

## Original Research Article

# Study correlating interleukin-6 levels with demographics, symptomatology and clinical outcomes among COVID-19 patients

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## ABSTRACT

**Background:** The objective of this study was to estimate the Interleukin-6 levels of COVID 19 patients and to find any associations between Interleukin-6 levels and age, gender, co-morbidities, symptoms, clinical outcomes and other biochemical parameters among COVID19 patients.

**Methods:** It was a cross sectional observational study conducted on 150 patients admitted to Victoria Hospital, Bangalore medical college from May 2020 to September 2020. Case record form with follow up chart was used to record the relevant demographic details, clinical data including symptoms, co-morbid conditions and various laboratory data. COVID 19 infection was diagnosed by RTPCR technique and severity of COVID-19 disease was classified according to WHO guidelines and guidelines laid by Ministry of Health and Family Welfare, India. Interleukin-6 levels were correlated with the above parameters.

**Results:** It was found that IL6 was elevated and found to be statistically significant with the presence of co-morbid conditions including Hypertension, with the presence of symptoms including fever, cough, breathlessness, with the severity of the disease, with the presence of intubation, with the mortality of the illness and strong association with neutrophil count, C-reactive protein, Ferritin and Neutrophil-Lymphocyte ratio.

**Conclusions:** IL6 can be used as a viable biomarker for knowing the severity of COVID19, to predict the outcome and prognosis of the patient and associations with various presenting symptoms, co-morbid conditions and other laboratory values.

**Keywords:** COVID-19, IL-6, Clinical outcome, Co-morbidity

## INTRODUCTION

Coronavirus disease known as COVID-19 is an infectious disease caused by a group of viruses called corona virus. Patients affected with this infection will experience mild to moderate respiratory illness and may go on to recover without any special treatment in most of the cases.<sup>1</sup> However, a fraction of them with underlying risk factors such as hypertension, diabetes, cardiovascular disease and obesity will go on to develop a more severe form of disease requiring intensive care.<sup>2</sup>

The human to human transmission of this virus has been attributed largely to coughing, sneezing and the spread of respirating droplets or aerosols.<sup>3</sup> The initial symptoms of this infection largely are fever, dry cough, shortness of breath and tachypnoea.<sup>4</sup> Other symptoms include sore throat, sneezing, nasal congestion, sputum production, anosmia and dyspepsia, rash on the skin, or discolouration of fingers or toes, and viral conjunctivitis.

Biochemical studies reveal increases in lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), C-reactive protein (CRP),

creatinine kinase (CK), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, D-dimer level, procalcitonin, urea, and creatinine.<sup>5</sup>

COVID-19 is responsible for wide range of clinical syndromes ranging from asymptomatic illness to severe pneumonia with acute respiratory distress syndrome requiring intubation. And has been implicated due to host inflammatory response depending on excessive production of inflammatory cytokines such as Interleukin 6 and TNF – alpha.<sup>6</sup>

And therefore, in this study we want to further demonstrate an association between Interleukin 6 levels with various clinical outcomes, symptomatology and patient demographics.

### ***Aims and objectives of the study***

To estimate the interleukin-6 levels of COVID-19 patients. To find an association between Interleukin-6 levels with age, gender, co-morbidities, symptoms, clinical outcomes and other biochemical parameters among COVID19 patients.

## **METHODS**

The study was conducted in Victoria hospital which is attached to Bangalore medical college and Research Institute, a tertiary care hospital in the region. Approval and clearance for the study was obtained from institutional ethics clearance. Patients were enrolled in the study after obtaining due informed consent based on inclusion criteria. Patients who came under exclusion criteria were excluded from the study. The study was conducted for a period of 5 months from May 2020 to September 2020. The imperative of informed consent is waived in light of the anonymous and observational character of the study. The study population was 150.

Case record form with follow up chart was used to record the relevant demographic details, clinical data and laboratory data.

COVID-19 infection was diagnosed by RTPCR technique. Patients underwent biochemical investigations including Interleukin-6 levels, hemogram, C-Reactive protein, Ferritin levels. Co-morbid conditions of patients including Diabetes, Hypertension, Ischemic heart disease, Chronic obstructive pulmonary disease, obstructive sleep apnoea, hypothyroidism were noted under past medical history.

Patients with relevant medical history were subjected to above biochemical investigations and their severity of COVID-19 disease were classified according to WHO guidelines and guidelines laid by Ministry of Health and Family Welfare, India.

The IL-6 levels of patients were then correlated with the above parameters to identify a relationship.

### ***Inclusion criteria***

Age more than 18 years. Patients who tested RTPCR positive for COVID19.

### ***Exclusion criteria***

Age less than 18 years. Patients who refused to give consent for the study.

### ***Statistical analysis***

Statistical Package for social sciences (SPSS) version 20. [IBM SPASS statistics (IBM corp. Armonk, NY, USA released 2011)] will be used to perform the statistical analysis.

Data will be entered in the excel spreadsheet. Descriptive statistics of the explanatory and outcome variables will be calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables. Inferential statistics like Chi-square will be applied for categorical variables. Inferential statistics like Kruskal Wallis test was applied to compare the quantitative data among the groups. Spearman's correlation was applied to correlate IL6 with quantitate variables. The level of significance is set at 5%.

Any other necessary tests found appropriate will be dealt at the time of analysis based on data distribution.

## **RESULTS**

Data was subjected to normalcy test (Shapiro-wilk test). Data showed non normal distribution. Hence non-parametric tests (Kruskal-wallis, Spearman's correlation) were applied.

As given in Table 1, out of 150 (100%) subjects, 13 (8.7%) subjects had IL-6 in the range of 0-5.9, 56 (37.3%) subjects had IL-6 in the range of 6 to 60 and 81 (54%) subjects had IL-6 above 60. Out of 13 subjects having IL-6 between 0 to 5.9, maximum subjects were in the age range of 36 to 45 years- 5 (3.3%). In subjects having IL-6 between 6 to 60, maximum subjects were in the age range of 46 to 55 years-18 (12%). Similarly, subjects having IL-6 more than 60 were higher in the age range of 46 to 55 years- 25 (16.7%). Chi-square test was applied to find the association between age and IL-6.

Chi-square test showed no statistical significant association between age and IL-6 ( $\chi^2 = 11.21$ ;  $p = 0.511$ ).

As given in Table 2, out of 150 (100%) subjects, 54 (36%) were females and 96 (64%) were males. Maximum females and males were having IL-6 more than 60. Chi-square test was applied to find the association between gender and IL-6.

Chi-square test showed no statistical significant association between gender and IL-6 ( $c^2= 1.03$ ;  $p=0.59$ ). As given in Table 3, IL-6 was more than 60 in subjects having co-morbidities like diabetes, hypertension, IHD, OSA and hypothyroidism whereas IL-6 was in between 6

to 60 in subjects having COPD. Chi-square test was applied to find the association between co-morbidities and IL-6. Chi-square test showed statistical significant association between hypertension and IL-6 ( $c^2= 9.76$ ;  $p=0.008$ ).

**Table 1: Distribution of the subjects based on age.**

Age		Interleukin-classified			Total
		0 to 5.9	6 to 60	More than 60	
15 to 25	Count	1	1	3	5
	%	0.7	0.7	2.0	3.3
26 to 35	Count	2	4	6	12
	%	1.3	2.7	4.0	8.0
36 to 45	Count	5	10	14	29
	%	3.3	6.7	9.3	19.3
46 to 55	Count	1	18	25	44
	%	0.7	12.0	16.7	29.3
56 to 65	Count	4	11	18	33
	%	2.7	7.3	12.0	22.0
65 to 75	Count	0	7	11	18
	%	0.0	4.7	7.3	12.0
Above 75	Count	0	5	4	9
	%	0.0	3.3	2.7	6.0
Total	Count	13	56	81	150
	%	8.7	37.3	54.0	100.0%
Chi-square value- 11.21					
P value-0.511					

**Table 2: Distribution of subjects based on gender.**

Gender		Interleukin-classified			Total
		0 to 5.9	6 to 60	More than 60	
Females	Count	4	23	27	54
	%	2.7%	15.3%	18.0%	36.0%
Males	Count	9	33	54	96
	%	6.0%	22.0%	36.0%	64.0%
Total	Count	13	56	81	150
	%	8.7%	37.3%	54.0%	100.0%
Chi-square value- 1.03					
P value-0.59					

**Table 3: Distribution of the subjects based on co-morbidities.**

Co-morbidities		Interleukin-classified			Total	Chi-square value	P value
		0 to 5.9	6 to 60	More than 60			
Diabetes	Count	3	18	33	54	2.09	0.35
	%	2.0	12.0	22.0%	36.0%		
Hypertension	Count	1	27	44	72	9.76	0.008*
	%	0.7	18.0	29.3%	48.0%		
IHD	Count	0	10	10	20	3.06	0.21
	%	0.0	6.7	6.7%	13.3%		
COPD	Count	1	6	4	11	1.62	0.44
	%	0.7	4.0%	2.7%	7.3%		

Continued.

Co-morbidities		Interleukin-classified			Total	Chi-square value	P value
		0 to 5.9	6 to 60	More than 60			
OSA	Count	0	3	6	9	1.15	0.56
	%	0.0	2.0%	4.0%	6.0%		
Hypothyroid	Count	1	4	7	12	0.1	0.95
	%	0.7	2.7%	4.7%	8.0%		

\*Significant

Table 4: Distribution of the subjects based on presence or absence of co-morbidities.

Co-morbidities		Interleukin-classified			Total
		0 to 5.9	6 to 60	More than 60	
Present	Count	5	40	58	103
	%	3.3%	26.7%	38.7%	68.7%
Absent	Count	8	16	23	47
	%	5.3%	10.7%	15.3%	31.3%
Total	Count	13	56	81	150
	%	8.7%	37.3%	54.0%	100.0%
Chi-square value- 6.03					
P value-0.049*					

\*Significant

Table 5: Distribution of the subjects based on symptoms.

Symptoms		Interleukin-classified			Total	Chi-square value	P value
		0 to 5.9	6 to 60	More than 60			
Fever	Count	4	28	54	86	7.86	0.02*
	%	2.7%	18.7%	36.0%	57.3%		
Cough	Count	2	35	58	95	15.27	0.00*
	%	1.3%	23.3%	38.7%	63.3%		
Breathlessness	Count	3	33	65	101	19.51	0.00*
	%	2.0%	22.0%	43.3%	67.3%		
Myalgia	Count	3	21	36	60	2.36	0.3
	%	2.0%	14.0%	24.0%	40.0%		
Fatigue	Count	2	17	28	47	1.95	0.37
	%	1.3%	11.3%	18.7%	31.3%		
Sore throat	Count	1	13	8	22	5.25	0.07
	%	.7%	8.7%	5.3%	14.7%		
Headache	Count	0	10	15	25	2.85	0.24
	%	0.0%	6.7%	10.0%	16.7%		

\*Significant

Table 6: distribution of the subjects based on presence or absence of symptoms

Symptoms		Interleukin-classified			Total
		0 to 5.9	6 to 60	More than 60	
Symptomatic	Count	5	47	78	130
	%	3.3%	31.3%	52.0%	86.7%
Asymptomatic	Count	8	9	3	20
	%	5.3%	6.0%	2.0%	13.3%
Total	Count	13	56	81	150
	%	8.7%	37.3%	54.0%	100.0%
Chi-square value- 33.00					
P value-0.00*					

\*Significant

**Table 7: Distribution of the subjects based on severity, intubation and outcome.**

			Interleukin-classified			Total	Chi-square value	P value
			0 to 5.9	6 to 60	More than 60			
<b>Severity</b>	Critical	Count	0	1	42	43	91.25	0.00*
		%	0.0%	.7%	28.0%	28.7%		
	Mild	Count	11	21	0	32		
		%	7.3%	14.0%	0.0%	21.3%		
	Moderate	Count	1	20	13	34		
		%	.7%	13.3%	8.7%	22.7%		
	Severe	Count	1	14	26	41		
		%	.7%	9.3%	17.3%	27.3%		
<b>Intubation</b>	No	Count	13	52	13	78	91.39	0.00*
		%	8.7%	34.7%	8.7%	52.0%		
	Yes	Count	0	4	68	72		
		%	0.0%	2.7%	45.3%	48.0%		
<b>Outcome</b>	Death	Count	0	4	69	73	94.21	0.00*
		%	0.0%	2.7%	46.0%	48.7%		
	Discharge	Count	13	52	12	77		
		%	8.7%	34.7%	8.0%	51.3%		

\*Significant

**Table 8: comparison of the clinical parameters based on interleukin-6 using Kruskal-Wallis.**

	0 to 5.9		6 to 60		more than 60		P value
	Median	IQR	Median	IQR	Median	IQR	
<b>TC</b>	7500.0	2850.0	8100.0	6563.0	10000.0	7350.0	0.134
<b>Neutrophils</b>	69.0	18.0	77.5	17.0	86.0	10.0	0.00*
<b>Lymphocytes</b>	25.0	17.0	15.0	15.0	8.0	10.0	0.00*
<b>Monocytes</b>	6.0	5.0	6.0	7.0	4.0	4.0	0.126
<b>CRP</b>	15.6	116.6	65.4	79.2	159.0	157.9	0.00*
<b>Ferritin</b>	301.8	455.6	711.5	609.4	1598.0	878.3	0.00*
<b>Total days in hospital</b>	9.0	4.0	12.0	8.0	10.0	9.0	0.012*
<b>ANC</b>	5037.0	2657.5	5843.0	6042.0	8265.0	7478.0	0.005*
<b>NLR</b>	2.8	2.1	4.9	6.1	10.0	12.6	0.00*
<b>TC-ANC</b>	2376.0	1910.0	2020.0	1531.5	1287.0	1174.0	0.00*
<b>d-NLR</b>	2.2	1.3	3.4	3.3	6.1	5.0	0.00*
<b>NMR</b>	10.4	18.4	12.8	20.2	21.5	22.8	0.009*
<b>LMR</b>	4.5	6.1	3.0	2.5	2.2	1.7	0.00*
<b>ALC</b>	2000.0	1709.5	1218.5	1154.8	832.0	848.5	0.00*
<b>LCRPR</b>	88.0	1345.7	20.7	36.4	5.7	4.9	0.00*
<b>CRP-IL6 ratio</b>	5.8	44.1	2.5	4.1	0.7	0.8	0.00*

\*Significant

**Table 9: Spearman's correlation between interleukin 6 and clinical parameters.**

Variables	Interleukin-6
<b>Age</b>	r value
	0.029
	P value
	0.725
<b>TC</b>	r value
	0.085
	P value
	0.304
<b>N</b>	r value
	0.411
	P value
	0.000*
<b>L</b>	r value
	-0.423

Continued.

Variables	Interleukin-6
	P value
	0.000*
	r value
	-0.103
Monocytes	P value
	0.208
CRP	r value
	0.581
	P value
	0.000*
Ferritin	r value
	0.642
	P value
	0.000*
Total days in hospital	r value
	-0.107
	P value
	0.191
ANC	r value
	0.177
	P value
	0.030*
NLR	r value
	0.417
	P value
	0.000*
TC-ANC	r value
	-0.322
	P value
	0.000*
d-NLR	r value
	0.406
	P value
	0.000*
NMR	r value
	0.197
	P value
	0.016*
LMR	r value
	-0.344
	P value
	0.000*
ALC	r value
	-0.391
	P value
	0.000*
LCRPR	r value
	-0.647
	P value
	0.000*

\*Significant.

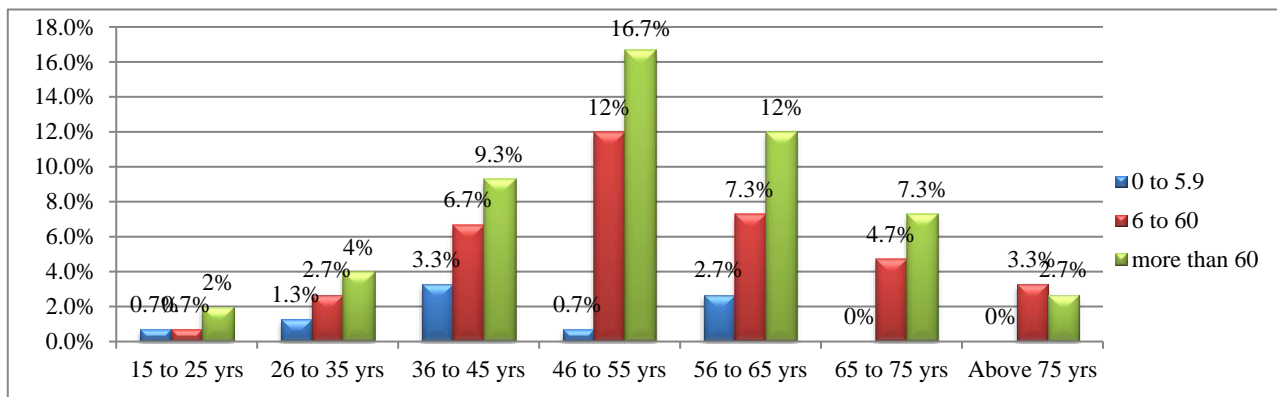


Figure 1: Distribution of subjects based on age.

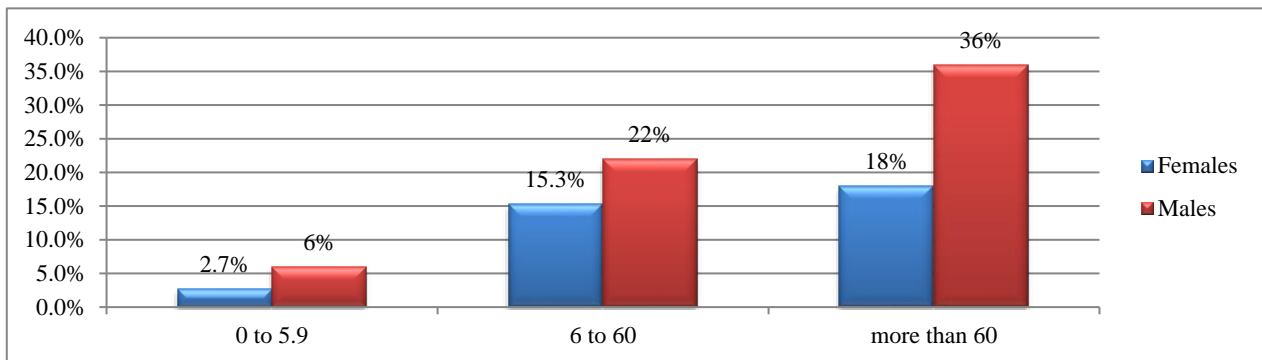
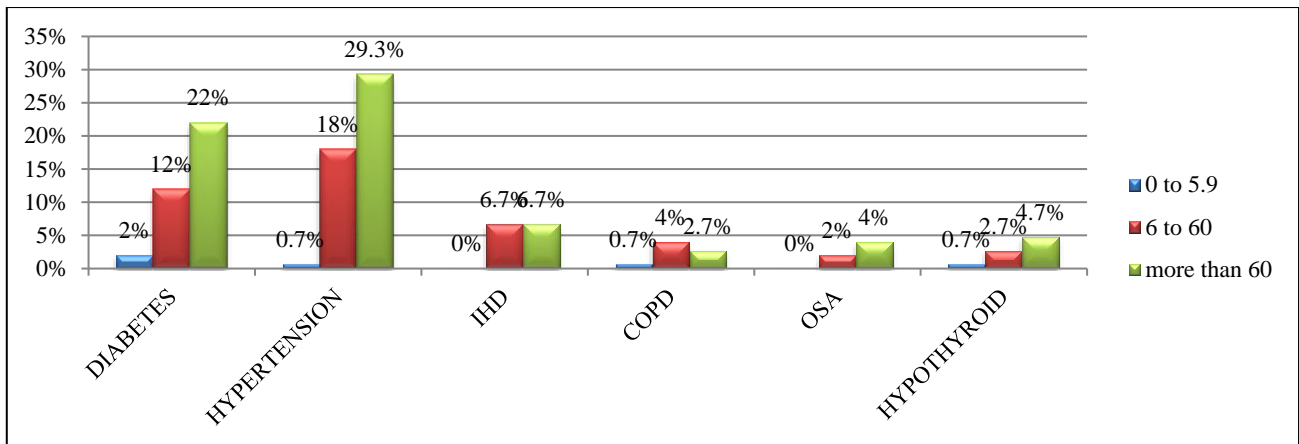
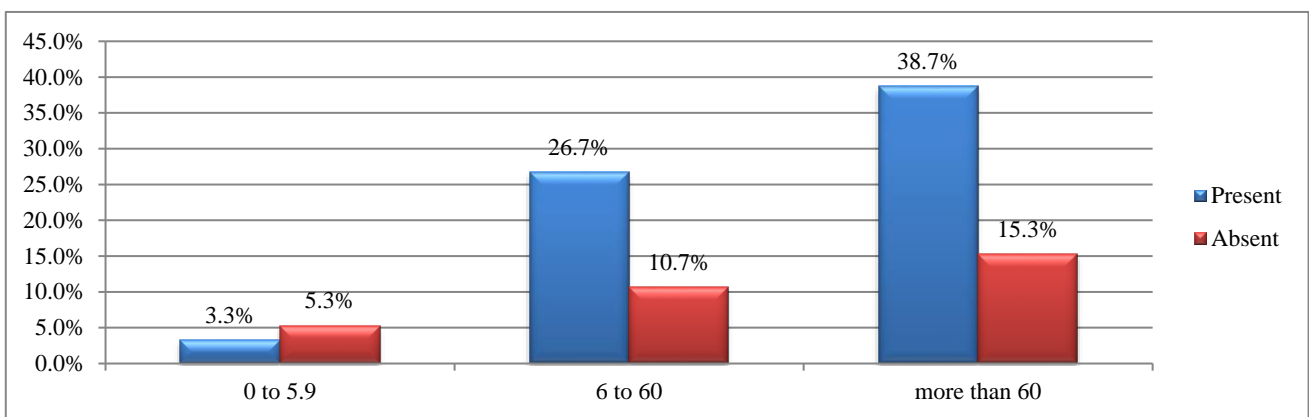


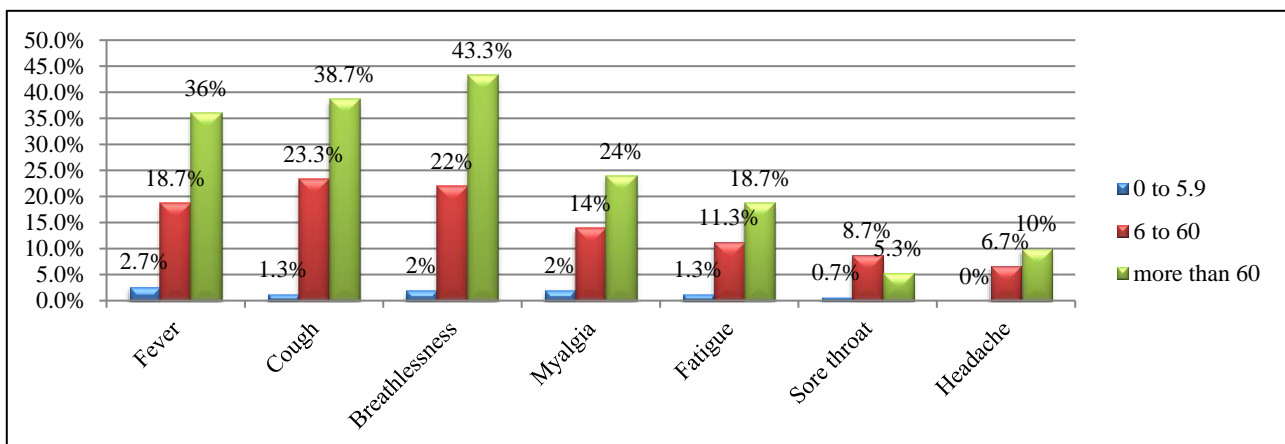
Figure 2: Distribution of the subjects based on gender.



**Figure 3: Distribution of subjects based on co-morbidities.**



**Figure 4: Distribution of subjects based on presence or absence of co-morbidities.**



**Figure 5: Distribution of subjects based on symptoms.**

As given in Table 4, in subjects having co-morbidities, IL-6 was more than 60 in 58(38.7%) subjects. Chi-square test was applied to find the association between co-morbidities and IL-6.

Chi-square test showed statistical significant association between presence or absence of co-morbidities and IL-6 ( $\chi^2 = 6.03$ ;  $p = 0.049$ ).

As given in Table 5, most of the subjects having fever, cough, breathlessness, myalgia, fatigue, headache were having IL-6 more than 60 whereas most of the subjects having sore throat were having IL-6 between 6 to 60. Chi-square test was applied to find the association between symptoms and IL-6.



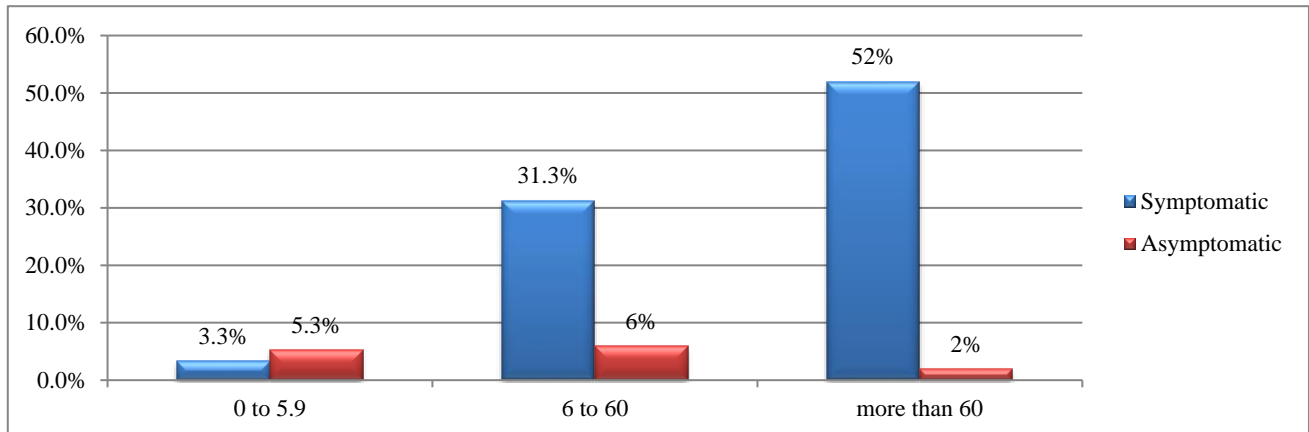
Chi-square test showed statistical significant association between fever and IL-6 ( $c^2= 7.86$ ;  $p=0.02$ ), cough and IL-6 ( $c^2= 15.27$ ;  $p=0.00$ ), breathlessness and IL-6 ( $c^2= 19.51$ ;  $p=0.00$ ).

As given in Table 6, in subjects having symptoms, IL-6 was more than 60 in 78(52%) subjects. Chi-square test was applied to find the association between symptoms and IL-6.

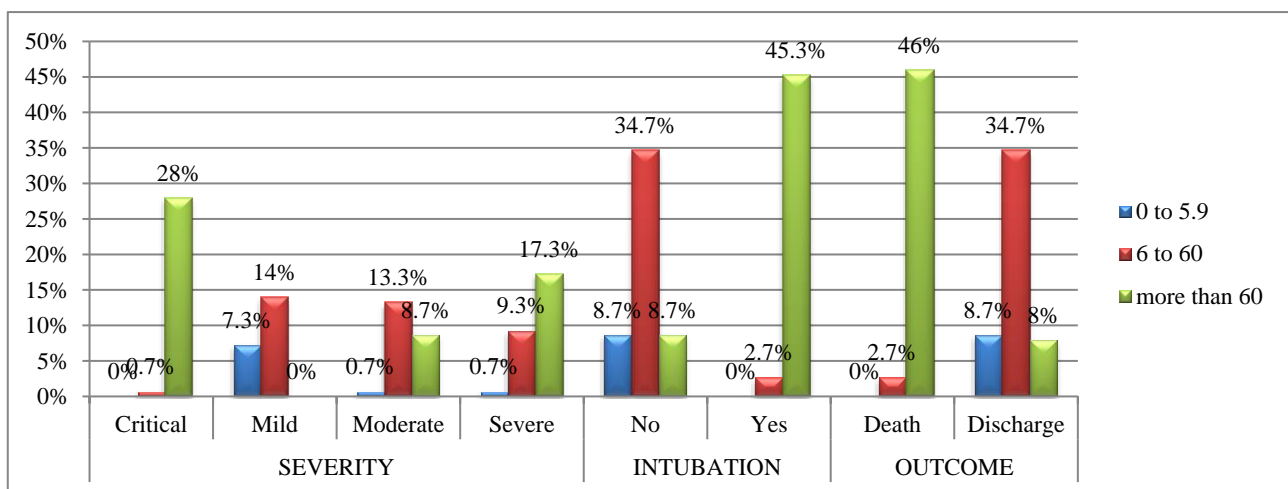
Chi-square test showed statistical significant association between presence or absence of symptoms and IL-6 ( $c^2=33$ ;  $p=0.00$ ).

As given in Table 7, most of the Critical and severe subjects had IL-6 more than 60 whereas mild and moderate subjects had IL-6 between 6 to 60. Chi-square test was applied to find the association between severity and IL-6.

Chi-square test showed statistical significant association between severity and IL-6 ( $c^2= 91.25$ ;  $p=0.00$ ).



**Figure 6: Distribution of subjects based on presence or absence of symptoms.**



**Figure 7: Distribution of subjects based on severity, intubation and outcome.**

As given in Table 7, most of the intubated subjects had IL-6 more than 60 whereas most of the non intubated subjects had IL-6 between 6 to 60. Chi-square test was applied to find the association between intubation and IL-6.

Chi-square test showed statistical significant association between intubation and IL-6 ( $c^2= 91.39$ ;  $p=0.00$ ).

As given in Table 7, most of the subjects who died had IL-6 more than 60- 69(46%). Chi-square test was applied to find the association between outcome and IL-6.

Chi-square test showed statistical significant association between outcome and IL-6 ( $c^2= 94.21$ ;  $p=0.00$ ).

Kruskal-wallis test was applied to compare the clinical parameters based on IL-6 groups as given in Table 8. Kruskal-wallis test showed statistical significant difference among the groups with respect to neutrophils, lymphocytes, CRP, Ferritin, total days in hospital, ANC< NLR, d-NLR, NMR, LMR, ALC, LCRPR, CRP-IL6 ratio ( $p\leq 0.05$ ).



Spearman's correlation was applied to correlate the clinical parameters with IL-6 as given in Table 9. IL-6 showed positive, moderate to strong and significant correlation with neutrophils ( $r=0.411$ ;  $p=0.00$ ), CRP ( $r=0.581$ ;  $p=0.00$ ), ferritin ( $r=0.642$ ;  $p=0.00$ ), NLR ( $r=0.417$ ;  $p=0.00$ ), d-NLR ( $r=0.406$ ;  $p=0.00$ ) whereas negative, very weak to weak, significant correlation was seen with lymphocytes ( $r= -0.423$ ;  $p=0.00$ ), total days in hospital ( $r= -0.107$ ;  $p=0.19$ ), TC-ANC ( $r= -0.322$ ;  $p=0.00$ ), LMR ( $r=-0.344$ , $p=0.00$ ), ALC ( $r=-0.391$ , $p=0.00$ ). Moderate, negative and significant correlation was seen with LCPCR ( $r=-0.647$ ,  $p=0.00$ ).

## DISCUSSION

Patients with COVID-19 were associated with high IL-6 values when compared with presence of symptoms and also individually associated with symptoms such as fever, cough and breathlessness. Similarly, high IL-6 values were associated with the presence of co-morbid conditions and also correlated with the presence of hypertension.

Patients with COVID-19 had high IL-6 values when compared with outcomes of admitted patients and also positive correlations with intubation and death of patients. Patients' IL-6 values were strongly elevated when their severity of diseases were severe and moderately elevated when their disease severity were mild to moderate.

Patients with COVID-19 had positive correlations of IL-6 values with other lab parameters like neutrophils, CRP, Ferritin, NLR.

In this study the above correlations were observed among the study population.

COVID-19 is a type of inflammatory syndrome and like any other inflammatory syndromes can have sepsis and ARDS as final outcomes and associated with elevated levels of IL-6.<sup>7</sup> The association between initial IL-6 concentrations greater than 80 pg/mL and outcomes such as respiratory failure and death has been confirmed in numerous studies.<sup>8</sup>

Cytokines are vital in regulating immunological and inflammatory responses. Among them, IL-6 is of major importance because of its pleiotropic effects.<sup>9</sup> An increase in IL-6 levels has previously been observed in patients with respiratory dysfunction, implying a possible shared mechanism of cytokine-mediated lung damage caused by COVID-9 infection. Furthermore, it seems 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.<sup>10</sup>

In a study conducted by Fang Liu et al titled 'Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19' they showed that the serum levels of interleukin-6 and C-reactive

protein were found to be elevated in patients who deteriorated during the course of illness which was similar to what we observed in this study.<sup>11</sup>

In a study conducted by Wilczynski et al titled 'A cytokine/bradykinin storm comparison: what is the relationship between hypertension and COVID-19?', the authors describe how hypertensive COVID19 patients having a worse outcome are associated with elevated interleukin-6 levels.<sup>12</sup>

In another meta-analysis by Aziz et al titled 'Elevated interleukin-6 and severe COVID-19: a meta-analysis' showed that elevated interleukin6 levels were associated with severe outcome of COVID19. IL-6 is responsible for elevation of acute phase reactants, such as C-reactive protein, serum amyloid A, fibrinogen, and hepcidin, and inhibition of albumin synthesis.<sup>13</sup> Similarly, in this study elevated interleukin6 levels had positive correlations with C-reactive protein.

Patients with severe COVID-19 disease present with increased leukocytosis, neutrophilia, lymphocytopenia and monocytois than those with non-severe disease.<sup>14</sup>

The results of this study shows the importance of pro inflammatory marker such as interleukin-6 with the identification of patients at risk and can be used for their prognosis also.

## Limitations of study

As this was a cross-sectional study we could not establish a follow up of the values of Interleukin 6 with the progression of illness and this remains the biggest limitation of this study. Further cohort studies are required to be done to strengthen the role of Interleukin6 as a prognostic marker in COVID-19.

## CONCLUSION

This study helps to establish the importance of Interlukin-6 as a viable biomarker among covid patients for stratification of their severity, outcome and also to predict the prognosis of the patients. This helps us to quickly identify patients with poor outcome. The study also reiterates the importance and occurrence of this marker with the presence of other co-morbid conditions like Hypertension indicating it as an important risk factor.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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