ORIGINAL ARTICLE

Interleukin 6 and Its Correlation with COVID-19 in Terms of Outcomes in an Intensive Care Unit of a Rural Hospital: A Cross-sectional Study

Dhruv Talwar[1], Sunil Kumar[2], Sourya Acharya[3], Nitin Raisinghani[4], Sparsh Madaan[5], Vidyashree Hulkoti[6], Annadatha Akhilesh[7], Shivam Khanna[8], Divit Shah[9], Shubham Nimkar[10]

Abstract

Background: Interleukin 6 (IL-6) encoded by the gene coded as IL 6 acts as a proinflammatory cytokine as well as an anti-inflammatory myokine. It is postulated that IL 6 is associated directly with the severity of coronavirus disease-2019 (COVID-19). Another domain that is thought to predict the severity of COVID-19 is the neutrophil:lymphocyte (N:L) ratio; a higher N:L ratio is postulated to be related to more severe outcomes. Thus, the present study was aimed to establish a correlation of COVID-19 with IL-6 in terms of clinical outcomes. We had also tried to find the relationship between IL-6 and N:L ratio and high-resolution computed tomography (HRCT) score.

Methods: We have conducted a cross-sectional study of 200 patients who were admitted to the intensive care unit (ICU) with reverse transcriptase-polymerase chain reaction (RT-PCR) positive for COVID-19 from January to May 2021. Serum IL-6, N:L ratio, and HRCT chest were conducted on admission.

Result: Out of 200 patients who were admitted to the ICU with COVID-19, while the IL-6 was higher in patients with increased N:L ratio and HRCT score, the association of IL-6 with clinical outcomes in terms of discharged and expired was found to be statistically not significant.

Conclusion: Serum IL-6 was found not to be a potent marker for clinical outcomes in ICU patients in terms of death vs survived. However, the IL-6 levels on admission can be correlated with the computed tomography (CT) severity scores as well as N:L ratio of patients admitted to an ICU.

Keywords: COVID-19, High-resolution computed tomography score, Interleukin 6, Neutrophil:lymphocyte ratio.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24075

Introduction

Ever since its worldwide spread, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has led to profound destruction in the terms of mortality and morbidity and it is showing no signs of slowing down. A major problem among the growing pandemic is management of critically ill patients in the intensive care unit (ICU). Early diagnosis and prediction of severity among the critically ill patients might aid in decreasing mortality as well as the increasing workload on the healthcare professionals and facilities.[1]

It is alarming to note that while experimental therapies are in use, there is no specific treatment for this deadly disease and the treatment mainly has a symptomatic approach toward the patients. It was observed that a higher value of inflammatory cytokines was present in COVID-19 patients pointing toward an inflammatory pathology for the rapid deterioration of COVID-19 patients. Hence, the measurement of these cytokines might help in the prediction of cytokine storm which in turn might lead to hypoxia and further worsening of critically ill patients in the ICU setups. The levels of inflammatory cytokines have been observed to be markedly more in severe cases as compared to moderate cases; hence, the usage of interleukin 6 (IL-6) can help in the prediction of severity of COVID-19 and might aid in planning a therapeutic approach which is more aggressive than usual preventing morbidity and mortality.[2]

A wide range of therapeutic interventions aiming toward the IL-6 are underscan and are undergoing experimental execution throughout the world. In this study, we had tried to establish a connection between COVID-19 with IL-6 in terms of clinical outcomes. We had also tried to find the relationship of IL-6 with neutrophil:lymphocyte (N:L) ratio and high-resolution computed tomography (HRCT) score on admission in an ICU in patients with COVID-19.

[1–4,6–10]Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

[5]Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India

Corresponding Author: Sunil Kumar, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed to be University), Wardha, Maharashtra, India, e-mail: sunilkumarmed@gmail.com

How to cite this article: Talwar D, Kumar S, Acharya S, Raisinghani N, Madaan S, Hulkoti V, *et al*. Interleukin 6 and Its Correlation with COVID-19 in Terms of Outcomes in an Intensive Care Unit of a Rural Hospital: A Cross-sectional Study. Indian J Crit Care Med 2022;26(1): 39–42.

Source of support: Nil

Conflict of interest: None

Methods

Study Population, Setting, and Data Collection

Patients with SARS-CoV-2 infection with reverse transcriptase-polymerase chain reaction (RT-PCR) positive for COVID-19 admitted

© The Author(s). 2022 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

to the ICU of Acharya Vinoba Bhave Rural Hospital, Sawangi, Wardha, from January to May 2021 were enrolled in this study. The enrolment criterion was that IL-6 was done for all the enrolled patients on admission. Two hundred patients were ultimately identified and included in our study.

Exclusion criterion was set as patients who were on steroids previously for any illness as it might effect the N:L ratio. Demographic data, comorbidity information, laboratory results, and outcomes were followed for all these 200 patients.

Laboratory Measurements

Reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 was used for detection of COVID-19 in the throat and nasal swabs. The Clinical Laboratory of Jawaharlal Nehru Medical College, Sawangi, was responsible for the detection of COVID-19 in swabs of these 200 patients. The laboratory has been authorized by the Indian Council of Medical Research (ICMR) for conducting the tests for COVID-19. Serum IL-6 was detected using immunoassay of electrochemiluminescence using Roche Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit for the detection of IL-6 of this kit is 1.5 pg/mL, whereas the upper limit for the detection is 5000 pg/mL without any prior dilution. The normal upper limit for IL-6 is set as 7 pg/mL.

Study Definition

Only severe and critical patients were enrolled in the study. Severe patient was defined as a patient who had shortness of breath with respiratory rate of more than 30 breaths per minute or oxygen saturation of less than 93% on room air at rest or PaO_2/FiO_2 less than 300 mm Hg.

Critical patients were defined as patients who had respiratory failure or shock or had any other organ failure.

Statistical Analysis

Descriptive statistics were applied to summarize the demographic data. Results are reported as medians and interquartile ranges or means with standard deviations or counts and frequency. One-way analysis of variance (ANOVA) was applied to detect significant differences among stratifications. Software SPSS v23 was used to analyze the statistical data.

Result

A total of 200 patients who were positive for COVID-19 by RT-PCR for nasopharyngeal swab and admitted to ICU were enrolled in our cross-sectional study. The demographic characteristics of the patients are mentioned in Table 1. The mean age of patients was 54.44 ± 15.33.148 in years (74.0%). In the patients, males were 148 (74.0%) and females were 52 (26.0%). Out of 200, 30 patients (15%) had a history of diabetes mellitus, 15 (7.5%) had hypertension, and 10 (5%) had both hypertension and diabetes mellitus, whereas patients with a history of other comorbidities such as ischemic heart disease, bronchial asthma, or thyroid disorder were 10 in number (5%).

In the patients with normal levels of IL-6, maximum patients (55%) had CT severity score of 8–17 indicating moderate severity whereas 45% of the patients had CT severity of 0–7 indicating mild severity, and only 20% patients had CT severity of more than 17 indicating severe COVID-19 on HRCT. However, in patients with raised IL-6 levels, maximum patients (91.11%) had CT severity score of >17 indicating severe COVID-19 and 5% patients had CT severity score of 8–17 and only 3.8% patients had CT severity less than 7 indicating minimum patients with mild CT severity category. Sixty percent of the patients with normal IL-6 had normal N:L ratio whereas only 40% had raised N:L ratio, and in patients with raised IL-6 levels, 26.11% had normal N:L ratio, whereas 85% patients had raised N:L ratio. This distribution is shown in Table 2. However, IL-6 was not significantly associated with the outcomes as shown in Table 3 (Figs 1 and 2).

Table 1: Summary of characteristics of patients in the study

Age/gender	*Mean ± S‖Median (IQR)‖Min–Max‖Frequency (%)*	
Age (years)	54.44 ± 15.33‖55.00 (43.00–65.25)‖18.00–89.00	
Gender		
Male	148 (74.0%)	
Female	52 (26.0%)	
Comorbidity	Yes	No
Diabetes mellitus	30 (15.0%)	170 (85.0%)
Hypertension	15 (7.5.0%)	185 (92.5.0%)
Hypertension and diabetes mellitus	10 (5%)	190 (95%)
Others (ischemic heart disease, bronchial asthma, or thyroid disorder)	10 (5%)	190 (95%)

Table 2: Distribution of patients in terms of normal and raised IL-6 and their characteristics in terms of HRCT score and N:L ratio

Parameters	*IL-6 less than 7 pg/L*	*IL-6 more than 7 pg/L*
HRCT score		
0–7	9 (45%)	7 (3.8%)
8–17	11 (55%)	9 (5%)
>17	4 (20%)	164 (91.11%)
N:L ratio		
<3.53	12 (60%)	4047 (26.11%)
3.53	8 (40%)	153 (85%)

Table 3: Association between IL-6 and outcome

Parameters	*IL-6 (pg/mL)*	
Outcomes		
Discharged	965.47 ± 2055.24	
Expired	997.57 ± 1240.51	*p* value: 0.228

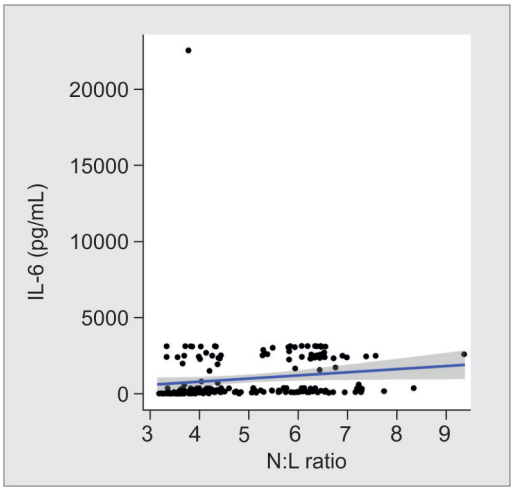

Fig. 1: Association of IL-6 with NL ratio

Nonparametric tests (Spearman's Correlation) were used to explore the correlation between the N:L ratio and IL-6, as at least one of the variables was not normally distributed. There was a moderate positive correlation between N:L ratio and IL-6 (pg/mL), and this correlation was statistically significant ($\rho = 0.48$, $p \leq 0.001$). For every 1 unit increase in N:L ratio, the IL-6 (pg/mL) increases by 207.04 units.

Nonparametric tests (Spearman's Correlation) were used to explore the correlation between the HRCT score and IL-6, as at least one of the variables was not normally distributed. There was a moderate positive correlation between HRCT score and IL-6 (pg/mL), and this correlation was statistically significant ($\rho = 0.47$, $p \leq 0.001$). For every 1 unit increase in HRCT score, the IL-6 (pg/mL) increases by 56.96 units. This is shown in Table 4.

The variable IL-6 (pg/mL) was not normally distributed in the two subgroups of the variable outcomes. Thus, nonparametric tests (Wilcoxon–Mann–Whitney *U*-test) were used to make group comparisons. The mean (SD) of IL-6 (pg/mL) in the outcome of the discharged group was 965.47 (2055.24). The mean (SD) of IL-6 (pg/mL) in the outcome of the expired group was 997.57 (1240.51). The median (IQR) of IL-6 (pg/mL) in the outcome of the discharged group was 207.3 (82.2–2173.52). The median (IQR) of IL-6 (pg/mL) in the outcome of the expired group was 201.45 (98.76–2444.78). The IL-6 (pg/mL) in the outcome of the discharged group was ranged from 0.1 to 22565.1. The IL-6 (pg/mL) in the outcome of the expired group was ranged from 0 to 3135.5. There was no significant difference between the groups in terms of IL-6 (pg/mL) ($W = 2916.000$, $p = 0.228$) as shown in Table 5. Strength of association (point-biserial correlation) of IL-6 with the outcomes was 0.01 (little/no association).

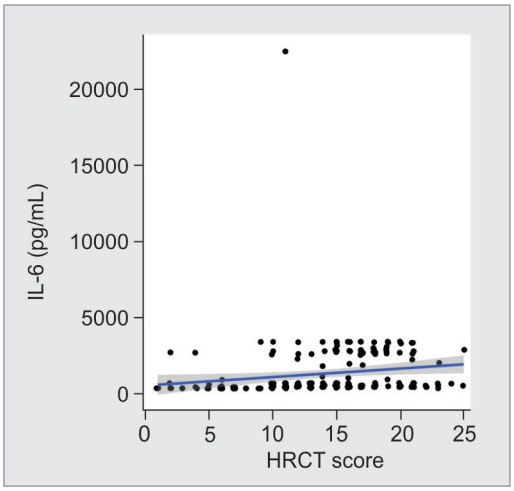

Fig. 2: Association of IL-6 with HRCT score

Table 4: Relationship of HRCT score and N:L ratio with IL-6

Parameters	*IL-6 (pg/mL)*	*p value*
HRCT score	Correlation coefficient (ρ) = 0.47	<0.001
N:L ratio	Correlation coefficient (ρ) = 0.48	<0.001
>7 pg/mL	1136.67 ± 2021.07	

Discussion

This single-center cross-sectional study describes 200 patients who were admitted to the ICU with COVID-19 infection and had severe or critical condition. Serum IL-6 levels were tested in all patients at admission. It is postulated that a multifactorial immune response might be related to the severity of COVID-19. The result of our study supports this postulate by indication of increasing IL-6 levels with an increase in N:L ratio and HRCT score in patients admitted to ICU with COVID-19. Thus, we have established a connection between IL-6 and the other markers of severity of COVID-19 disease in terms of increased HRCT score and high N:L ratio.

It was observed that higher IL-6 levels were related to a higher N:L ratio and a higher CT severity score on HRCT thorax. However, mortality was not related to higher IL-6 levels; therefore, we concluded that high IL-6 levels cannot predict mortality in ICU patients with COVID-19.

Various studies done on IL-6 suggest that proinflammatory cytokines such as IL-6 are responsible for acute lung injury witnessed in COVID-19. Thus, blocking this IL-6 pathway might be the key to minimize lung injury in COVID-19.[3]

However, it should be remembered that IL-6 levels can also be correlated with sepsis and it plays a minimal role in sepsis owing to its short half-life.[4]

Interleukin 6 levels in sepsis were documented to be higher (>1000 pg/mL) which was much more than the subjects of our cross-sectional study.

As a strong proinflammatory cytokine, IL-6 is a potent pyrogen.[5] We postulate that since an increase in IL-6 was associated with raised HRCT score and N:L ratio, blocking the receptor for IL-6 might lead to a decrease in fever spikes and a reduction in respiratory distress in COVID-19 patients. However, this chain of thought is incomplete until double-blinded randomized controlled trials are conducted worldwide for the same. Some studies including meta-analysis have found IL-6 to be associated with increased mortality in COVID-19.[6] The potential of this link between COVID- 19-associated mortality and IL-6 lies in the treatment trials with IL-6 antagonist like monoclonal antibody known as tocilizumab.[7] Tocilizumab has earlier shown promising results in conditions like rheumatoid arthritis, neuromyelitis optica, giant cell arteritis, and cytokine release syndrome.[8] Synthesis of IL-6 is under the control of rid5a and regnase-1 and of microRNAs.[9] Although the expression of IL-6 is in strict control by transcriptional and posttranscriptional mechanisms, if there is dysregulated continual synthesis of IL-6, it turns into a pathological phenomenon leading to inflammation and autoimmunity.[10]

Table 5: Comparison of the two subgroups of the variable outcomes in terms of IL-6 (pg/mL) ($n = 200$)

	Outcome		*Wilcoxon–Mann–Whitney U-test*	
IL-6 (pg/mL)	*Discharged*	*Expired*	*W*	*p value*
Mean (SD)	965.47 (2055.24)	997.57 (1240.51)	2916.000	0.228
Median (IQR)	207.3 (82.2–2173.52)	201.45 (98.76–2444.78)		
Range	0.1–22565.1	0–3135.5		

Unlike various studies which have found IL-6 as a good marker of outcome in COVID-19, we found IL-6 not to be significantly associated with the outcome of death or cure, thus making it a poor marker of chances of mortality in patients with COVID-19 admitted to ICU.

Limitations

Our study has a number of limitations. We have conducted a cross-sectional study only involving severe and critically ill patients of the ICU. We have not included the treatment strategies in this study; hence, we cannot comment on the efficacy of various treatment regimens in COVID-19. Lastly, IL-6 was not repeated serially due to financial constraints as our center is a rural hospital; hence, we could not report the serial IL-6 levels during the recovery of COVID-19 patients.

Conclusion

Through our study, we have concluded that IL-6 levels measured on admission to the ICU cannot be correlated with clinical outcomes of COVID-19 patients in an ICU. This might be the reason behind IL-6 monoclonal antibodies failing to be game-changer drugs in reducing mortality in COVID-19 which they were initially thought to be. IL-6 levels on admission in patients with COVID-19 were found to correlate with CT severity scores and N:L ratios in an ICU. Our study also suggests that the CT severity scores and N:L ratios (which are correlated with IL-6 levels) are probably not useful in predicting outcomes in COVID-19 patients once they are admitted to an ICU. These markers might be useful if checked earlier in the course of illness that requires further studies to verify.

Orcid

Dhruv Talwar https://orcid.org/0000-0003-1643-9109
Sunil Kumar https://orcid.org/0000-0001-9905-4831
Sourya Acharya https://orcid.org/0000-0003-1969-0817
Nitin Raisinghani https://orcid.org/0000-0003-2181-0347
Sparsh Madaan https://orcid.org/0000-0002-1634-9608
Vidyashree Hulkoti https://orcid.org/0000-0002-5257-5813
Annadatha Akhilesh https://orcid.org/0000-0002-6417-075X
Shivam Khanna https://orcid.org/0000-0002-6217-751X
Divit Shah https://orcid.org/0000-0001-8173-0459
Shubham Nimkar https://orcid.org/0000-0003-4748-5116

References

1. Zhang J, Hao Y, Ou W, Ming F, Liang G, Qian Y, et al. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. J Transl Med 2020;18(1):406. DOI: 10.1186/s12967-020-02571-x.
2. Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, et al. Interleukin-6 as prognosticator in patients with COVID-19. J Infect 2020;81(3):452–482. DOI: 10.1016/j.jinf.2020.06.008.
3. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. Rev Med Virol 2020;30(6):e2141. DOI: 10.1002/rmv.2141.
4. Montesarchio V, Parrella R, Iommelli C, Bianco A, Manzillo E, Fraganza F, et al. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. J Immunother Cancer 2020;8(2):e001089. DOI: 10.1136/jitc-2020-001089.
5. Conrozier T, Lohse A, Balblanc JC, Dussert P, Royer PY, Bossert M, et al. Biomarker variation in patients successfully treated with tocilizumab for severe coronavirus disease-2019 (COVID-19): results of a multidisciplinary collaboration. Clin Exp Rheumatol 2020;38(4):742–747. PMID: 32573419.
6. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol 2020;92(11):2283–2285. DOI: 10.1002/jmv.25948.
7. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol 2019;15(8):813–822. DOI: 10.1080/1744666X.2019.1629904.
8. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis 2020;71(15):756–761. DOI: 10.1093/cid/ciaa247.
9. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight 2019;4(4):e123158. DOI: 10.1172/jci.insight.123158.
10. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091. DOI: 10.1136/bmj.m1091.