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IL-6 AS A POTENTIAL BIOMARKER FOR DISEASE SEVERITY IN COVID-19 PATIENTS

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Abstract

Background: COVID-19 was declared as a pandemic by the WHO on March 11, 2020. It was caused by SARS-CoV-2 and this infection was spreading, posing a serious threat to the health of people worldwide. IL-6 and other components of the inflammatory cascade contribute to host defense against infections. We aim to assess the IL 6 levels in COVID-19-infected patients and their association with the severity and mortality of the disease. **Materials and Methods:** Patients (n=100) who were RT-PCR positive for COVID-19 admitted to the tertiary care centre from March 2021 to June 2021 were enrolled in this study as per inclusion/exclusion criteria. IL-6 levels were analyzed, and SPO2 was recorded on days one, seven, and fourteen. **Result:** Most of the patients were males (70%) with a mean age of 58.71 ± 15.49 years. Mean IL-6 levels at day 1, day 7, and day 14 were 167.11 ± 307.47 pg/ml, 227.55 ± 359.54 pg/ml, and 141.70 ± 427.41 pg/ml respectively. Mean SPO2 levels at day one, day seven, and day fourteen were 93.70 ± 3.34, 93.95 ± 4.48 and 96.83 ± 6.00 respectively. The patients who succumbed were older in age (66.44 ± 12.59 years) and mean IL-6 levels at day one, day seven, and day fourteen were 577.47±636.45pg/ml, 955.00±439.45 pg/ml, and 1490.88±93.43 pg/ml respectively. **Conclusion:** IL-6 levels play an important role in the severity of disease. Patients with older age and higher levels of IL-6 and suffering from hypoxemia are at more risk. IL-6 and hypoxemia can be used as a prognostic-markers among these patients to differentiate the severity of the disease.

INTRODUCTION

In December 2019, SARS-CoV-2 infection was rapidly spreading, posing a serious threat to the health of people worldwide, and the disease it caused was named coronavirus disease (COVID-19) by the International Committee on Taxonomy of Viruses, resulting in the World Health Organization officially declaring it as a pandemic on March 11, 2020.[1] COVID-19 infection has a variable clinical presentation from asymptomatic to milder symptoms, including fever, dry cough, dyspnoea, myalgia, sore throat, and headache, to more severe and emergent manifestations including confusion, chest pain, hypoxemia, pneumonia, and other complications requiring intensive care unit (ICU) admission and mechanical ventilation. Diarrhea, anosmia, and ageusia have also been reported in a few studies and neurologic manifestations.[2]

The diagnosis of the 2019 novel coronavirus can be made by reverse-transcriptase polymerase chain reaction (RT-PCR). Computed tomography (CT) findings include peripheral ground glass densities in which multilobar, lower lobes, and posterior segments are seen and sometimes accompanied by subsegment patchy consolidations.[3] The scientific community is in urgent need of reliable biomarkers related to coronavirus disease 2019 (COVID-19) disease progression, to stratify high-risk patients. Effective biomarkers would be helpful for screening, clinical management, and prevention of serious complications.[4]

Laboratory biomarkers are less expensive, faster, and easier to obtain. As such, they have been the preferred modality to monitor and predict outcomes and prognosis of disease. The SARS-CoV-2 virus enters the host cells and in turn, a cascade of immune response pathways is generated, leading to an increase in the pro-inflammatory cytokine (IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, CCL3, and TNFα) population. This "cytokine storm" attracts neutrophils, lymphocytes, and

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macrophages to the site of infection. The critical condition of COVID-19 patients has also resulted from severe lung injury, cardiovascular injury, and severe liver impairment. All the cytokines mentioned above are crucial and specific to predicting COVID-19 patient mortality. Therefore, it is of utmost importance to conduct a thorough study of the related biomarkers to understand the severity of COVID-19 patients.[5]

Interleukin 6 (IL-6), a multi-functional cytokine (a protein) produced by a range of cells, plays a central role in host defense mechanisms and is involved in the induction of B (lymphocyte) cell differentiation.[6] However, excessive synthesis of IL-6 can lead to a severe acute systemic inflammatory response known as a "cytokine storm," which confers increased risks of vascular hyperpermeability, multiorgan failure, and eventually death. This suggests that higher IL-6 levels may be an important predictor of COVID-19 severity. IL 6 is the most common cytokine reported in SARS CoV 2 infection which is reflected in clinical manifestations, radiological features, management modalities, and outcomes.[7,8]

The present study aims to assess the IL 6 levels in COVID-19-infected patients and to evaluate its association with the severity and mortality of the disease, the requirement for additional management therapies, and outcomes.

MATERIALS AND METHODS

Study Design: Patients with SARS-CoV-2 infection and who were RT-PCR positive for COVID-19 admitted to the tertiary care centre from March 2021 to June 2021 were enrolled in this study. All COVID-19-positive patients referred to the Central Clinical Laboratory (CCL) irrespective of age and gender were included in the study except for those patients suffering from other diseases in which IL-6 levels can be increased. A total of 112 patients were enrolled, but out of these only 100 patients were included in the study as per inclusion/exclusion criteria.

Sample Collection: Throat and nasal swabs samples were used for the detection of COVID-19 infection by RT-PCR in the microbiology laboratory of the institute. The laboratory has been authorized by the Indian Council of Medical Research (ICMR) to conduct the tests for COVID-19. COVID-19-positive patients were referred to the Central clinical laboratory (CCL) for further investigations: Including quantification of IL-6.

IL-6 assessment: The Beckmann Coulter Access IL-6 assay was used for the quantitative determination of IL-6 levels in the serum of COVID-19-positive patients. IL-6 range between 0.00 - 7.00 pg/ml was normal as per the assay kit instructions. We divided the patients into three categories on the basis of IL-6 levels: Mild (IL-6 range: 0.00-20.00 pg/ml), moderate (IL-6 range: 21.01-80.00pg/ml) severe (IL-6 range: > 80.01 pg/ml).

Data analysis: Data was analyzed by EXCEL spreadsheet; results were documented in proportions and percentages. Statistical analysis was done using SPSS v23 software. [IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.]

RESULTS

A retrospective & and observational study was done among 100 patients who tested positive for COVID-19 by RT-PCR on nasopharyngeal swabs and were admitted to the tertiary care hospital. The mean age of patients was 58.71 ± 15.49 years. Most of the patients were males {n=70/100(70%)}. A total of nine (9%) patients were succumbed during the study. A detailed description of the age, gender, oxygen saturation, and IL-6 is given in Table 1. Most of the patients were older in age.

There was not a significant difference between males and females in their age. Patients who succumbed during these 14 days were older in age and these patients had higher IL-6 levels which were continuously increasing even after the treatment. The oxygen saturation levels also were dipping continuously. These patients were critical and were admitted to the ICU with continuous oxygen support and monitoring. All other parameters were also fluctuating among these 9 patients.

There was a decrease in the IL-6 levels from day one to day 14 in all patients except for the nine patients who succumbed during the study. We found that on the day of admission, most of the patients belonged to the moderate (44%) IL-6 category followed by severe (40%) and mild (16%) IL-6 category. IL-6 category on day seven had mixed results which were a little bit unpredictable, while on day 14, most of the patients were under the mild (82%) IL-6 category. A detailed description is given in [Table 2 and Figure 1].
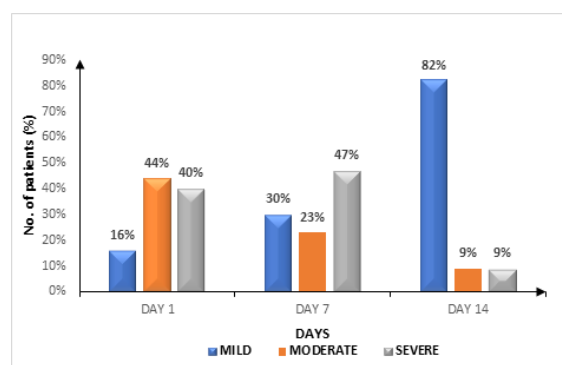
Figure 1.: IL-6 category of COVID-19 patients Day 1, Day 7, Day 14.

Table 1: Mean age, gender, oxygen saturation, and IL-6 values among COVID-19 patients

S.no.	Parameters	All (n=100) (Mean ± S.D)	Males (n=70) (Mean ± S.D)	Females (n=30) (Mean ± S.D)	Dead (n=9) (Mean ± S.D)

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1.	Age (years)	58.71 ± 15.49	58.17 ± 16.35	59.97 ±13.45	66.44 ± 12.59
2.	IL- 6 Day 1 (pg/ml)	167.1 ±307.47	175.10 ± 305.66	148.45 ± 316.11	577.47±636.45
3.	SPO2- Day 1(%)	93.70 ± 3.34	93.55 ± 3.31	94.05 ± 3.44	90.19 ± 4.39
4.	IL- 6 Day 7 (pg/ml)	227.5±359.54	221.81±341.75	240.94 ±403.92	955.00±439.45
5.	SPO2 -Day 7(%)	93.95 ± 4.48	93.80 ± 4.30	94.29 ± 4.92	84.98 ± 2.21
6.	IL- 6 Day 14 (pg/ml)	141.70 ± 427.41	116.28 ± 394.49	201.01± 498.13	1490.88±93.43
7.	SPO2 -Day 14 (%)	96.83 ± 6.00	97.27 ± 5.18	95.79 ± 7.60	78.06 ± 1.791

Table 2: IL-6 category of COVID-19 patients Day one, Day seven, Day 14.

S.no.	IL-6 Category	Day 1 (n=100)	Day 7 (n=100)	Day 14 ((n=100)
1.	Mild	16	30	82
2.	Moderate	44	23	9
3.	Severe	40	47	9

DISCUSSION

This was a single-centre study of 100 patients with COVID-19 infection who were admitted to the hospital. Serum IL-6 levels were measured and oxygen saturation was recorded in all patients at the time of admission, seven days later, and fourteen days later. Most of the patients recovered and responded to treatment, IL-6 levels in all these patients were reduced, and oxygen saturation readings returned to normal as the patients' health stabilized. Several research on IL-6 imply that proinflammatory cytokines like IL-6 are to blame for the acute lung injury seen in COVID-19. Thus, inhibiting this IL-6 route could be the key to reducing COVID-19 lung injury.[9] In our study, IL-6 is associated with the severity of the disease which is also supported by other studies.[1,2,10]

CONCLUSION

In our study, IL-6 levels play an important role in the severity of disease. Patients with older age and with COVID-19 infection have higher values of IL-6 along with lower oxygen saturation levels. So, IL-6 can be used as a prognostic marker among these patients to differentiate the severity of the disease. Also, the oxygen saturation along with IL-6 can help in designing a strategy to deal with the load of COVID-19 patients.

Limitations of the study

This retrospective study was done in a single centre, and only two factors were assessed among COVID-19-positive patients.

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Disclosure Statement

There are no competing interests to declare.

REFERENCES

1. Asghar MS, Haider Kazmi SJ, Khan NA, et al. Poor Prognostic Biochemical Markers Predicting Fatalities Caused by COVID-19: A Retrospective Observational Study From a Developing Country. Cureus. 2020;12(8):e9575. Published 2020 Aug 5. doi:10.7759/cureus.9575

2. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med. 2021;26(3):107-108. doi:10.1136/bmjebm-2020-111536

3. Ozen M, Yilmaz A, Cakmak V, et al. D-Dimer as a potential biomarker for disease severity in COVID-19. Am J Emerg Med. 2021;40:55-59. doi:10.1016/j.ajem.2020.12.023

4. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-399. doi:10.1080/10408363.2020.1770685

5. Bag SS. The Role of Blood Biomarkers to Indicate the Clinical Severity of COVID-19 Prognosis. Biomark J.2020 Vol. 7 No. 1: 1. doi: 10.36648/2472-1646.7.1.70

6. Biswas TK, Biswas M, Bandyopadhyay R. An Overview of Coronavirus COVID-19 with their Pathogenesis and Risk Assessment of the Disease Utilizing Positive Predictive Value of the Clinical and Laboratory Data. Transactions of the Indian National Academy of Engineering. 2020;5(2):417-427. doi:10.1007/s41403-020-00147-1

7. Liu Z, Li J, Chen D, et al. Dynamic Interleukin-6 Level Changes as a Prognostic Indicator in Patients With COVID-19. Front Pharmacol. 2020;11:1093. Published 2020 Jul 17. doi:10.3389/fphar.2020.01093

8. Hu Y, Zhan C, Chen C, Ai T, Xia L. Chest CT findings related to mortality of patients with COVID-19: A retrospective case-series study. PLoS One. 2020;15(8):e0237302. Published 2020 Aug 25. doi:10.1371/journal.pone.0237302

9. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. Rev Med Virol. 2020;30(6):1-9. doi:10.1002/rmv.2141

10. Jones SA, Hunter CA. Is IL-6 a key cytokine target for therapy in COVID-19?. Nat Rev Immunol. 2021;21(6):337-339. doi:10.1038/s41577-021-00553-8.

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