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Interleukin-6 evaluation as a biomarker for disease severity and mortality in covid 19 patients

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Abstract: Background: In pandemic situations, it is essential that the limited resources are used judiciously to achieve most benefits. Prediction of the disease severity at the earliest will help in better allocation, thus, positively affecting prognosis and treatment.
Aim and objective: To investigate patient characteristics and specific biomarker IL 6 as possible early predictors of disease severity of SARS-COV-2 infection.
Material and Methods: Retrospective single-centric record based observational study conducted at intensive care unit of tertiary care hospital in Central , India. 124 consecutive RT-PCR positive coronavirus disease-2019 (COVID-19) adult patients. Demographics, and Inflammatory markers were compared with respect to severity of disease.
Results: The study involved 124 individuals who were affected, out of which 32 patients were categorised as having severe disease, while the remaining 92 patients were categorised as having non-severe disease. Male gender was the predominant demographic in both the severe group. all the symptomps are observed more in frequency among severe group. Immune-inflammatory Markers such as IL-6 The mean value of interleukin-6 in NS-Group patients was 17.6792 27.08 pg/ml, while in S-Group patients it was 97.6515 96.032 pg/ml.
Conclusion: Our study found that high peripheral blood IL-6 levels independently predict COVID-19 severity.IL-6 affected COVID-19 severity and may have been useful for monitoring severe cases. It emphasizes the cytokine storm in COVID-19 progression and suggests IL-6 blockade for severe patients.

Keywords: COVID-19 ARDS; Indian intensive care unit; Inflammatory biomarker; IL6; Severity.

1. Introduction

A group of single-strain RNA viruses known as coronaviruses infect a variety of hosts, including people, and primarily cause respiratory infections [1]. A brand-new betacoronavirus called SARS-CoV-2 first surfaced in China at the end of 2019 and has since spread to nearly 90 million people worldwide, killing more than 1.9 million people and causing a global pandemic (coronavirus disease 2019, COVID-19) [2,3]. Despite the fact that the majority of cases only have mild symptoms, 20% of patients experience severe pathology, including acute bilateral pneumonia that can progress to acute respiratory distress syndrome and multi-organ failure. Age and the presence of comorbid conditions increase the risk of serious illness and death [4].

The first phase of SARS-CoV-2 infection, which is characterized by a high level of viral replication, is then followed by a counterproductive host immune response [5]. Regarding the severity and prognosis, this infection has been divided into three clinical stages [6,7]. Myalgia, a dry cough, a headache, and a subfebrile temperature are examples of mild, non-specific symptoms that characterize stage I, but there are no abnormal laboratory or radiological findings. Cough, high fever, dyspnea, abnormal thoracic imaging, lymphopenia,

and elevated levels of inflammatory markers are the hallmarks of stage II. It is further divided into two groups based on whether hypoxemia is present (IIb) or not (IIa). Stage III culminates in severe respiratory failure with a poor prognosis and clinical signs of a severe systemic inflammatory syndrome. Several inflammatory markers have extremely high values during this stage of the disease, and macrophage activation syndrome may occur.

There have been several COVID-19 treatments tested, which can be categorized into three main groups: medications with an immediate antiviral effect, medications with an immunomodulatory effect, and convalescent plasma neutralizing antibodies [8]. Due to the evidence of quicker clinical improvement and a decrease in mortality in the subset of hospitalized patients receiving oxygen, remdesivir has so far been regarded as the most prominent medication among the first group [9,10]. There are still questions about the treatment's effectiveness and the types of patients who might benefit the most from this therapy, however, as these data conflict with those from other studies [11,12].

A therapeutic approach known as immunomodulation has been recommended due to the difficulty in preventing the spread of viruses and the lack of a proven antiviral treatment [13]. Given the excessive production of proinflammatory cytokines, which is known to be essential in the pathophysiologic process of severe COVID-19 [14], this approach is especially pertinent. In these circumstances, the immune system's loss of negative feedback results in an overabundance of inflammatory cytokines, which has detrimental effects and a poor prognosis. Interleukin-1 (IL-1), interleukin-1RA, IL-2, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-17, IL-18, tumor necrosis factor (TNF-), interferon-gamma (IFN-gamma), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (The fact that some of them, including IL-6, IL-8, and TNF-, are considered independent markers of the severe disease is crucial. For a better comprehension of the pathological process in COVID-19 and consequently for the identification of the most suitable therapeutic targets and timing of drug administration, a deeper understanding of the SARS-CoV-2-induced cytokine storm, including its triggering mechanisms, molecular components, and kinetics, is required. Studies have been published on the potential effects of both specialized (anti-IL-6, anti-IL-1, anti-GM-CSF, and anti-TNF) and generalized (corticosteroids) treatments thus far [13]. Corticosteroids, particularly dexamethasone, have been the most frequently used immunomodulatory treatments for COVID-19 due to mounting evidence of their effectiveness in lowering mortality in hospitalized patients receiving oxygen, particularly those supported by mechanical ventilation. Nevertheless, it is still unclear what dosage, when exactly to administer it, and how long to treat each patient. Additionally, a more focused medication would be preferable, particularly in light of the current immune dysfunction.

IL-6 has been considered to be particularly significant in the pathogenesis of COVID-19 and may be inhibited by currently available medications, out of all the upregulated cytokines that may represent selective therapeutic targets. Controlling several viral infections depends on the inflammatory interleukin IL-6, which is primarily produced by macrophages and T lymphocytes in response to pathogens. While IL-6 at homeostatic levels aids in the healing of infections and tissue lesions, its exaggerated production significantly aids in cytokine storms. IL-6 has been associated with radiologic changes and disease stages in COVID-19 in a positive manner. Additionally, when taken alone or in conjunction with other factors, the potential prognostic value of IL-6 has been investigated in relation to the requirement for mechanical ventilation, mortality, or both. However, the majority of studies only measure IL-6 at the time of patient admission, which may not be a suitable strategy given the dynamic inflammatory process that takes place when SARS-CoV-2 infection occurs. Only tocilizumab (an IL-6 receptor antagonist), which is currently the only medication that is available and specifically inhibits the IL-6 pathway, has a sufficient body of evidence in COVID-19. A recently released meta-analysis on the effectiveness of tocilizumab in those patients found that cumulative evidence from cohort studies suggests an association between tocilizumab and lower mortality, whereas cumulative evidence from randomized controlled trials (RCTs) suggests a risk reduction of mechanical ventilation but no effect on mortality. Elevated IL-6 level was not used as an inclusion criterion in any of the five RCTs that were chosen, only 3 of the 19 cohort studies. Given this information, tocilizumab and other IL-6R antagonists may be used more extensively.

2. Material and methods

To investigate patient characteristics and specific biomarker IL 6 as possible early predictors of disease severity of SARS-COV-2 infection. Retrospective single-centric observational study conducted at intensive care unit of tertiary care hospital in Central , India. 124 consecutive RT-PCR positive coronavirus disease-2019 (COVID-19) adult patients. All sufferers were identified in accordance to diagnosis and treatment guideline issued through MoHFW India and WHO. Data were collected retrospectively from the patient medical records and were limited largely to demography, clinical, and laboratory parameters at the time of admission. Interventions performed were based on independent decision of the physician in charge. We obtained the following data for each patient: age, gender, presenting clinical symptoms, and initial laboratory findings including complete blood count with differential count, and specific biomarker— IL-6, and analyzed with respect to severity of patiebts. Further, we compared these variables between severe and non severe patients.Patients were labeled into, non-severe and severe based on the severity of symptoms. Severe patients have to meet at least one of the following criterions: First, shortness of breath with respiration rate (RR) >30 times/min. Second, oxygen saturation <93% in resting state. The statistical analysis was done using Microsoft excel and free online available website.

3. Results

In this study, we divided patients into two groups based on our criteria: non-severe and severe. A total of 124 affected people took part in the study; 32 patients were classified as having severe cases, and 92 patients were classified as having non-severe cases. Both in the severe group and across the entire study, male sex predominated. With a standard deviation of 2.8 years, the mean age of all patients was 43; the severe group's mean age was 51.47 years, whereas the non-severe group's mean age was 40.02 years. The severe group had a mean BMI of 26.04, which was higher than the non-severe group; the mean BMI was 24.01 with a standard deviation of 3.53. 94% of cases have anorexia, which is followed by headache (88.4%), bitter or loss of taste (87.2%), fatigue (86%), sore throat (80.4%), dizziness and nighttime sweating (79.2%), anxiety (78.4%), cough (77.6%), and dyspnea (71.2%). Myalgia is a symptom that 66.4% of people with fever experience. These other symptoms are seen much more frequently than other gastrointestinal symptoms, (Table 1).

Immune-inflammatory Markers such as IL-6 The mean value of interleukin-6 in NS-Group patients was 17.6792 27.08 pg/ml, while in S-Group patients it was 97.6515 96.032 pg/ml. The observed p-value is.005. 39 patients from the S-Group were discharged from hospital out of a total of 65 patients. Even though 26 people were unlucky and passed away during the treatment, 14 of them have a higher IL-6 level. The NS group as a whole suffers no losses due to mortality (Table 2).

4. Discussion

In the current study, data from 65 patients in the severe category were analyzed, and 26 individuals (40%) in this group died. This mortality rate is comparable to the findings of Chilimuri et al. [1] in New York, where 43% of COVID-19 patients died [1]. The mean age of patients in the severe group (51.47$\pm$5.8 years) was significantly higher than that of the non-severe group (40.0$\pm$23.0), which aligns with the study by Mahase et al. [2] that reported a significantly higher risk of mortality in older individuals compared to younger ones.

Yang et al. [2] also observed a statistically significant difference in mean age between the severe (64.6$\pm$11.2) and non-severe (51.9$\pm$12.9) groups [5]. The primary pathophysiology of severe ARDS is COVID-19 infection, and elderly adults are at a significant risk of developing ARDS. According to the literature [3], older individuals who contract SARS-CoV show stronger immune responses compared to younger individuals. This robust immune response leads to differential gene expression associated with inflammation and decreased expression of type I interferon beta, which had previously been suppressed. Moreover, age-related alterations in T-cell and B-cell activity, along with excessive production of type 2 cytokines, may contribute to uncontrolled virus replication and prolonged pro-inflammatory responses, potentially leading to adverse outcomes.

In this study, only the severe group experienced mortality, which can be attributed to severe lung tissue damage occurring before the onset of dyspnea or low SpO2 levels, thereby increasing the risk of developing ARDS and death. Du RH et al. found that the presence of dyspnea, fatigue, and sputum production was significantly associated with an elevated risk of mortality in COVID-19, which aligns with the findings of our study. Furthermore, in our investigation, the severe group, which had a mortality rate of

Table 1. Demographic and clinical characteristics in patients with COVID-19

Variables		**All patients(n=124)**		**Non-severe group(n=92)**		**Severe group (n=32)**	
Gender	Male	73		53		20	
	Female	51		39		12	
Age (years)		43 ±2.8		40.02 ±3.0		51.47 ±5.8	
Body mass index		24.01±3.53		23.71±3.04		26.04±5.63	
		No.	Percentage	No.	Percentage	No.	Percentage
Symptoms	Fever	84	68	52	56.75	32	100
	Rhinorrhea	71	57.2	50	54.05	21	66.15
	Nasal congestion	53	42.8	42	45.94	11	33.84
	Sorethroat	100	80.4	74	80.54	26	80
	Headache	110	88.4	82	88.64	28	87.69
	Dizziness	98	79.2	65	70.27	29	89.23
	Chill	51	41.2	36	39.45	15	46.15
	Drymouth	50	40.4	30	32.43	20	63.07
	Bittertaste/loss of taste	108	87.2	87	94.59	21	66.15
	Fatigue	107	86	86	93.51	21	64.61
	Anorexia	117	94	87	94.59	30	92.30
	Nightsweat	98	79.2	72	78.37	26	81.53
	Myalgia	82	66.4	62	67.02	21	64.61
	Chest pain	35	28	14	15.67	20	63.07
	Chest distress	30	24	16	17.29	14	43.07
	Shortnessof breath	79	64	48	52.43	31	96.92
	Cough	96	77.6	70	76.21	26	81.53
	Expectoration	31	25.2	20	22.16	11	33.84
	Nausea	43	34.8	31	34.05	12	36.92
	Diarrhea	15	12	9	9.72	6	18.46
	Abdominal pain	22	17.6	19	21.08	2	7.69
	Anxiety	97	78.4	74	80	24	73.84
	Delirium	2	2	1	0.54	2	6.15

Table 2. Immune-inflammatory parameters

Variables	All patients(n=250)	Non-severe group(n=185)	Severeg roup(n=65)	P value
Interleukin-6(pg/ml)	38.472 ±32.521	17.6792 ±27.08	97.6515 ±96.032	0.005

40%, exhibited significantly elevated inflammatory markers such as IL-6. Previous research suggests that the severity of COVID-19 is driven by an abnormal and excessive host immune response. Liu et al. [9], in their subsequent analysis of Channappanavar and Perlman's study from 2017, demonstrated that cytokine storm may contribute to the detrimental effects observed after SARS-CoV-2 infection. IL-6, due to its pleiotropic nature, is believed to play a crucial role in cytokine storm, as argued by Gupta et al. Additionally, Chilimuri et al. [1] found significant associations between mortality and increased levels of D-dimer, C-reactive protein (CRP), and ferritin [1]. Elevated D-dimer levels in COVID-19 cases indicate alterations in the coagulation cascade, which may contribute to the development of severe microembolic disease. Autopsies of COVID-19 patients have revealed microembolic thrombi in the lung and other vital organs, indicating activation of the coagulation system. Matsumoto et al. [14] also reported a significant correlation between disease severity and CRP levels, reflecting the extent of lung lesions and severity of the disease.

5. Conclusion

Our study demonstrated that high level of peripheral blood cytokine IL-6 is independent risk elements for assessing the severity of COVID-19.IL-6 played a pivotal function in the severity of COVID-19 and had a potential value for monitoring the process of severe cases. It reminds us to emphasize the cytokine storm in the progression of COVID-19, and IL-6 blockade treatment possibly a therapeutic strategy for treating the severe patients.

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