# INTERLEUKIN-6 AS A POTENTIAL INFLAMMATORY BIOMARKER IN PATIENTS INFECTED WITH COVID-19

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**BACKGROUND**: The ongoing worldwide Corona virus Disease 2019 (COVID-19) pandemic has posed a huge threat to global public health. Numerous inflammatory markers are elevated in patients with severe disease relative to patients with milder conditions. These markers include C-reactive protein (CRP) and interleukin-6 (IL-6). CRP is a type of protein produced by liver that serve as an early biomarker of infection and inflammation. IL-6 is one of the main mediators of inflammatory and immune response initiated by infection and injury in lungs.

**AIMS:** To correlate serum CRP and serum IL-6 level in covid-19 patients and its relationship with severity of the disease.

**METHEDOLOGY**: The study was conducted on three groups mild (N=30), moderate (N=30) and severe (N=30) covid-19 positive patients. Age matched covid-19 negative as controls (N=30) also recruited for this study. Serum IL-6 levels in covid-19 patients were measured by using an immunoenzymatic chemiluminescence assay whereas serum CRP and measured by immunoturbidimetry method.

**RESULTS**: We found that serum IL-6 levels and serum CRP level were significantly increased in covid-19 patient as compared to normal healthy controls. Our result shows that serum IL-6 levels and serum CRP level were increased as disease progress from mild to severe condition of Covid-19 patients.

**CONCLUSIONS**: Serum IL-6 increased in covid-19 due to enhanced cell mediate immune response while CRP increased due to inflammatory response, infection and tissue damage. Our results suggest that monitoring inflammatory markers may serve as an early warning system for progression to severe COVID-19.

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**INTRODUCTION**:

The ongoing worldwide Corona virus Disease 2019 (COVID-19) pandemic has posed a huge threat to global public health. The pathogen has been identified as a novel single stranded ribonucleic acid (RNA) beta corona virus named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which shares an approximately 79% similarity at nucleotide level with severe acute respiratory syndrome corona virus. COVID-19 represents a spectrum of clinical severity ranged from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death. Therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality.[1]

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19. Moreover, increased levels of serum IL-6 are shown to be involved in COVID-19 pathogenesis and may serve as a potential biomarker for monitoring disease progression.[2]

The outbreak of corona virus disease (COVID-19) in December 2019, caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). It poses a severe threat to global public health. Some studies suggest that numerous inflammation markers are elevated

in patients in the intensive care unit or patients with severe disease relative to patients with milder conditions.[3]

Some evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19. Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. IL-6 is a pleiotropic cytokine with a wide range of function. IL-6 produced from a single gene encoding a product of 212 amino acids, which is cleaved at the N terminus to produce a 184 amino acids peptide with a molecular weight between 22-27 kDa.[5]

IL-6 production is rapidly induced in the course of acute inflammatory response associated with injury, trauma, stress, infection, brain death, neoplasia, and other conditions. IL-6 is produced by fibroblast, activated T cell, activated monocytes or macrophages and endothelial cells. IL-6 is a pro-inflammatory cytokines, that secreted into the serum and induce a transcriptional inflammatory response through interleukin-6 receptor, alpha. IL-6 is a non specific marker and hence is not diagnostic for any specific disease. IL-6 was proposed to be associated with the severity of corona virus disease.[6]

The present study was proposed to correlate the serum levels of IL-6 with severity of COVID-19 and monitoring of the disease.

**METHODOLOGY**

The study was initiated after obtaining approval from the Institutional Ethics Committee, SRG Hospital & Jhalawar Medical College, Jhalawar Rajasthan. This study was carried as a retrospective study between January and July 2023. Nasopharyngeal swab was taken as

sample for RT-PCR. This study was conducted first time in *Hadoti* region of Jhalawar, Rajasthan. In this study, we have divided patients into three groups common (N=30), severe (N=30) and critical (N=30) cases of Covid-19 patients. The diagnosis and severity classification was based on Clinical Guidance for management of adult Covid-19 patients (Ministry of Health & Family welfare) and WHO interim guideline.

Classification of cases were as follow

A. Common cases: Covid-19 patients showing Fever, dry cough, nasal congestion, sore throat, lost sense of smell or taste, conjunctivitis, mild fatigue and imaging showed pneumonia

B. Severe Cases: Adult cases meeting any of the following criteria: Respiratory distress ($\geq$ 30 breath/Min.), Oxygen saturation $\leq 93\%$ at rest, Arterial partial pressure of Oxygen (PaO2)/ Fraction of inspired oxygen (FiO2) $\leq$ 300mmHg and Chest imaging that show obvious lesion progression within 24 hours.

C. Critical Cases: cases meeting any of the following criteria, Respiratory failure and requiring mechanical ventilation, shock, with other organ failure that requires ICU care.

Diagnosis of cases

Etiological: A positive RT-PCR detection of 2019-n CoV Nucleic acid.

Quantitative estimation of IL-6 is done by fully automated, chemiluminescent immunoassay in serum.

Biostatistics: Descriptive statistics were applied to summarize data. Results were reported as mean with standard deviation. One-way ANNOVA was applied to detect significant difference among stratifications. Statistical Package for Social Science (SPSS) 25.0 software was used for statistical analysis and illustration.

**RESULTS**:

The mean concentration of IL-6 was 2.36±0.64 pg/ml, 5.84±1.12 pg/ml, and 21.21±6.57 pg/ml for the common, severe, and critical groups respectively ($P <$ 0.001). Our result shows that serum IL-6 levels increased as disease progress toward critical condition.

| Covid-19 Groups | Number | Mean IL-6 (±S.D.) | p-Value | F-Value |
|---|---|---|---|---|
| Normal | 30 | 2.36±0.64 | <0.0001 | |
| Severe | 30 | 5.84±1.12 | <0.0001 | 201.85 |
| Critical | 30 | 21.21±6.57 | <0.0001 | |
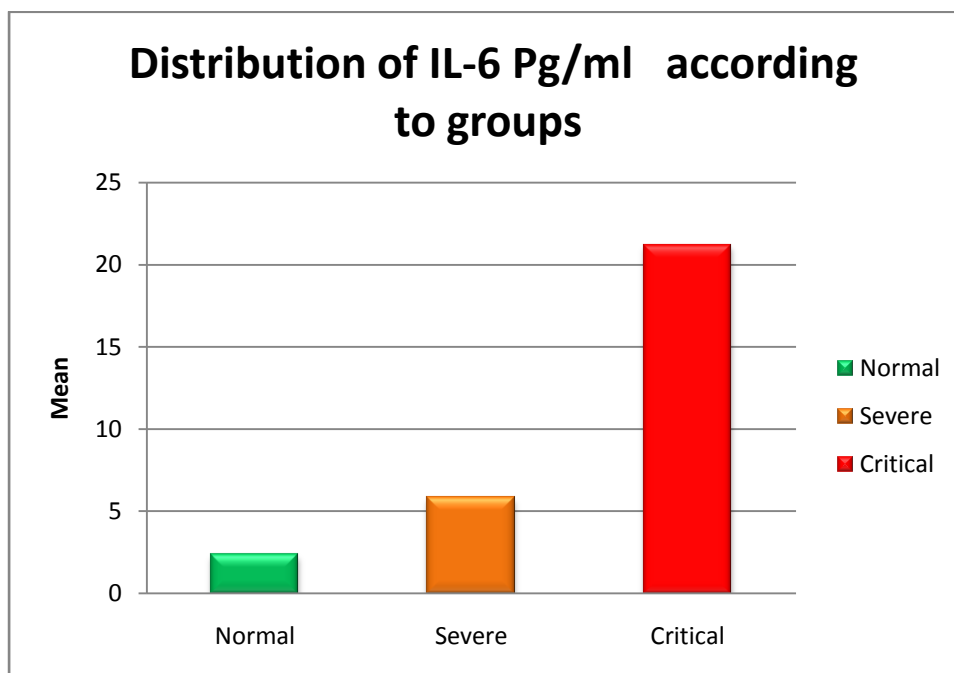


**DISCUSSION**

We evaluated the association of serum biomarkers IL-6 in 90 patients diagnosed with COVID-19 infection. Serum IL-6 concentration was tested and analyzed in all groups of Covid-19 patients. We obtain consistently high level of IL-6 in severe and critical group of patients as compare to normal group of covid-19 patients. We observed that serum IL-6

levels were significantly higher in patients with critically illness admitted in ICU compared with patients with severe and normal illness.

Variable biomarkers were identified to predict the outcomes and severity of COVID-19 infections. **Pan ji *et al* (2020)** conducted a meta-analysis and found the association between inflammatory markers and severity of covid-19 patients. They observed the elevated levels of serum interleukins-6 (IL-6) in severe covid-19 patients. **Furong Jeng *et al* (2020)** reported the associations of inflammatory markers with the severity of COVID-19. Their meta-analysis highlights the association of inflammatory markers like Interleukin-6 (IL-6) with the severity of COVID-19. Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

We had a similar observation in our study. We also observed a positive correlation of serum levels of IL-6 with the severity of disease.

**Zing Jhang *et al* (2020)** conducted a retrospective single-institutional study of 901 consecutive confirmed cases of covid-19. Serum IL-6 concentrations were tested on admission and/or during hospital stay. Serum IL-6 should be included in diagnostic work-up to stratify disease severity. They found elevated levels of IL-6 in covid-19 patients and also confirmed the finding that serum IL-6 should be included in diagnostic work-up to stratify disease severity. It is recognize that excessive, multifunctional host immune response may play an important role in development and maintenance of critical stage of covid-19.

**CONCLUSION**

Serum IL-6 should be included in diagnostic work-up to stratify disease severity. Therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality. Our research work will be helpful in making novel strategies for diagnosis, treatment and prognosis of Covid-19 patients. This study may be helpful to reduce mortality due to covid-19.

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