Radio-Clinical Findings in COVID-19 Patients: A Hallmark of Systemic Inflammation

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Abstract

Background: COVID -19 is a great threat to the human health worldwide and injury to the lungs is the main outcome of COVID-19 infection. In this context, it is believed that clinical -radiological findings along with biochemical alteration play a crucial role in diagnosis of disease. Aim: The aim of the present study was to ascertain the association of serum IL-6 levels with severity of lung injury in COVID-19 patients. Methodology: 130 patients of COVID-19 (93 males and 37 females) were included in this study and classified as mild, moderate and severe according to the revised guidelines on clinical management of COVID-19. Radiological findings in terms of high resolution computed tomography (CT) scan chest had been performed in only those COVID-19 patients in whom IL-6 test have been done. The collected data were analyzed statistically using standard methods and were compared by using Pearson correlation coefficient and Analysis of variance. Result: Marked elevated levels of serum IL6 were observed in COVID-19 patients and these levels showed a highly significant correlation (p-value < 0.001) with disease severity as characterized by raised CT score. In addition, serum IL-6 levels were

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negative correlated with SpO2 status in COVID-19 patients (r= -0.021; p<0.001) which reflect the need of intensive treatment of COVID-19 patients with very high IL-6 levels. Conclusion: Regular monitoring of IL-6 levels plays a crucial role in accessing the disease severity. Furthermore, these findings may help the clinicians to better understand the role of IL-6 in COVID -19 associated lung injury and also plan the therapeutic management of these patients, and thus, reducing the mortality of this global pandemic.

1. Introduction:

Since antiquity, healthy life is a desire of every human being, and it is not only absence of disease or maintaining physical strength but also a quality of life with maintaining health along with cognitive abilities. In addition, numerous scientific efforts have been done to achieve successful and healthy life. Despite this, till date conundrum of immortality is unrevealed and ingress of systematic deterioration of health accompanied with an envelope of health related complications followed by death is an accepted fact of life. Interestingly, it has been documented in the pages of past several centuries that infectious disease pandemics have contributed significantly in increasing the mortality rate by affecting physical and mental health of the population. This devastating incidence is continued in current millennium too, even in the form of coronavirus disease (COVID 19).

Till date, 18 Crore confirmed cases of COVID-19 and 39.1 Lakhs deaths have been documented worldwide. In general, SARS-COV-2 transmission is mainly airborne via droplets generated by both symptomatic and asymptomatic patients. However, the data related of asymptomatic patients mediated transmission is scanty. Moreover, research on asymptomatic viral contamination is as of now progressing worldwide to explain the prevalence and mortality of COVID-19. Clinically, COVID-19 appeared as a multifaceted disease as this virus affects a large number of organ system, and responsible for increased rate of morbidity and mortality. As per available and documented records, mortality rate vary from country to country but 80.9% patients of COVID-19 develop a mild infection, 13.8% severe pneumonia and 4.7% respiratory failure, septic shock or multi-organ failure.[1]

Interestingly, injury to the lungs is the main outcome of COVID-19 infection. This has caused a serious burden to our national health care system. It has been observed that inflammation is a key factor in COVID-19 and Interleukin-6 (IL-6), a pro-inflammatory cytokine, has been reported to be associated with disease severity and mortality in patients with corona virus disease 2019. However, dynamic changes in IL-6 levels and their prognostic value as an indicator of lung injury in COVID-19 patients have not been fully elucidated. The monitoring of IL-6 level is crucial in understanding the patho-physiological process of acute respiratory distress syndrome however, whether IL-6 levels can predict the severity of pulmonary injury has not been fully investigated in patients with COVID-19. [2]

Cytokines are vital in regulating immunological and inflammatory responses. Among them IL-6 is of major importance because of its pleiotropic effects. Circulating IL-6 levels are closely linked to the severity of COVID-19 infection. Previous retrospective studies indicated that an elevated level of IL-6 was associated with a high fatality of COVID-19 infection.[3] Furthermore, it seems that the highly pathogenic SARS-COV-2 is associated with rapid virus replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6 induced severe respiratory distress. Therefore, the present study was undertaken to assess the association between IL-6 levels and lung-injury in COVID-19 patients which was evaluated by CT scan and clinical findings. In addition, an attempt has been also made to study the correlation of IL-6 with chest CT score in COVID-19 patients with disease severity.

2. Material and methods:

The present retrospective study was conducted in the Departments of Biochemistry, Radiology and Medicine, School of Medical Sciences & Research and Sharda Hospital, Greater Noida. The study was conducted after obtaining ethical clearance from the Institutional Ethical Committee from March 2020 to September 2020. 250 COVID-19 patients visiting the Department of Medicine, both OPD and IPD, Sharda Hospital were evaluated. The

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medical records were screened to identify adult patients who had received treatment for confirmed COVID-19 at Sharda Hospital. Out of 250 patients, 130 cases of COVID-19 as per selection criteria were identified from the records and included in the study considering the inclusion and exclusion criteria of the study.

Inclusion Criteria: COVID-19 patients confirmed by RT-PCR test before admission, who gave informed consent for study and of more than 18 years were included. These patients were admitted in the Department of Medicine in COVID Isolation, COVID wards and COVID ICU of Sharda Hospital. In addition, those patients whose IL-6 test and CT scan have been performed within 48 hours of IL-6 test were included.

Exclusion Criteria: COVID-19 patient with less than 18 years of age were excluded from the study. In addition, pregnant women, patients suffering from community based Pneumonia, acute myocardial infarction, acute pancreatitis, patients on immuno-suppressant drugs, patients of Hepatitis B, C, HIV and malignancy were also excluded.

Detailed history and relevant general and systemic examination of subjects were recorded from the case history sheets of enrolled patients who were admitted in the COVID Isolation, COVID wards and COVID ICU of Medicine department.130 cases of SARS COV 2 positive patients already confirmed by RT-PCR test before admission have been taken in this study.

Serum IL-6 (R&D Systems, USA; sensitivity less than 0.7 pg/ml) levels were measured using commercially available ELISA kits, according to manufacturer's instructions. The laboratory results of serum IL-6 and radiological findings of CT scan chest of the enrolled patients which were available retrospectively in the data records of Biochemistry section of the Central Lab and Radiology department were recorded. Serum IL-6 test and CT scan chest were advised by the treating consultants and performed in the Biochemistry laboratory and Radiology department respectively. The records of only those COVID-19 patients in whom IL-6 test have been done and CT scan chest had been performed within 48 hours of IL-6 test were noted. These investigation results for each patient, as
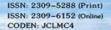
available in the records were recorded and compiled.

Based on the clinical records, the severity of the disease was classified as mild, moderate and severe according to the revised guidelines on clinical management of COVID-19 issued by Govt. of India, Ministry of Health & Family Welfare.[4] The records of radiological findings of CT scan chest were used to study the severity of COVID-19 using CT severity scoring system of European Radiology.[5] The records of the levels of IL-6 were used to correlate with the disease severity based on clinical and radiological findings.

__Statistical analysis__: The data collected from COVID-19 patients were entered manually in Microsoft Excel sheet of windows 2007 and values were expressed as Mean ± SD. In addition, all statistical data were analyzed by using the freely available 24th version of SPSS. The difference between the variables have been evaluated using the student 't' test. The relation between serum IL-6 with age, CT score and SpO_2 was determined by using Pearson correlation coefficient. Analysis of variance (ANOVA) was also performed among the study group parameters of COVID-19 patients. The p value of ≤ 0.05 will be considered as significant and < 0.001 is highly significant. The p-value of > 0.05 is considered as non-significant.

3. Results

A total of 130 COVID-19 patients were included in this study comprising of 93 males and 37 females. Most of the patients (n=36) were in the age group of 31 to 40 years which was 27.7% as presented in Figure 1. Interestingly, 72 % COVID-19 patients were male which reflects that males were more susceptible to get infected by this virus, as represented in Figure 2. Serum IL-6 levels, radiological and clinical findings in COVID-19 patients of different severity were represented in Table 1. Serum IL6 levels showed a highly significant correlation (p< 0.001) with disease severity in the COVID-19 patients. 60 patients with mild disease symptoms (46.1%) had slightly raised serum IL6 levels (5.40-9.13 pg/ml),18 patients with moderate disease symptoms (13.8%) had raised serum IL6 levels (21.14-50.71 pg/ml) and 52 patients with severe disease (40%) had extremely

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raised serum IL6 levels (34.42-80.24 pg/ml). COVID-19 patients with raised CT score also showed a highly significant correlation (p<0.001) with the disease severity in the patients. Patients with mild disease had slightly raised CT score (3.09-5.54), Patients with moderate disease had more CT score (7.56-12.66) and patients with severe disease had highly raised CT score (14.14-16.52). Thus, radiological findings in terms of a highresolution computed tomography (CT) scan chest indicated severe lung involvement in patients with extremely high IL-6 levels ($P < 0.001$).

In addition, association of serum IL-6 levels with age, CT score and oxygen saturation status (SpO_2) is presented in Table 3. It was observed that serum IL-6 was significantly associated with CT scan score in COVID-19 patients. Similarly, serum IL-6 levels was negative associated with SpO_2 (r= -0.021; p<0.001) in the study group subjects as represented in Figure 3.

4. Discussion:

Coronavirus disease 2019 (COVID -19) is presently estimated to have 34,296,237 confirmed cases in India and 246,951,237 confirmed cases and 5,004,855 deaths globally. The COVID -19 is a great threat to the communities worldwide.[6] It is obvious that COVID-19 is now emerging as a major global health problem not only in adult population but also in the population of any age group. COVID-19 cases are frequently accompanied by IL-6 peaks.[7] It has been documented that the integration of imaging and clinical data can aid in the prediction of severe course of disease in COVID-19 pneumonia. This aids in patient stratification and triage, which is critical especially in an over loaded health care system as was observed in Italy and more recently in New York.[8,9] Although most cases are mild to moderate, some patients developed severe symptoms characterized by respiratory dysfunction and/or multiple organ failure.

It has been suggested that one of the possible mechanisms underlying rapid disease progression is cytokine storm. In the present study, the association of serum IL-6 with radiological and clinical findings in COVID-19 patients was observed. Higher IL-6 levels were associated with

the increased disease severity in these patients. Chen et.al reported a similar finding with significant elevation in the level of inflammatory cytokine IL-6 in the critical ill COVID-19 patients.[7] High levels of IL-6 have been found to be associated with increased CT scores in these patients and, therefore, higher CT scores have been associated with the disease severity of the patients.[10]

Recently, Bhandari et al. observed that high mortality among COVID-19 patients was associated with extremely raised IL6 levels and higher CT scores.[11] The COVID-19 patients with the co-morbidities like diabetes mellitus, essential hypertension, chronic kidney disease, meningitis, hypothyroidism etc. are more likely to have severe disease and may have higher mortality. The COVID-19 patient tends to have raised IL6 levels due to the increased inflammation which is triggered by the cytokine storm.[12] In the present study, the majority of patients with extremely raised IL-6 levels were associated with the high CT score images ($P = 0.001$). Patients with extremely raised IL-6 levels required intensive treatment as compared to normal IL-6 group in terms of therapy, noninvasive ventilation, and intensive care unit care. These findings may help the clinicians to better understand the role of IL-6 in COVID -19 associated lung injury and also planning the therapeutic management of these patients, thus, reducing the mortality of this global pandemic.

Conclusion: On the basis of the findings of present study, it is COVID-19 patients with extremely raised IL6 levels and higher CT scores are more prone to develop severe and critical disease along with higher mortality. Therefore, elevated IL6 levels along with higher CT scores can be used as the predictor for the severity of the disease and to assess the adverse outcomes. Besides, the IL-6 estimation for the identification of SARS-CoV-2 is fundamental for clinical practice, especially for asymptomatic patients, and ought to be performed when COVID-19 patients are passing on the medical clinic too to affirm viral freedom. Furthermore, it is obvious that the COVID-19 patients with the comorbidities like diabetes mellitus, essential hypertension, chronic kidney disease, meningitis, hypothyroidism etc. are more

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likely to have severe disease and may have higher mortality.

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Table 1.0: Serum IL-6 levels, radiological and clinical findings in COVID-19 patients of different severity

		N	Mean	Std. Deviation	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
IL6 (pg/ml)	Mild	60	7.26	7.22	5.40	9.13
	Moderate	18	35.93	29.73	21.14	50.71
	Severe	52	57.33	82.29	34.42	80.24
	Total	130	31.26	57.99	21.20	41.32

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CTSS	Mild	60	4.32	4.75	3.09	5.54
	Moderate	18	10.11	5.13	7.56	12.66
	Severe	52	15.33	4.27	14.14	16.52
	Total	130	9.52	6.87	8.33	10.72
Spo2 (%)	Mild	60	96.87	1.07	96.59	97.14
	Moderate	18	93.56	0.98	93.07	94.04
	Severe	52	96.21	2.04	95.64	96.78
	Total	130	96.15	1.86	95.82	96.47

Table 2.0: Analysis of variance (ANOVA) in COVID-19 patients of different severity

		Sum of Squares	df	Mean Square	F	p-value
IL-6	Between Groups	70291.429	2	35145.714	12.281	<0.001
	Within Groups	363457.732	127	2861.872		
	Total	433749.161	129			
CTSS	Between Groups	3384.227	2	1692.114	79.292	<0.001
	Within Groups	2710.203	127	21.340		
	Total	6094.431	129			
SpO2	Between Groups	152.172	2	76.086	32.639	<0.001
	Within Groups	296.051	127	2.331		
	Total	448.223	129			

where,

p<0.001 : Highly significant

Table 3.0: Correlation analysis of study group parameters in COVID-19 patients

Parameters		Age	IL-6	CTSS	SpO2
Age	Pearson Correlation	1	.221[*]	.535[**]	-.309[**]
	p-value		0.012	0.000	0.000
IL-6	Pearson Correlation	0.221[*]	1	0.393[**]	-0.021[*]

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	p-value	0.012		0.001	0.010
CTSS	Pearson Correlation	.535**	.393**	1	-0.146
	p-value	0.000	0.000		0.097
SpO2	Pearson Correlation	-0.309**	-0.021	-0.146	1
	p-value	0.000	0.812	0.097	

* Correlation is Highly significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

Figure 1: Distribution of COVID-19 patients on the basis of Age group

Figure 2: Distribution of COVID-19 patients on the basis of gender

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a) IL-6 vs Age

r = 0.221; p = 0.012

b) IL-6 vs CTSS

r = 0.393; p = 0.001

c) IL-6 vs SpO$_2$

r = -0.021; p = 0.010

Figure 3: Correlation of Serum IL-6 levels with clinico-radiological findings in COVID-19 patients