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A Study of Il-6 as a Predictor of Severity Ofcovid-19 in a Tertiary Care Hospital Inpune

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ABSTRACT

Background:COVID-19 is a clinical entity caused by novel corona virus recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). IL-6 is one of the main mediators of inflammatory and immune response initiated by infection or injury and increased levels of IL-6 in COVID-19 patients.Hence, this study was conducted to determine the IL-6 levels and its association with the severity of COVID-19 and assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

Methods: This was a retrospective observational study conducted in 600 bedded multispeciality tertiary care teaching hospital with availability of 24 hours emergency services. from 28 march 2020 to 1 August 2020, total 79 patients fulfilling the inclusion criteria were recruited. Statistical analysis for significance of association between severity of COVID19 for age, co-morbidity, levels of IL-6 etc. was carried out using Chi-Square test or Fisher's exact probability test.

Results: In this study, mean age of the study subjects was 49.83 years with age range of 21 to 88 years. Mean IL6 levels were significantly increased as per increasing severity of disease.($p<0.05$) Mean IL-6 level was 9.03 ± 6.05 pg/ml in mild, 105.11 ± 58.34 pg/ml in moderate and 516.00 ± 343.69 pg/ml in severe disease.

Conclusion: It was concluded that the IL6 levels were significantly increased with increasing severity of COVID-19. IL-6 was able to detect the severity of COVID-19 with sensitivity of 96.6%, specificity of 94.73%, PPV of 98.3%, NPV of 90% and accuracy 96%.

Keywords: Interleukin 6, COVID-19, SARS-COV-2, Severity of COVID-19

I. INTRODUCTION

COVID-19 is a clinical entity caused by novel corona virus recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] (Maggo 2020) SARS-CoV-2 can be transmitted through the respiratory tract, principally causing respiratory infections and developing severe pneumonia, respiratory failure, and even death in infected patients.[2,3]

The pandemic COVID-19 is clinically characterized byextremely variable course. Though most patients experience only mild symptoms, a significant proportion of patients develop severe disease progression with increasing hypoxia up to acute respiratory distress syndrome (ARDS).[3-5]

Studies by **Mehta et al.**[6]and**Stebbing et al**.[7], has suggested that inflammatory responses play a critical role in the progression of COVID-19. Inflammatory responses produced by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes to induce the release of cytokines and chemokines.[8]

Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly related with the high risks of the development of severe COVID- 19.[9] However, these results remain controversial as there was no significant difference observed in the levels of IL-6, ESR and CRP by other studies.[10]

IL-6 is one of the main mediators of inflammatory and immune response initiated by infection or injury and increased levels of IL-6 are found in more than one half of patients with COVID-19.[11] A meta-analysis by **Azziz et al**.[12], revealed that the mean IL-6 levels were more than three times higher in patients with complicated COVID-19 compared to those with non-complicated disease, and IL-6 levels were associated with mortality risk.[13]

Ulhaq et al., reported that the highly pathogenic SARS-CoV-2 is associated with rapid virus replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress suggesting that evaluation of IL-6 level has potential benefits for assessing the worsening clinical features and disease progression in COVID-19.[14]

However, there is paucity of studies showing association of IL-6 with the severity of COVID-19. Hence, this study was conducted to determine the IL-6 levels and its association with the severity of COVID-19 and assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

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II. MATERIALS AND METHODS

This was a retrospective observational study conducted in 600 bedded multispeciality tertiary care teaching hospital with availability of 24 hour emergency services.Sample size was calculated with 95% confidence interval and 80% power. Sample size came to be 79. After obtaining an approval from institutional ethics committee, using convenience sampling method, from 28 march 2020 to 1 August 2020, total 79 patients fulfilling the inclusion criteria were recruited.

Inclusion criteria: All patients of age more than 18 years with RT-PCR proven symptomatic COVID -19 infection hospitalised at our institution from 28 March 2020 to 1 August 2020. Exclusion criteria:All patients who were treated as COVID - 19 on clinical and radiological findings but were negative for COVID-19 RT-PCR and patients below 18 year of old age.

On the basis of clinical presentation and clinical parameters, (according to clinical management protocol: COVID-19, Government of India) patients were classified into mild, moderate and severe category.

The data related to following investigations was analysed from these patients that were proven to be positive for COVID-19 RT-PCR-IL-6 (Interleukin-6),CBC (Complete blood count),Liver function tests (S.bilirubin, SGPT, SGOT, S. alk.phosphatase),S.Creatinine, BloodUrea,Chest Xray,ECG,Oxygen Saturation on pulse oximeter (SpO2),Arterial Blood Gases (in select individuals),HRCT - Thorax (in select individuals)

Statistical analysis was carried out with the help of Microsoft Excel and Epi info 7.2 software. The description of the data was done in form of arithmetic mean +/- SD (or median) for quantitative data while in the form of frequencies and percentage for qualitative (categorical) data. The significance of association betweenseverity of COVID19 for age, co-morbidity, levels of IL-6 etc were tested using Chi-Square test or Fisher's exact probability test. For comparison of categorical variables (i.e. to examine the associations between qualitative/quantitative variables), ANOVA test was used as needed. P-values of < 0.05 were considered significant. Cohen-Kappa statistic was used to assess the statistical agreement between IL6- levels and the outcome measures.

III. RESULTS

In the present study, 53 (67.1 %) patients were males and 26 (32.9%) were females with mean age of 49.83 years. Maximum 19 (24.1%) study subjects were belonging to age group of 21 - 30 years followed by 15 (19 %) in age group 61-70 years and 12(15.2%) in 31 – 40 year group, 12 (15.2%) in 51 – 60 year group, 8 (10.1%) in age group 41-50 years. Age group 81-90 years had minimum 6 (7.6%) study subjects.All the study subjects reported symptoms of cough, fever and chest pain.Out of 79 study subjects, only 50 (63.3%) reported symptoms of dyspnoea.Out of 79 study subject, 47(59.5%) had one or more comorbidities. Among these 47, 39(82%) had diabetes, 27(57%) had Hypertension, 2(4.2%) had Rheumatoid Arthritis while 1 (2.12%) patient suffered from Chronic Liver Disease.

Mean respiratory rate and heart rates both increased as per increasing severity of these. The difference was found to be significant with p value <0.05 for both respiratory rates and heart rates.Out of 79 study subjects , 25 (31.6%) had normal chest x ray while 54(68.4%) had abnormal chest x ray.Out of 79 study subject, 62(78.5%) had changes in HRCT. Among these 62, 62(100%) had ground glass opacities, 17(27.4%) had consolidation, 46(74.1%) had bilateral infiltrations. Mean serum bilirubin, SGOT, SGPT, Alkaline phosphate were increased as per increasing severity of disease.The difference was found to be significant with p value<0.05 for all the four variables.

Mean Sr. creatinine and urea were increased as per increasing severity of disease.The difference was found to be nonsignificant for Sr. creatinine with p value>0.05 and significant for urea with p value<0.05. Mean WBC increased as per increasing severity and mean lymphocytes decreased as per increasing severity.The difference was found to be significant for WBC and lymphocytes with p value<0.05.Mean oxygen saturation decreased as per increasing severity of the disease.The difference was found to be significant with p value<0.05.

18 (22.8%) subjects were mechanically ventilated out of 79. There was significant relation between severity of disease (Mild and Moderate Vs. Severe) and Age of study subjects (age 20-60 years Vs. 61-90 years) and presence of comorbidities.(P<0.05). As per Cohen's kappa Statistics, the value of Cohen's Kappa is 0.2 which suggests that there is no interrater reliability between the two variables i.e Clinical severity and IL-6 value 201 pg/ml.

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Table 1- Assessment of level of IL6 according to severity of disease.

Study Subjects	**Severity of Disease**			
	Mild (Mean ± SD)	**Moderate** (Mean ± SD)	**Severe** (Mean ± SD)	**P value**
IL 6	9.03 ± 6.05	105.11 ± 58.34	516.00 ± 343.69	0.0001

D.f :2 Chi sq test p value 0.0001

Table 2- Association between severity of disease (Mild and Moderate Vs. Severe) and level of IL6.

		Severity of the disease		**P Value**
		Mild and Moderate	**Severe**	
IL 6 values	**IL 6 values < 201**	58(a)	1(b)	<0.0000001*
	IL 6 values ≥ 201	2 (c)	18(d)	
Total		60	19	

Df: 1
*Fischer's Exact Test P Value 0.00001
From table 2, the following parameters were derived:
Sensitivity = 96.6 %, Specificity= 94.73 %, Positive Predictive Value (PPV)= = 98.3 %, Negative Predictive Value (NPV)= 90 %, Accuracy = 96 %

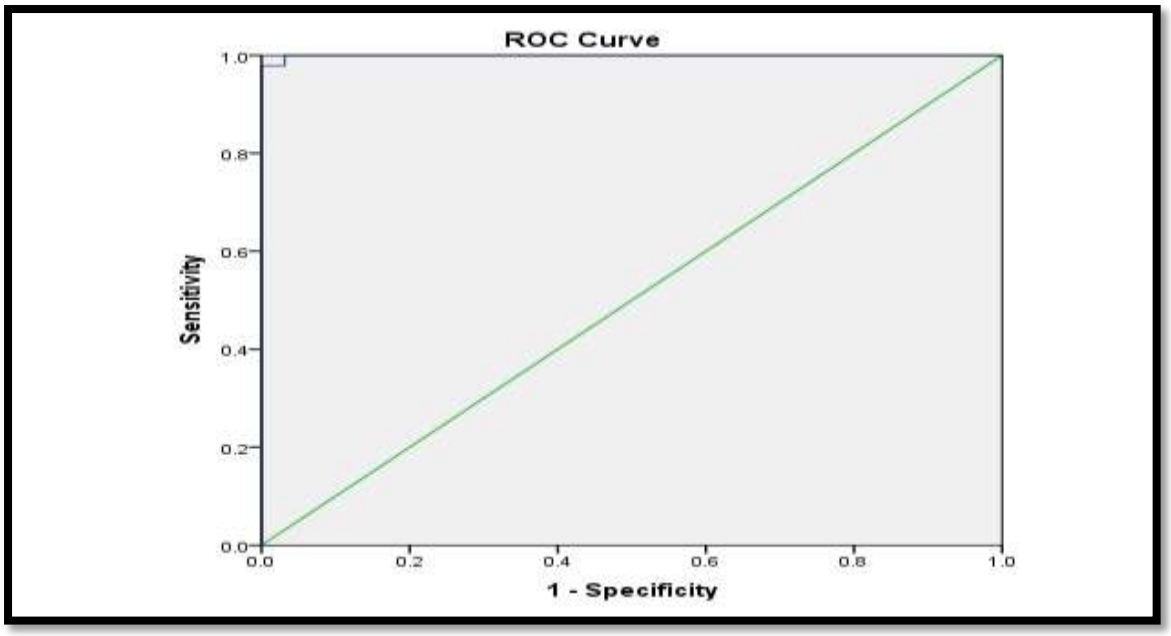

Figure 1: Receiver operating characteristic (ROC) curve for IL6 for identifyingmild COVID-19.

Figure 1 depicts that, Area under the curve (AUC) was 0.99 suggesting that assessing IL 6 level is a good marker of identifying the severity of disease. Using the ROC Curve data and coordinates of the curve for the present data set, we suggest a cut-off value less than or equal to 35 pg/mL for identifying patients with mild COVID-19.

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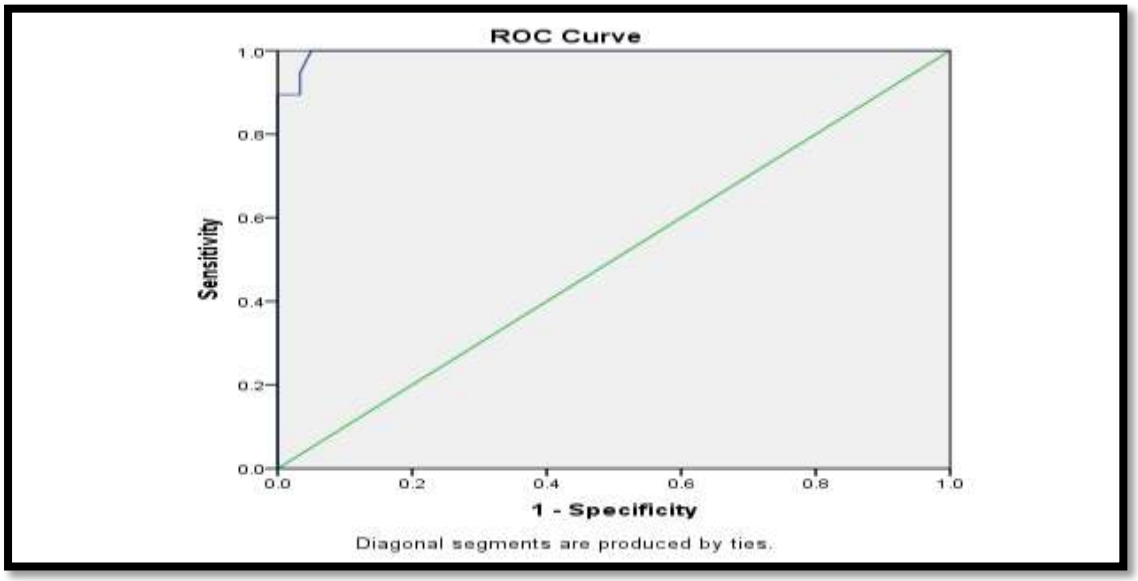

Figure 2: ROC curve for IL6 for identifying severe COVID 19

Figure 2 depicts that, For identifying the level of IL 6 that acts as best cut off to define the disease as severe, when ROC curve was plotted. AUC comes to be 0.996 which suggest that IL 6 vales is a good marker of identifying the severity of disease.Using the ROC Curve data and coordinates of the curve, we suggest a cut-off value greater than or equal to 201 pg/mL for identifying patients with severe COVID-19.

IV. DISCUSSION

In the present study, gender wise distribution of study subjects was made. 53 (67.1 %) were males and 26 (32.9%) were females showing male predominance. In this study, mean age of the study subjects was 49.83 years with age range of 21 to 88 years. Maximum 19 (24.1%) study subjects were belonging to age group of 21 - 30 years followed by 15 (19 %) in age group 61-70 years and 12(15.2%) in 31 – 40 year group, 12 (15.2%) in 51 – 60 year group, 8 (10.1%) in age group 41-50 years. Age group 81-90 years had minimum 6 (7.6%) study subjects. This was similar to study by **Grifoni et al**.[13], who tested the role of IL-6 as risk factor for negative outcome compared with other demographic and clinical variables or biomarkers collected at hospital admission.

In our study, all the study subjects reported symptoms of cough, fever and chest pain.Out of 79 study subjects, only 50 (63.3%) reported symptoms of dyspnoea.In consistency with our findings, in a study by **Durrani et al.[15],** which was conducted to analyze Chest X-ray findings in COVID 19 positive patients, Cough was the predominant presenting complaint in 67% patients, followed by fever in 60%, Shortness of breath 37%, sore throat six 20%, loss of sense of smell and taste four 13% and GIT complaints in three 10% patients.

In the present study, out of 79 study subjects, 47(59.5%) had one or more comorbidities. Among these 47, 39(82%) had diabetes, 27(57%) had Hypertension, 2(4.2%) had Rheumatoid Arthritis while 1 (2.12%) patient suffered from Chronic Liver Disease.Similarly, in a study by **Durrani et al**.[15], only 27% patients of COVID-19 were without any comorbidity.

In the present study, mean IL6 levels were significantly increased as per increasing severity of disease.($p<0.05$) Mean IL-6 level was 9.03 ± 6.05 pg/ml in mild, 105.11 ± 58.34 pg/ml in moderate and 516.00 ± 343.69 pg/ml in severe disease.

In relation with our study, study by **Herold et al.[16]**, reported that IL-6 level at assessment was strongly associated with respiratory failure in COVID-19 patients. Also, another study by **Herold T. et al.[16]** reported that the risk of respiratory failure for patients with IL-6 levels of ≥ 80 pg/ml was 22 times higher compared to patients with lower IL-6 levels.Meta-analysis by **Aziz et al**.[12], reported that the mean serum IL-6 was 56.8 (41.4-72.3 pg/mL) and 17.3 pg/mL (13.5-21.1 pg/mL) for severe and nonsevere COVID-19 group, respectively.

In our study, for identifying the level of IL-6 that acts as best cut off to define the disease as mild, ROC curve was plotted. Area under the curve came out to be 0.99 suggesting that IL-6 value is a good marker of identifying the severity of disease. Using the ROC Curve data and coordinates of the

curve for the present data set, we suggest a cut-off value less than or equal to 35 pg/mL for identifying patients with mild COVID-19. Also, for identifying the level of IL-6 that acts as best cut off to define the disease as severe, ROC curve was plotted. Area under the curve came out to be 0.996 which suggest that IL-6 vales is a good marker of identifying the severity of disease. Using the ROC Curve data and coordinates of the curve, we suggest a cut-off value greater than or equal to 201 pg/mL for identifying patients with severe COVID-19.

In accordance with our study, in a study by **Grifoni et al.[13],** ROC curve AUC was 0.75 (95% CI 0.64–0.84) for IL-6 as predictor of progression to severe COVID-19. From their study, it was concluded that IL-6 levels at hospital admission are good prognosticator for the combined endpoint progression to severe disease and/or in-hospital mortality and IL-6 seems to be the best prognosticator for negative outcome. In consistency with our results, study by **Herold et al.[16],** reported cutoffs for IL-6 level as >35 pg/mL at presentation and the risk for respiratory failure in patients with IL-6 levels exceeding 210 pg/mL was 100%.

Similarly, **Liu et al.[17],** in their study reported that ROC analysis showed that the elevated IL-6 group had the largest areas under the ROC curve (AUCs) of 0.870 for disease severity. IL-6 at a cutoff of 86 $pg \cdot mL^{-1}$ was the most specific (0.89) for predicting death in COVID-19 in a study by **Laguna et al.[18]**However, meta-analysis by **Aziz et al.[12],** which was conductedto compare IL-6 in severe and nonsevere patients suggested a cut-off of more than 55 pg/mL for identifying patients at high risk of severe COVID-19 and a cut-off of more than 80 pg/mL can be used for identifying patients at high risk of mortality, which was not consistent with our study.

In the present study, there was significant relation between severity of disease (Mild and Moderate Vs. Severe) and level of IL6. In our study, there was no interrater reliability between the two variables i.e Clinical severity and IL-6 value 201 pg/ml. IL-6 was able to detect the severity of COVID-19 with sensitivity of 96.6%, specificity of 94.73%, PPV of 98.3%, NPV of 90% and accuracy 96%.Similarly, in a study by **Herold et al.[16],**sensitivity and specificity of IL-6 to detect patients at risk for respiratory failure were 84% and 63% respectively.

Limitations: It was a retrospective observational study, due to retrospective nature of this study the inferences derived require further validation with the help of cohort studies and randomized controlled trials (RCTs).Sample size was small, further studies with larger sample sizes are needed to validate our findings.

V. CONCLUSION

It was concluded that the IL6 levels were significantly increased with increasing severity of COVID-19.IL-6 was able to detect the severity of COVID-19 with sensitivity of 96.6%, specificity of 94.73%, PPV of 98.3%, NPV of 90% and accuracy 96%.Thus, it is rational to perform initial evaluation of IL-6 level upon hospital admission of COVID-19 patients considering its potential benefits to assess worsening clinical features and disease progression in COVID-19.

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