

INTERLEUKIN 6, AN IMPORTANT BIOMARKER OF CYTOKINE STORM IN COVID-19

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Abstract

Background: The Corona virus disease, COVID-19 is characterised by varied clinical course. Most patients experience only mild symptoms and get cured while others develop severe disease with increasing hypoxia ending in acute respiratory failure. In current scenario, disease progression mainly relies on clinical manifestations and some investigations. It has been suggested that one of the possible mechanism underlying rapid progression is a Cytokine storm.

Objective: The study was aimed to early detection of IL-6 that could help in identifying Cytokine storm and direct patients to specific treatment so as to reduce severity of disease.

Material and Methods: This is the study done on patients presented with symptoms of corona virus disease. These patients were examined clinically and investigated according.

Result: 321 patients were found positive for Corona virus out of which 206 males & 115 females. Fever (84%) and cough (71.4%) are the most common symptoms. 167 patients had increased IL-6 who presented with severe symptoms. These patients were followed up strictly and proper treatment given. Out of which maximum patients responded well within 15 days and 27 patients required hospitalisation and were managed.

Conclusion: Early detection of IL-6 along with clinical assessment of the patient condition could help clinician identifying and treating those most at risk of deterioration. Therefore early identification of Cytokine storm and managing hyper inflammation could be a key route to reduce severity and mortality in COVID-19 patients.

Keywords: COVID-19, IL-6, Cytokine storm.

Introduction:

Corona virus disease has become pandemic and is of global concern today. Drastic measures were taken worldwide like quarantine of millions of people. The early detection and control of pro inflammatory response is very important and helpful in early stage of viral infection. Cytokines are

proteins produced by immune cells that are responsible for severe overreactions by immune system of body, known as Cytokine storm which is associated with COVID-19 and other serious illnesses. Emerging data suggest that many patients of COVID-19 may die because of excessive response of their immune system which is characterised by the abnormal release of circulating cytokines.

Cytokine storm is the term used for maladaptive cytokine release in response to infection or some other stimuli. Although its pathogenesis is complex but there is loss of regulatory control of pro inflammatory cytokine production both at local and systemic levels. Severe inflammatory response lead to weak adaptive immune response, resulting in immune imbalance, Therefore circulating biomarkers that represent inflammation and immune state are potential predictors for prognosis of COVID-19 Patients(1). Recent studies showed that some hematologic parameters were clearly altered in COVID-19 patients. The disease progress

rapidly and the mortality becomes high. Clinicians could target new treatment approach by identifying the Cytokine storm. Therefore early detection is very important

Objective:

1. Early detection of IL-6 that could help identifying Cytokine storm
2. Directing patients towards specific treatment that could modify and control their exaggerated immune system response.

Material and Methods

This was study done on patients presenting with symptoms related to Corona virus from December 2020 to March 2021 in an OPD at my clinic in Bhopal. The patients presented with symptoms of Covid 19 were investigated for corona virus disease out of which 321 patients found positive for COVID-19. These patients thoroughly examined relevant investigations like CBC, LFT, RFT, N/L ratio, S ferritin, CRP, D Dimer, IL-6 and radiological investigations like X ray chest and HRCT chest were done whenever and whichever required. Suspected severe patients advised IL-6 along with other relevant investigations.

Patients with raised IL-6 and other inflammatory markers were treated accordingly and followed up.

Results:

Out of 321 patients who were positive for COVID 19, 206 were males and 115 females. Fever (84%) and cough (71.4%) were the two most common symptoms observed. Less common symptoms were weaknesses (21%), headache and body ache (18.4%), diarrhoea (15.6%), loss of appetite (9%) loss of smell(6.7%)and loss of taste (5.6%). Few patients presented with breathlessness. Patients with severe illness were significantly older and with co morbidity than patients with mild to moderate illness. 167 patients presented with severe symptoms and underwent IL-6 along with other relevant investigations like CBC, N/L ratio, S ferritin, CRP, D Dimer LDH,LFT, RFT, X ray chest, HRCT chest etc .patients with raised IL-6 were immediately taken care and treated with appropriate drugs. some of them required hospitalisation . Patients are strictly followed up. Raised IL-6 values are correlated well with other inflammatory markers. Maximum patients responded well within 15 days and IL -6 level started falling and came normal . 27 patients took time and required hospitalisation for 4to 12 weeks.

Discussion:

In patients with COVID-19 severe infection there is exaggerated immune response resulting in excessive cytokine level in blood i.e, Cytokine storm. These massively increased Cytokines, damage the cells and tissue of body instead of supporting body to fight against virus. This is dangerous situation and can be fatal. cytokine test along with a clinical assessment of the patients condition could help doctor identifying and treat those most at risk of deteriorating (2).In our study we also noticed the same.

Cytokine storm is a systemic inflammatory response to inflammation and drugs leading to excessive activation of immune cells and generation of pro inflammatory cytokines (3)

Many cytokines are involved in cytokine storm in COVID-19 patients including IL-6,IL-1,IL-2,IL-10,TNF-alfa and IFN- γ ; however a crucial role seems to of IL-6, whose raised levels in serum have been correlated with respiratory failure, ARDS and adverse clinical outcome . The damage caused by neutrophils, monocytes and T cells results in lung parenchyma changes such as diffuse alveolar damage which leads to ARDS(4).

We also found that Neutrophil to lymphocyte ratio (NLR) significantly raised in COVID-19 Patients, as is also observed by various others studies .Some studies reported that elevated neutrophils and reduced lymphocytes were also correlated with COVID-19 disease severity and death (5-6). A recent study by PengJ et al states that NLR may represents a reliable marker for evaluating severity of Covid 19. It may be understood that a cellular level of immune deficiency state is related with poor prognosis of disease. It is also documented that Glucocorticoid-mediated stimulation of hypothalamic- pituitary adrenal axis might also exacerbate lymphopenia (7).

In our study we found that around half of patients had raised level of IL-6 which is close to study by Z hang Z. L. etall.

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IL -6 is one of the main mediators of inflammatory and immune response initiated by infection or injury and increased levels are found in more than half of patients with COVID-19(8) .we also noticed in our study that females were less commonly affected with COVID-19 than males that too females in reproductive age groups suggesting, possibly oestrogen may have some protective effect. However, due to limited number of patients in the study, much more data is required to verify whether the difference in positive group between males and females was just by chance or could be an important factor to be considered.

We observed in the study that patients who presented with severe respiratory symptoms had significantly increased IL-6 values as is also seen in study by LuR, ZhaoX et all. Cytokine release syndrome is a systemic inflammatory response that can be caused by infection, some drugs and other factors, characterised by a sharp increase in symptomatology including pulmonary inflammation and extensive lung damage.(9). Previous retrospective studies indicated that an elevated level of interleukin-6 was associated with high case fatality of COVID-19 Patients (10).

We advocate repeated measurements of IL-6 as is also advised by the study which says that Repeated measurements of IL -6 can help clinicians in identifying critically ill COVID-19 patients with the highest risk of poor prognosis (11). It is not the one time value but repeated measurements will show the the trend of IL-6 and should be treated accordingly. In our study we also observed deranged parameters of liver and kidney function tests along with raised blood sugar &disturbed lipid profile in many patients as is also observed in number of other studies also .IL-6 can promote T cell population expansion and activation of B cell differentiation, regulate the acute phase response and affect the hormone like properties of vascular disease, lipid metabolism, insulin resistance, mitochondrial activity, neuropsychological behaviour (12).

Our study supports the hypothesis that targeting the cytokine storm induced by virus using anti IL-6 drugs could be a valid therapeutic approach together with supportive care plan for improving outcomes in COVID-19 patients. Of course it should be interpreted with pros and cons and proper collection of sample is also very important to get perfect values of IL-6. As discussed too with clinicians who are treating Covid patients that it's values should be correlated with clinical manifestations and condition of patients.

Conclusion

Vast data suggest and document that there are mild to severe cytokine storms occur in patients of COVID-19.

Therefore treatment of cytokine storm has become an important part in saving COVID-19 Patients. Recent studies suggest that few haematological and radiological parameters are clearly altered in COVID-19 patients, which should also be considered and taken care of. Interleukin-6 plays a crucial role in cytokine release. If this signal transduction pathway of IL-6 is blocked it may be very effective for the treatment of severe COVID-19 patients. Hence we conclude that early detection of increased IL -6 levels and identifying cytokine storm along with managing hyperinflammation could be a key route to reduce severity and mortality in COVID-19 patients.

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