European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 04, 2022

Original Research Article

A retrospective cohort study to assess the levels of IL-6 in COVID-19 infected patients and to evaluate its association with the severity of the disease in Jodhpur, Rajasthan

[1]Bharat Mundel, [2]Jitendra Patawat, [3]Mohammad Yaseen, [4]Khushant Jangid

[1,3]Medical Officer, Medicine, Jodhpur, Rajasthan, India
[2]Medical Officer, Medicine, Rajsamand, Rajasthan, India
[4]Assistant Professor, Department of Medicine, Dr. S.N. Medical College, Jodhpur, Rajasthan, India

Corresponding Author:
Khushant Jangid

Abstract

Background: The SARS-CoV-2 virus replicates rapidly, triggering a storm characterized by increased levels of cytokines such as IL-6. Such an inflammatory response causes inflammation of the respiratory system and other bodily systems, with subsequent occurrence of ARDS or respiratory failure. The estimation of IL-6 levels could be an important tool to assess disease severity in COVID-19 patients.
Methodology: A retrospective cohort study was conducted on 45 patients in Department of Medicine, MDM Hospital, Dr. S.N Medical College, Jodhpur, Rajasthan. A predesigned and pre-structure Performa was used.
Conclusion: IL-6 is an adequate predictor of severe disease in patients infected with the COVID-19 virus. The finding of current study guide clinicians and healthcare providers in identifying potentially severe or critical patients with COVID-19.

Keywords: Covid 19, severity, IL-6

Introduction

Outbreak of COVID-19 in China and its potential of rapid spread throughout the country and, subsequently, to other countries WHO declared it as a global health emergency on 31 January 2020; subsequently, on 11 March 2020, they declared it a pandemic situation [1]. At present, we are not in a position to effectively treat COVID-19, since no specific antiviral drugs for treating human corona virus infection are available. Most nations are currently making efforts to prevent the further spreading of this potentially deadly virus by implementing preventive and control strategies [2].
Patients infected with SARS-CoV-2 (COVID-19) develop potentially life-threatening pathologies involving acute inflammation, cytokine storm [3, 4, 5], septic shock complications, coagulation dysfunction, metabolic acidosis, hypoxia, and multiple organ failure [6]. Clinical deterioration often occurs 7-10 days after the onset of symptoms, in association with declining viral titres [7], suggesting that pathology is driven by inflammation rather than direct viral injury. Inflammatory markers are often substantially elevated in patients with severe COVID-19 [8-10].

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Due to a higher volume of patients, it is imperative to look for predictors that can guide us in allocating resources for these patients and be prepared in advance as presently our health systems have been stretched to their limits. In the multitude of blood tests and imaging conducted on these patients [11], CRP and D-Dimer levels are measured in many health-care settings [12].
Various biomarkers, especially inflammatory markers like C-reactive protein (CRP), ferritin, fibrinogen, D-dimer and Interleukin 6 (IL-6) are associated with Covid-19 progression [13, 14]. However, no reliable indicators are yet available to predict disease severity and progression. There are some studies recently published which positively correlated the level of plasma IL-6 level with the COVID 19 disease severity and progression. Therefore, this study is planned to evaluate the role of IL-6 in the pathogenesis of COVID-19 infection. However, the accumulating evidence of their correlation supports the notion of the use of IL-6 levels as a diagnostic index of the severity of COVID- 19 infection. Moreover, it may be possible to develop a point-of- care IL-6 test for patients with fever or other basic clinical symptoms that is non-invasive, highly predictive of health outcomes, and which may inform clinical decision-making [15].

Materials and Method

Place of study: Department of Medicine, MDM Hospital, Dr. S.N Medical College, Jodhpur, Rajasthan.
Study design: Retrospective cohort study.

Sample size

Sample size was calculated at alpha error 0.05 and study power 80%, using the below formula for hypothesis testing for two independent population proportion-
$N = [Z1-\propto/2\sqrt{2}(1-P)+Z1-\beta\sqrt{P1}(1-P1)+P2(1-P2)]2\ (P1 - P2)2$

Where,
N = Sample size
$(Z1-\propto/2)$ = Standard normal deviate for Type 1 error (taken as 1.96 for 95% confidence level or alpha error 0.05).
$Z1-\beta$= Standard normal deviate for Type 2 error (taken as 0.84 for 80% study power).
P1 = Proportion of severe disease in Patients with raised IL6 [taken as 40% (0.4) as per finding of Bhandari *et al*. [73].
P2 = Proportion of complications in patients with normal IL6 [taken as 6.67% (0.0667) as per finding of Bhandari *et al*. [73].
P = (P1 + P2)/2
Sample size was calculated to be a minimum of 30 subjects. Sample size was increased to 45 subjects in each group. Thus, a total of 90 COVID 19 patients were included in the study.

Study period: Study was done after approval by ethics committee.
Study universe: Record of COVID-19 positive patients available in record room of MDM hospital, Dr. S.N Medical College, Jodhpur from 1.04.2020 to 31.07.2020 were analysed.
Study tool: predesigned and pre-structure Performa was used.

Inclusion criteria

Records of all the patients who were admitted after 01.04.2020 having age > 18 year of either gender with COVID-19 RT-PCR positive and has Il-6 value within 72 hours of admission.

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Exclusion criteria: Known case of Rheumatoid arthritis, acute myocardial infarction during hospitalization, acute pancreatitis.

Statistical analysis

Qualitative data were expressed in percentage, proportion, graph, and tables and analyzed by chi square test. Quantitative data were expressed in mean, standard deviation and analyzed by t-test. p value <0.05 were taken as significant. Relative risk for mortality and severity of disease were calculated.

Observation

Table 1: Distribution according to age

Age	Severe (N=45)		Non-Severe (N=45)	
	N	%	N	%
≤30 years	2	4.44	0	0.00
31-40 years	10	22.22	2	4.44
41-50 years	14	31.11	25	55.56
51-60 years	11	24.44	12	26.67
≥ 61 years	8	17.78	6	13.33
Total	45	100.00	45	100.00
Mean± SD	49.60±12.59		50.62±9.25	
P-value	0.6625			

The mean age of cases in severe group is 49.60 years with majority (31.11%) in age group 41-50 years. Similarly, the mean age of cases in non-severe group is 50.62 years with majority (55.56%) cases in age group 41-50 years. There is statistically no significant difference in age between two groups with p-value 0.6625.

Table 2: Distribution according to gender

Gender	Severe (N=45)		Non-Severe (N=45)	
	N	%	N	%
Male	20	44.44	20	44.44
Female	25	55.56	25	55.56
total	45	100.00	45	100.00
Chi-square statistic is 0. The p-value is 1				

There are 44.44%males and 55.56% in both groups. Statistically no significant difference in gender between two group P-value is 1.0.

Table 3: Distribution according to vital

Vitals	Severe (N=45)		Non-Severe (N=45)		P-value
	Mean	SD	Mean	SD	
Systolic blood Pressure	128.40	13.97	127.78	13.22	0.8293
Diastolic blood pressure	83.11	6.25	81.87	6.21	0.3477
Pulse rate	116.22	8.55	108.62	7.08	<0.0001
SpO2 %	81.82	5.85	90.42	2.09	<0.0001
Respiratory rate	30.04	4.36	25.24	3.36	<0.0001

The mean Systolic blood pressure is 128.4, diastolic blood pressure is 83.11, Pulse rate is 116.22, SpO2 % is 81.82 and Respiratory rate is 30.04 in severe group. Similarly, in non-

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severe group mean Systolic blood Pressure is 127.78, Diastolic blood pressure is 81.87, Pulse rate is 108.62, SpO2 % is 90.42 and Respiratory rate is 25.24. There is statistically no significant difference among systolic and diastolic blood pressure among two groups (P-value >0.05) but with respect to pulse rate, SpO2 and respiratory rate there was significant difference among two group with high pulse and respiratory rate and low SpO2 in severe group (P-value <0.05).

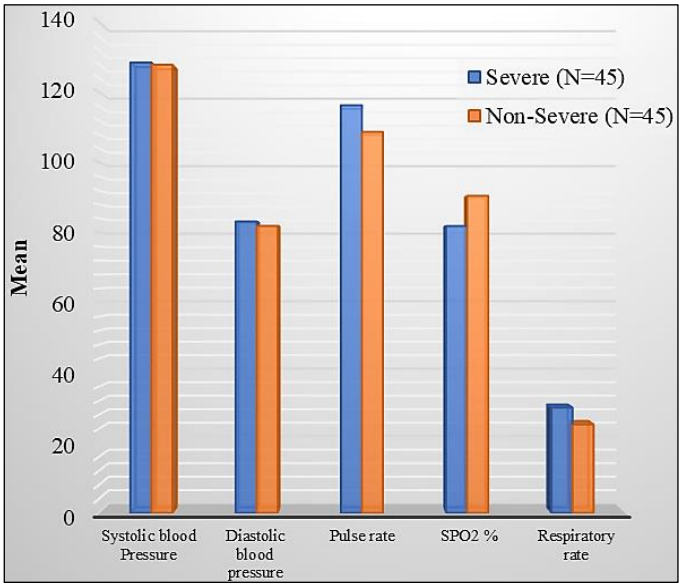

Fig 1: Distribution according to vital

Table 4: Distribution according to interleukin-6

IL-6	Mean	SD
Severe (n=45)	103.82	51.27
Non-Severe (n=45)	52.27	31.85
P-value	<0.0001	

Here mean IL-6 in severe group is 103.82 and in non-severe group mean IL-6 is 52.27. Although, IL-6 is raised in both the group but statistically significant increase in IL-6 in severe group as compared to non-severe group (P-value <0.0001).

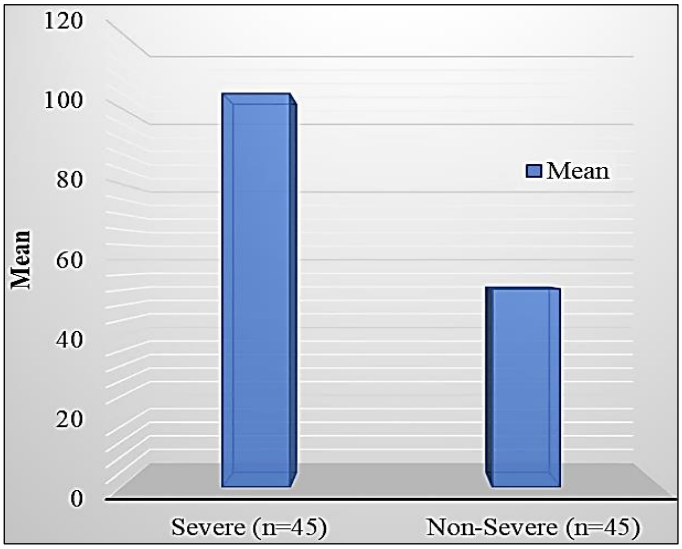

Fig 2: Distribution according to interleukin-6

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Table: Distribution according to IL-6

IL-6	Severe		Non-Severe	
	N	%	N	%
Normal (0-5.9 pg/ml)	0	0.00	0	0.00
Raised (6.0-60.0 pg/ml)	8	17.78	33	73.33
Extremely Raised (>60.0 pg/ml)	37	82.22	12	26.67
Chi-square statistic is 27.999. The p-value is <0.00001.				

In severe group 17.78% has raised IL-6 and 82.22% has extremely raised IL-6. In non-severe group 73.33% has raised IL-6 and only 26.67% has extremely raised IL-6. The difference is statistically significant (P-value <0.0001).

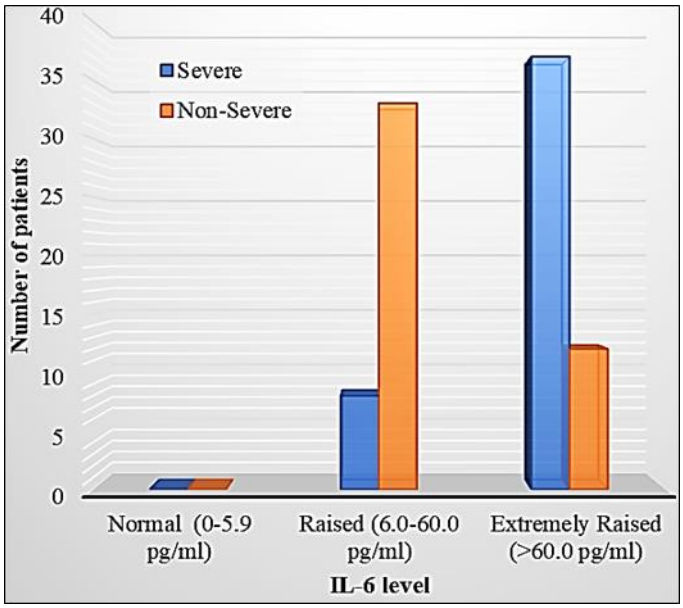

Fig 3: Distribution according to IL-6

Discussion

A cytokine storm causing critical respiratory distress in COVID-19 is an immune disease characterized by high-level activation of immune cells and excessive production of massive inflammatory cytokines and chemical mediators. Therefore, it has been suggested that the blockade of inflammatory cytokines in COVID-19 patients is a possible therapeutic tool. In clinical settings, many anti-inflammatory drugs, such as corticosteroids and IL-6 receptor inhibitors, are candidates for therapeutic strategies against COVID-19. However, the optimal timing for the administration of these drugs remains unclear. Too early administration can adversely lead to a decrease in viral clearance. The use of corticosteroids has detrimental effects on the survival of patients not requiring oxygen. IL-6 plays an important role in lung repair responses following viral insults, which means that the timing of administration of IL-6 receptor inhibitors could affect proper tissue remodeling. Therefore, although the indication for medical interventions, including anti-inflammatory drugs administration, should not be based solely on IL-6 levels, this reliable marker could help physicians to judge appropriate timing for interventions [84].

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

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The mean age of cases in severe group is 49.60 years with majority (31.11%) in age group 41-50 years with 44.44% males and 55.56% females. Similarly, the mean age of cases in non-severe group is 50.62 years with majority (55.56%) cases in age group 41-50 years with 44.44% males and 55.56% females. There is statistically no significant difference in age between two groups with p-value 0.6625. In concordance with our results Bhandari *et al.* [16] reported that no significant variations were found in age and gender distribution for IL-6. El-Shabrawy *et al.* [17] found that severe and non-survivor patients were elderly. Wang *et al.* [18] also reported that age of the patients is associated with worse disease progress and a higher mortality rate [86].

Here, mean Systolic blood pressure is 128.4, diastolic blood pressure is 83.11, Pulse rate is 116.22, SpO2 % is 81.82 and Respiratory rate is 30.04 in severe group. Similarly, in non-severe group mean Systolic blood Pressure is 127.78, Diastolic blood pressure is 81.87, Pulse rate is 108.62, SpO2 % is 90.42 and Respiratory rate is 25.24. There is statistically no significant difference among systolic and diastolic blood pressure among two groups (P-value >0.05) but with respect to pulse rate, SpO2 and respiratory rate there was significant difference among two group with high pulse and respiratory rate and low SpO2 in severe group (P-value<0.05). El-Shabrawy *et al.* [17] found that there was derangement of vitals in severe cases as compared to non-severe cases.

Here mean IL-6 in severe group is 103.82 and in non-severe group mean IL-6 is 52.27. Although, IL-6 is raised in both the group but statistically significant increase in IL-6 in severe group as compared to non-severe group (P-value <0.0001). El-Shabrawy *et al.* [17] reported patients with severe COVID-19 had higher levels of IL-6 in comparison with non-severe patients. Regards IL-6 diagnostic performance criteria, IL-6 seems to be a useful marker for early recognition of severe disease. IL-6 showed significantly predictive power even after adjustment to different models that include clinical and laboratory significant parameters. So, IL-6 can be considered as an independent predictor of COVID-19 severity. A meta-analysis was performed on nine studies to evaluate the role of IL-6 in assessing the COVID-19 severity. Aziz *et al.* [18] also reported A significantly higher serum IL-6 levels were confirmed in patients with severe COVID-19 in comparison to non-severe ones.87 These findings support that viral infection mediates lung injury via cytokines effects [19].

In severe group 17.78% has raised IL-6 and 82.22% has extremely raised IL-6. In non-severe group 73.33% has raised IL-6 and only 26.67% has extremely raised IL-6. The difference is statistically significant (P-value<0.0001). Zhang *et al.* [20] found 80% normal and 20% had elevated IL-6 in severe group and 25.8% normal and 74.2% had elevated IL-6 in critical group. It contributes to COVID-19-associated cytokine storms, largely enhancing vascular permeability and impairing the organ function.

Conclusion

IL-6 is an adequate predictor of severe disease in patients infected with the COVID-19 virus. The finding of current study guide clinicians and healthcare providers in identifying potentially severe or critical patients with COVID-19 at the initial stage of the disease. Repeated measurements of IL-6 can help the clinicians in identifying critically COVID-19 patients with the highest risk of poor prognosis.

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