung cells while killing the virus, thus severely damaging the ventilation function of the lungs. This damage appears on computed tomography (CT) images of the lungs as large white areas, called "white lung" [11,12], and can result in respiratory failure and death. IL-6 is an

important multi-functional pro-inflammatory cytokine [13]. As an acute inflammatory factor, IL-6 mainly stimulates the proliferation and differentiation of cells involved in immune responses and improves their function, as well as participating in inflammatory and fever responses. Several retrospective studies have shown that increased levels of IL-6 are associated with death in patients with severe COVID-19 infection [14,15]. Elevated IL-6 is also associated with disease severity and course, suggesting that this cytokine may be a marker for disease monitoring in patients with severe COVID-19 [16]. Serum concentrations of IL-6 and C-reactive protein (CRP) can effectively assess disease severity, suggesting that IL-6 and CRP may be independent factors predictive of the severity of COVID-19 [17]. The present study evaluated whether serum concentration of IL-6 could predict critical illness in patients with severe COVID-19.

II. Material And Methods

2.1 Study Population

The observational study was carried out at the Department of Biochemistry, Sheikh Bhikhari Medical College and Hospital, Hazaribag, Jharkhand, from 10th May 2021 to 10th june 2021. A total of 110 COVID-19 patients enrolled from COVID ward of Sheikh Bhikhari Medical college and Hospital, Hazaribag, Jharkhand in this study and divided into non-severe and severe groups. Non-sever group included 72 patients and severe group included 38 patients. All patients with COVID-19 who enrolled in the recent study were diagnosed according to the WHO interim guidance for COVID-19 (6th edition) [18]. In other words, all patients with the physician- and laboratory confirmed (positive nasopharyngeal/throat swab specimens by reverse transcription-polymerase chain reaction (RTPCR)) COVID-19 infection were included, while suspected cases with similar clinical symptoms were excluded. One of the following criteria was used to determine severe COVID-19 illness: respiratory rate >30 bpm, oxygen saturation <93% on room air, arterial oxygen partial pressure (PaO2)/ oxygen concentration (FiO2) ≤300 mm Hg, and intensive care unit (ICU) admission.

2.2 Analysis of serum interleukin-6

Serum concentrations of IL-6 were determined using IL-6 detection kits and the Cobas E601 electrochemiluminescence (ECL) analyzer (Roche, Basel, Switzerland). All reagents were within their period of validity, with quality control and calibration of these reagents meeting manufacturers' requirements. Methods After a 12-h overnight fast, 2–3 mL of venous blood were drawn in the morning from patients with COVID-19 and healthy individuals and tested within 2 h. Blood samples were centrifuged at 4000 rpm for 5 min, and serum concentrations of IL-6 were measured using the ECL method and IL-6 detection kits. All tests were performed by skilled laboratory authorized personnel in accordance with the manufacturers' instructions. The normal reference range for IL-6 was 0–7 pg/mL

2.3. Statistical Analysis.

Statistical data were analyzed using SPSS version20.0. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared by t tests, whereas non-normally distributed continuous data were expressed as median (range) and compared by the Wilcoxon rank sum test. Categorical data were expressed as number (percentage) and compared by the chi square test.The predictive value of the interleukin-6 was evaluated by measuring the area under the receiver operating characteristic curve (AUC). A "p value" below 0.05 was considered statistically significant and $p < 0.001$ considered statistically highly significant.

III. Results

A total of 110 inpatients were declared COVID-19 positive during the study duration. Out of these, 138 patients were included in the severe group, while 102 patients were included in the non-severe group. Mean age of sever group was 58 ± 14 years and mean age of non-severe group was 51±11 years. The average age was higher in the severe group than in the non-severe group ($p = 0.07$) as shown in Table1. Out of 110 patients 68 patients were male and 42 patients were female. Out of 42 female 16 female were included in sever group and 26 female in non-sever group. Out of 68 male, 30 male were included in severe group and 38 male were included in non- sever group as mentioned in table 2 and figure1. The severity ratio for males was higher than for females, but this difference was not significant ($p = 0.54$). Median serum interleukin-6 being 44 ± 70ng/ml and 10 ± 21 ng/ml was found to be significantly higher in the severe group compared to the non-severe cases group respectively (p value = 0.01) as shown in table1.

Table 1
Age and serum interleukin-6 levels in severe Vs Non-severe

Groups	**Age (years)**	**Interleukin-6 (ng/mL)**
Severe case (n=102)	58 ± 14	44±70 ng/ml
Non-severe case (n=136)	51 ± 11	10±21 ng/ml
p value	0.07	0.01

p <0.05 statistically significant and p <0.001 highly significant

Table 2
Gender distribution in Groups

Groups	Male	Female
Severe	30	16
Non-severe	38	26

p value= 0.54
p <0.05 statistically significant and p <0.001 highly significant

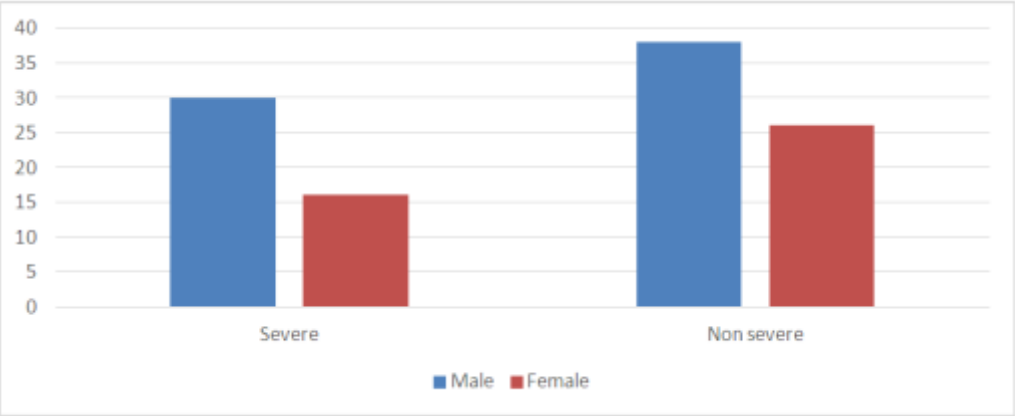
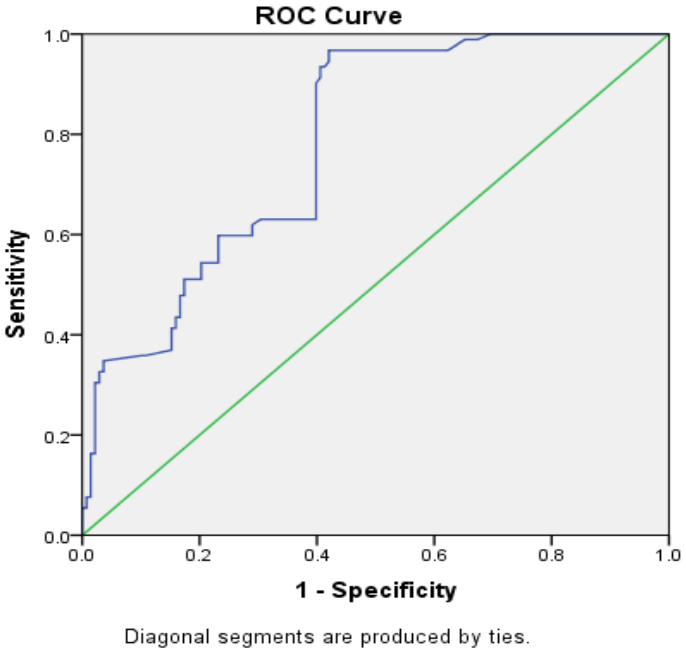


Figure 1. Gender distribution in two study group

ROC curve analysis was used to compare the performance of serum interleukin level as a predictor of severity with an AUC of 0.78 as illustrated in Fig.2. The optimal cut-off for the prediction of severity was 23.9 pg/mL with a sensitivity of 74% at a compromised specificity i.e. 51%.



AUC-0.78

Figure 2: Receiver operating characteristic (ROC) curves of interleukin-6 for predicting the disease severity in COVID-19 patients

IV. Discussion

In our study the serum levels of IL-6 behave as a more appropriate biomarker of disease severity. IL-6 may also play a key role in the development and progression of novel coronavirus pneumonia [18,19]. Circulating IL-6 concentrations have been closely associated with the clinical severity of COVID-19. For example, serum IL-6 levels were found to be significantly higher in severely ill patients than in those with mild symptoms [20], suggesting that IL-6 levels are closely associated with the occurrence of severe COVID-19 in adults and could predict the severity of illness in patients with COVID-19. IL-6 levels were also found to be significantly elevated in patients with respiratory insufficiency, suggesting that IL-6 plays an important role in lung injury due to SARS-CoV-2 infection [21]. Severe respiratory distress in patients with highly pathogenic SARS-CoV-2 was found to be caused by IL-6 elevation. Increased levels of IL-6 and CRP were found to be predictive of the need for mechanical ventilation, indicating that measurement of IL-6 can guide the escalation of treatment in patients with COVID-19 – related hyperinflammatory syndrome [22]. IL-6 is a multifunctional cytokine that transmits cell signaling and regulates immune cells. This factor has a strong proinflammatory effect with multiple biological functions and plays an important role in inflammation, tumor, and hematological diseases (23). The inflammatory response plays a critical role in COVID-19, and inflammatory cytokine storm increases the severity of COVID-19. It has demonstrated the important role that IL-6 plays in the pathophysiology of SARS-CoV-2 coronavirus infection. The present work evaluates the role that the quantification of IL-6 in serum plays in the clinical progress of patients diagnosed with COVID-19. In this report, we provided evidence that IL-6 levels are closely linked to the severity of COVID-19 infection.

V. Conclusion

Interleukin-6 levels are an indicator of disease severity and prognosis of disease. Those patients who have higher IL-6 levels have poor prognosis, so IL-6 levels must be monitored during the course of disease.

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

" 'Hemanti designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. 'Rajiv kumar Mahli' managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript."

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