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ORIGINAL RESEARCH

Evaluation of IL-6 levels and their association with CT findings and prognosis in covid-19 patients in western UP

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Abstract
Aim: This study was performed to monitor the levels of interleukin-6 (IL-6) in COVID-19 patients and its correlation with clinical presentation, severity, HRCT chest and outcome in SARS COV-2 (COVID-19) infection.
Methods: The study included 100 admitted COVID-19 patients, classified as either asymptomatic, mildly sick, seriously ill, or critically ill. The data of patients regarding medical history, clinical presentation, co-morbidities, laboratory investigation, HRCT chest report, management and outcome were extracted from the medical records for final evaluation and their interpretation for correlation among the groups.
Results: Higher levels of IL-6 in COVID-19 positive Patients frequently exhibited symptomatic presentation, severity and critical illness, Elevated IL-6 level was reported among 23% of the subjects. In this study, mean HRCT CHEST severity score was found to be more among subjects with elevated IL-6 level as compared to patients with normal levels of IL-6. When CT severity score was compared according to normal and elevated IL-6 level, significant difference was found (p value <0.05). Elevated IL-6 level was reported among 76.19% and 8.86% of the non-survivor and survivor subjects respectively. When mortality was compared according to normal and elevated IL-6 level, the difference exhibited was significant (p<0.05).
Conclusion: This Study exhibited higher IL-6 in patients with COVID- 19 infection was associated with disease severity and mortality. Hence it can be considered as a biomarker for disease severity and mortality.
Keywords: IL-6, COVID-19, CT SCORE

Introduction

The first case of COVID-19 was reported in December 2019 in Wuhan, China, and the WHO has since declared a public health emergency due to the virus's potential to cause a global pandemic[1]. There are numerous unanswered questions about how this virus got from sick animals (like bats and pangolins) to humans and then spread all over the world. Each infected person is said to be able to infect an average of 3.8 others, making the claimed transmission rate of COVID-19 extremely high. Patients with COVID-19 have seen widely varying mortality rates, which have been affected by factors such as age and the existence of underlying diseases[2]. Symptoms such as cough, fever, shortness of breath, loss of appetite, exhaustion, sputum production, nausea, joint pain, vomiting & diarrhea are common in COVID-19 positive people. While many people were asymptomatic, this does not mean that no one is affected. Complications from a serious disease include pneumonia, multi-organ failure, acute respiratory distress syndrome (ARDS), septic shock, & disseminated intravascular coagulation. The activation of host immune responses coincides with viral amplification, and this combination is thought to be sufficient for virus clearance and eventual cure. Still, the reasons why certain patients experienced more severe disease progression, such as MODS, remain unclear. It has been postulated that a cytokine storm was a key factor in the etiology of severe instances of COVID-19[3.] A "cytokine storm" occurs when an abnormally high number of cytokines are produced in a short amount of time.
COVID-19 patients have extensive T-lymphocyte and mononuclear macrophage activation, leading to the production of cytokines, most notably interleukin-6 (IL-6). These acute inflammatory reactions, as well as the cytokine storm, are observed in the lungs and other tissues of COVID-19 patients due to the binding of this cytokine to its IL-6 receptor on the target cells. Clinical presentations, radiographic characteristics, therapeutic approaches, and final results all reflect the prevalence of IL-6 in COVID-19 infection. Hence the present study was conducted to analyse cytokine profiles of COVID-19 patients and its association with the severity of the disease, CT finding and outcomes.

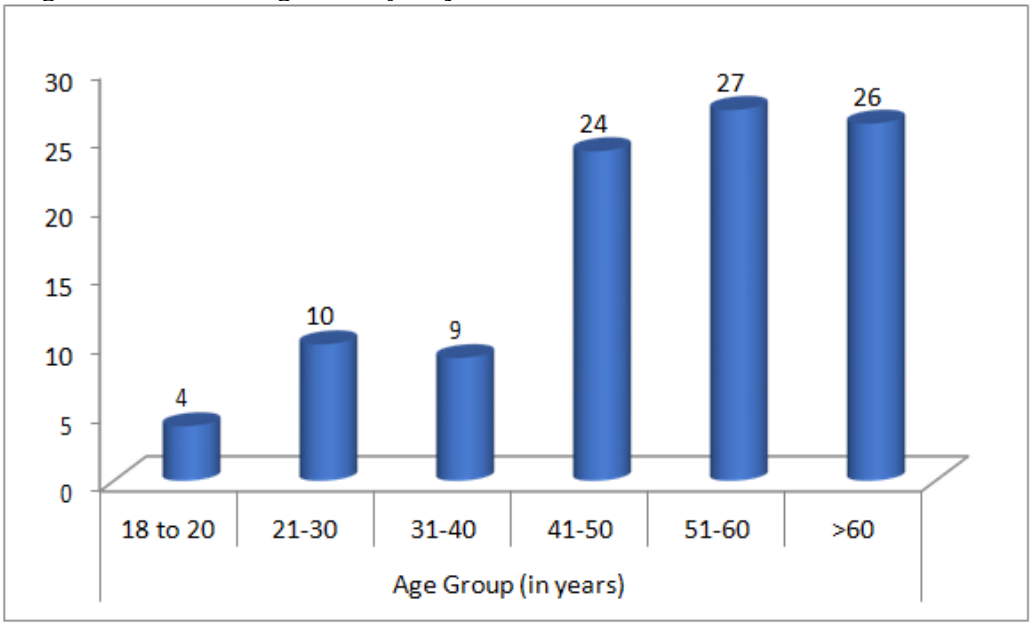
Methods

Study design- This was a descriptive, observational study of 100 patients who tested positive for COVID. Aim of the study was to evaluate IL-6 levels in COVID-19 patients and its association with CT finding and prognosis. Objectives of the study was to evaluate IL-6 levels in patient of COVID-19, to evaluate CT findings in patients of COVID-19, to associate IL-6 levels with CT findings in patients of COVID-19. All COVID-19 positive patients under age group Age 18-65 were included for the study. Patients with Chronic liver disease, Pregnant women, COPD, Rheumatoid arthritis, Asthma, Cancer, patients who have not signed a written informed consent were excluded from the study . The gathered data was placed into an Excel spreadsheet and totalled for statistical analysis. Based on the mean and standard deviation of each group, statistical analysis was carried out "(SPSS 22.00 for windows; SPSS inc, Chicago, USA)". The student t-test and the chi-square test were used to analyse the statistical significance of the differences between the two groups, with the threshold of significance set at $p<0.05$.

Results

A total of 100 COVID-19 positive patients were selected in this study, out of which 62 were males and 38 were females. The participants included in the study between the age of 18-20 were 4%, between 21-30 age were 10%, between 31-40 were 9% , between 41-50 were 24% , between 51-60 were 27% and 26% of the participants selected were over the of 60 years (graph 1).

Graph 1: Age distribution among the study subjects



It was found that 54%, 35%, 24%, 11%, 8%, 6%, 5%, 3%, 2%, and 2% of the individuals in the current research experienced fever, cough, dyspnoea, loss of taste, loss of smell, lethargy, headache, diarrhoea & arthralgia, respectively (table 1).

Table 1: Symptoms among the study subjects

Symptoms	N=100	%
Fever	54	54
Cough	35	35
Dyspnoea	24	24
Loss of Taste	11	11
Loss of Smell	8	8
Lethargy	6	6
Headache	5	5
Myalgia	3	3
Diarrhea	3	3
Arthralgia	2	2

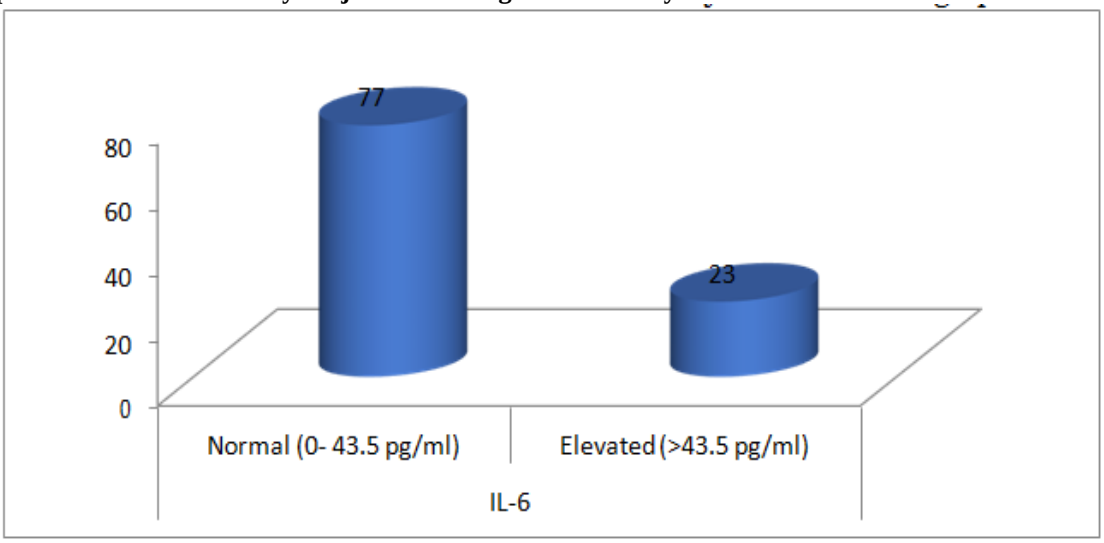
Obesity was seen in 33%, diabetes was seen in 40% and hypertension was seen among 56% of the subjects (table 2).

Table 2: Co-morbidities among the study subjects

Co-morbidities	N=100	%
Obesity	33	33
Diabetes	40	40
Cardiovascular Disease		
Hypertension	56	56
Coronary Artery Disease	5	5
Congestive Heart Failure	4	4
Chronic Respiratory Disease		
Asthma	7	7
Chronic Obstructive Pulmonary Disease	6	6
Obstructive Sleep Apnea	1	1
Kidney Disease		
Chronic	5	5
End Stage	2	2
Liver Disease		
Cirrhosis	2	2
Hepatitis B	1	1
Hepatitis C	1	1

Elevated IL-6 levels were exhibited in 23% of the subjects as shown in graph 2.

Graph 2: Distribution of study subjects according to the severity of IL-6 level



On presentation Temperature >38ºC was registered in 54%, oxygen saturation <90% in 24%, respiratory rate > 24 breaths/min in 20% and heart rate >100 beats/min was reported in 53% of the subjects. Length of hospital stay was 4.92 days among the subjects. Mean CT severity score was 7.01±6.74. Mortality was revealed among 21% of the subjects. In this study, mean CT severity score was revealed to be more among subjects with elevated IL-6 level as compared to normal IL-6 levels (table 3). When CT severity score was compared according to normal and elevated IL-6 level, significant difference was found, Elevated IL-6 level was reported among 76.19% and 8.86% of the non-survivor and survivor subjects respectively.

When mortality was compared according to normal and elevated IL-6 level, significant difference was found as $p<0.05$.

Table-3 Comparison of IL-6 level according to CT severity score

IL-6	CT Severity Score		t test	p value
	Mean	SD		
Normal (0- 43.5 pg/ml)	3.37	2.95		
Elevated (>43.5 pg/ml)	12.21	6.89	13.04	<0.01*

Discussion

There is a lack of data describing the clinical presentation and prognosis of Indian individuals who had to be

hospitalized because of this condition. Most of the Chinese hospitalized patients in a retrospective cohort study were male with a median age of 56 years; 26 percent needed ICU care; and 28 percent died. Although the Chinese and Indian populations are around the same size, the two are very different when it comes to smoking rates and the incidence of co-occurring disorders. There is limited information on the relevance of IL-6 levels in patients with COVID-19 and their association with CT finding and prognosis, especially in the Indian context. That is why it is a unique study.

Age distribution

The participants included in the study between the age of 18-20 were 4%, between 21-30 age were 10%, between 31-40 were 9% , between 41-50 were 24% , between 51-60 were 27% and 26% of the participants selected were over the of 60 years. Because of this, the majority of our participants were middle-aged or older. Subjects' ages ranged from 18 to 63 in a study by Safiya Richardson et al[4]. Our findings were comparable to these.

Symptoms

Cases of COVID-19 have been described with a wide variety of symptoms, from relatively minor concerns like fever and cough to more severe cases like difficulty breathing. Fever, Coughing, chills, aching muscles, shortness of breath (SOB), sore throat, loss of smell and taste for no apparent reason, diarrhoea, and headache are among the most prevalent signs. When people have pneumonia, their symptoms can start off mild but quickly increase over the course of 5–7 days. About 1 in 6 infected people become critically ill, often with respiratory distress; this rate is highest among the elderly and those with pre-existing illnesses. It was found that 54%, 35%, 24%, 11%, 8%, 6%, 5%, 3%, 2%, and 2% of the individuals in the current research experienced fever, cough, dyspnoea, loss of taste, loss of smell, lethargy, headache, diarrhoea & arthralgia, respectively. Fever was found to be the most common symptom among patients with COVID-19 (82.8%), followed by dry cough (68.3%) and fatigue (33.3%) in a meta-analysis study. A productive cough (28.5%), muscle pain (14.4%), shortness of breath (17%), a sore throat (11.4%), & a headache (10.2%) were also reported. Diarrhoea (4.5%), vomiting (4.1%), nausea (3.2%), rhinorrhoea (3.2%), stomach pain (0.16%), and chest pain (0.11%) were the least prevalent symptoms[5.] Even though many of the same symptoms were reported across trials, the frequency of those symptoms varied considerably. This could be because to a dissimilar study population, study location, or innate immunity.

Co-morbidities

COVID-19 is a new and poorly studied condition, hence there is a dearth of information about it. However, it became clear from the surfacing cases that the presence of comorbidities raises the risk of infection and hence has a significant impact on the prognosis. Current studies and clinical experience indicate that the risk of COVID-19 infection is higher among the elderly, especially those in long-term care facilities, and in those of any age who have significant underlying co-morbid medical conditions. The elderly are a particularly susceptible group, and those who already have a chronic illness, such as diabetes, heart disease, or lung disease, are at much higher risk of developing a major illness and passing away from it. 33%, 40%, 56%, 5%, 4%, 7% & 6% of the participants were found to be obese, diabetic, hypertension, coronary artery disease, congestive heart failure, asthma & COPD respectively. Hepatitis B affected 1%, and hepatitis C affected 1%. Hypertension (15.5%) and diabetes (11.0%) were found to be the most prevalent comorbidities among COVID-19 patients in a study conducted by Hasani WSR et al[6]. Our findings were comparable to these.

Association between Interleukin-6 Levels and CT Severity and Mortality

23% of the people surveyed had abnormally high levels of IL-6. Subjects with high IL-6 levels were shown to have a higher mean CT severity score than those with normal IL-6 levels. A statistically significant difference was discovered between CT severity scores for people with a normal

IL-6 level and those with an elevated IL-6 level. A whopping 76.19% of the non-survivors and 8.86% of the survivors reported having an elevated IL-6 level. Comparing death rates between people with normal and increased IL-6 levels, a statistically significant ($p<0.05$) difference was discovered. A similar observation, an increase in the level of the inflammatory cytokine IL-6, was observed by Chen et al[7]. Higher IL-6 levels at admission have been linked

to increased risk of complications and sickness severity in COVID-19 patients (Liu et al., 2020)[7], however the association between IL-6 and death was not assessed. When it comes to SARS-CoV-2, IL-6 is a major player on the pro-inflammatory scene. It has a role in the cytokine storms caused by COVID-19, which significantly increase vascular permeability and impair organ function[8]. The rapid replication of SARS-CoV-2 causes a "storm" of elevated cytokines like IL-6. Inflammation of the respiratory system and other body systems results from this inflammatory response, leading to acute respiratory distress syndrome (ARDS) or respiratory failure. Estimating IL-6 levels may be a useful way to gauge the seriousness of the disease in people with COVID-19.

This IL-6 level may be useful for gauging the seriousness of a COVID-19 infection, which could then be used to determine the best course of therapy.
In this study, mean CT severity score was found to be more among subjects with elevated IL- 6 level as compared to normal IL-6 level. When CT severity score was compared according to normal and elevated IL-6 level, significant difference was found.

Conclusion

Patients infected with COVID- 19 infection with extremely raised levels of IL- 6 are undoubtedly at increased risk of severe and fatal infection because of increased inflammatory drive, precipitated by cytokine storm, leading to increased risk of mortality. Patients infected with COVID-19 with very high levels of IL-6 are at great risk of developing fatal infection requiring intensive medical care and might need mechanical ventilator support. IL- 6 levels can be referred as predictive marker of the disease severity and mortality in SARS-COV 2 patients and can also be considered as highly accurate laboratory measure to predict impending adverse outcomes.

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