ROLE OF INTERLEUKIN – 6 AS A PROGNOSTIC MARKER IN COVID-19 PATIENTS IN A TERTIARY CARE CENTRE IN INDORE DISTRICT, STATE M.P.

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has spread rapidly around the world since its emergence and has wreaked havoc globally. As hospitals around the world are being overwhelmed due to the COVID-19 pandemic, it is of utmost urgency to identify biomarkers which would accurately predict patient outcome at an early stage. Many studies suggested that numerous markers of inflammation like CRP, ESR, LDH, D-Dimer, Serum Ferritin and Interleukin -6 were found to be significantly elevated in patients with severe disease relative to patients with milder conditions. Amongst which IL-6 appears to be the most important driver of immune dysregulation and ARDS in Covid-19. According to known evidence, IL-6 is superior to CRP and other markers of inflammation in predicting respiratory failure in Covid-19 (1, 2).

Method: All patients had a positive covid-19 Reverse Transcriptase Polymerase Chain Reaction (PCR) test results. Patients with the history of comorbidities such as Hypertension (HTN), Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), Asthma, Heart failure, Chronic renal Failure (CRF) were included. The clinical and laboratory findings including Haemoglobin, WBC counts, Differential Counts, Liver Function Tests, C-Reactive Protein (CRP), Ferritin and Interleukin -6 (IL-6) were obtained from the database. **Results:** A total of 50 patients were included in the study. The median age of study population was found to be 52.5 years. It was observed that there were significantly increased serum IL-6 levels as the age increased. The serum levels of both IL-6 and CRP were markedly increased in morbid patients. Higher plasma IL-6 levels translated to more severity (determined by days of hospital stay, mechanical ventilation and mortality).

Conclusion: This study proves that serum IL-6 level is an accurate and a reliable indicator in predicting the prognosis of the patients in terms of longer hospital stay, greater need of mechanical ventilation, and/ or increased mortality.

Keywords: IL-6& Covid-Biomarkers.

Introduction

Although the individual components of Cytokine Storm are varied such as Interleukin-1Ra, Interleukin-8 etc, but IL-6 has emerged of particular interest in the context of SARS-CoV-2 infection after being identified as the most significant predictor of mortality in recent retrospective studies of patient survival in COVID-19. Herein, we review the current understanding of the origin and mechanisms of Cytokine Storm (CS) associated with SARS-CoV-2 infection(1). Its main focus is on the identification and implication of IL-6 and other proinflammatory cytokines and pathways in Cytokine Storm-driven ARDS, and discuss the potential utility of anti-IL-6 and other cytokine-targeting immunomodulatory biologics for the treatment of this critically ill population(2).

Increased levels of IL-6 and its pro- inflammatory activity leads to the development of insulin resistance and hypertension in obese individuals.(3)

Adiponectin is an important cytokine produced by the adipose tissues and has anti-inflammatory property, through which it plays a key role in increasing the insulin sensitivity. Also through its protective effect over the

vascular endothelium, it reduces the risk of development of hypertension in obese patients.

In obesity the adiponectin levels are decreased which along with elevated IL-6 level alters the homeostasis between the pro and anti-inflammatory cytokines.(4) This imbalance ultimately results in increased risk of production of numerous pro-inflammatory cytokines from the adipose tissue in obesity. Important among them are IL-1, IL-6, Resistin, and C-Reactive Protein.

Among these interleukin-6 (IL-6) is an important pro-inflammatory cytokine which through various mechanism induce insulin resistance in patients with obesity.

Interleukin 6 (IL-6) originally denoted as a protein secreted by leucocytes, is now recognized to be produced by non-immune cells as well (5,6).

Aim: To Study the Role of Interleukin – 6 as a Prognostic Marker in COVID-19 Patients.

Objectives:

1. To determine IL-6 levels of the covid patients admitted at Index Medical College Hospital and Research Centre, Indore.
2. To find other comorbidities which may affect the prognosis of the covid patients.
3. To study and correlate the role of IL-6 levels as a prognostic marker in assessing the severity and outcome of the disease.

Materials and Methods:

This study was initiated with a retrospective design that enrolled patients hospitalised at Index Medical College Hospital and Research Centre, Indore between December

2020 and February 2021. All patients had a positive COVID-19 RT-PCR test results. Patients with the history of comorbidities such as Hypertension (HTN), Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), Asthama, Heart failure, Chronic renal Failure (CRF) were included. The clinical and laboratory findings including Haemoglobin, WBC counts, Differential Counts, Liver Function Tests, C-Reactive Protein (CRP), Serum Ferritin and Interleukin-6 (IL-6) were obtained from the database. Patients were divided into 2 categories where patients admitted to ICU were entered in the first group (serious category) and the patients admitted in the wards were in the second group (mild group).

Result:

Table 1: Gender Distribution

S. No.	Total patients	Male patients	Female patients
1	50	27	23

Result shows that males were more affected than females.

Table 2: Age Distribution

S. No.	Plasma IL-6 levels (pg/ml)	Age (years)			
		13-30	31-50	51-70	71-90
1	01-50	03	09	08	00
2	51-100	03	09	09	00
3	101-200	00	00	02	02
4	201-320	00	00	01	04

A total of 50 patients were included in the study. The median age of study population was 52.5 years. Increased IL-6 levels with the increased age. The chi-square statistic is 1.2919. The p-value is 0.036408. The result is significant at p value < .05.

Hence it was found that Serum IL-6 levels increased with the advancing age.

Table 3: CRP levels

S. No.	Plasma IL-6 levels (pg/ml)	CRP levels (mg/L)		
		01-10	11-20	21-35
1	01-50	12	12	03
2	51-100	07	06	01
3	101-200	01	00	03
4	201-320	00	00	05

Both IL-6 and CRP levels increased in morbid patients. The chi-square statistic is 5.03. The p-value is 0.04696. The result is significant at p < .05.

Hence we concluded that Serum IL6 levels were superior to CRP in predicting the outcome of the patient.

Table 4: Severity of cases

S. No.	Plasma IL-6 levels (pg/ml)	Severity of cases (no. of patients)			% of Morbid patients
		Mild	Serious	Death	
1	01-50	10	16	00	61.53%
2	51-100	06	09	00	60%
3	101-200	00	00	04	100%
4	201-320	00	00	05	100%

Higher the plasma IL-6 levels- more the severity (determined by of days of hospital stay). The chi-square statistic is 2.5461. The p-value is 0.04811. The result is significant at p < .05.

Hence, it was observed that severity of the disease was directly associated with serum IL-6 levels. (determined by of days of hospital stay). Hence higher the IL-6 levels, more was the severity.

Figure 1: Severity of cases

Table 5: Need for mechanical ventilation

S. No.	Plasma IL-6 levels (pg/ml)	No. of patients needing mechanical ventilation		% of Patients needing mechanical ventilation
		Yes	No	
1	01-50	18	11	62.06%
2	51-100	07	05	58.3%
3	101-200	04	00	100%
4	> 200	05	00	100%

Higher plasma IL-6 levels mean greater need for mechanical ventilator support. The chi-square statistic is 7.2535. The p-value is .026602. The result is significant at $p < .05$. Therefore it was concluded that higher plasma IL-6 levels translated to greater need for mechanical ventilation.

Figure 2: Need for mechanical ventilation

Discussion:

The use of biomarkers such as IL-6 and CRP to recognize early the hyperinflammatory state of SARS-CoV-2 infection has been proposed as a trigger point for using immunologic therapies(7). Importantly, many such immunotherapies are already available for different treatment indications including those that target the IL-6 and IL-6R. And a reliable indicator such as IL-6, leading to an early detection of the possibility of an impending cytokine storm can dramatically reduce covid 19 associated morbidity and mortality(8).

Conclusion: The Covid-19 related cytokine storm syndrome explained the greater morbidity and mortality in the patients. Therefore this study proves that IL-6 levels are an accurate and reliable indicator in predicting the outcome in covid patients in terms of longer hospital stay, greater need of mechanical ventilation and/ or increased mortality in patients. With such a reliable marker at hand for predicting the covid 19 associated complications, this can be used as an effective tool to reduce the death toll substantially.

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