STUDY OF SERUM LEVEL OF INTERLEUKIN-6 IN COVID 19 PATIENTS: PROGNOSTIC VALUE AND ITS RELATION TO DISEASE PROGRESSION

Nasser Keshar[1], Safy Kaddah[1], Samah Selim[1], Waleed R Arafat[4], Amira Ismaiel[1], Amal Ibrahim[1], Marwa Abdo[2], Alkhateeb Alkemary[3], Naglaa B Ahmed[1*]

ArticleHistory:Received:13.04.2023 **Revised:**18.05.2023 **Accepted:**22.04.2023

Abstract

Background: The pathogenesis of COVID-19 pneumonia encompasses a spectrum of inflammatory cytokines. An essential component of the cytokine storm is interleukin-6 (IL-6).

The aim of the work is to trace the relationship between the blood level of IL-6 in hospitalized COVID-19 cases and various clinical and laboratory parameters, CT chest imaging, and the requirement for tocilizumab. Additionally, its predictive validity for the requirement for intensive care unit (ICU) admission, the requirement for mechanical ventilation, the occurrence of complications, and mortality.

Patients and method: The study encompassed 140 cases who had COVID-19 PCR results that were positive. All cases underwent a thorough history review, physical examination, lab tests, a CT scan of the chest, and an ELISA to detect the level of IL-6 in their serum.

Results: Ninety-six individuals (68.6%) had serious or life-threatening illnesses. The following variables (gender, complications, thrombosis, lung affection in chest CT, the location of management, oxygen treatment, need for tocilizumab, the requirement for anticoagulation, and COVID-19 outcome) and the blood level of IL-6 showed a statistically marked disparity

The levels of IL-6 was inversely correlated with the percentages of lymphocytes, oxygen saturation, and hemoglobin. However, IL-6 had a significant positive correlation with ferritin, D-dimer, neutrophil/lymphocyte (N/L) ratio, and proportion of neutrophils. IL-6 continues to be an independent predictor for admission to the intensive care unit (ICU) on multivariate logistic regression.

Conclusion: Serum IL-6 has been associated with worse outcomes and is crucial to the progression of COVID-19 illness.

Keywords: Interleukin-6, COVID-19, Prognosis, Mortality

[1]Department of Chest Diseases, Faculty of Medicine, Cairo University, Egypt
[2]Department of Rheumatology, Faculty of Medicine, Cairo University, Egypt
[3]Department of internal medicine, Faculty of Medicine, Cairo University, Egypt
[4]Department of Chest Diseases, Faculty of Medicine, Banisuef University, Egypt
[*]Corresponding Email:Naglaa.bakry@kasralainy.edu.eg

DOI: 10.48047/ecb/2023.12.5.279

1. INTRODUCTION

A family of single-stranded RNA viruses called coronaviruses causes respiratory infections in humans (1). The new beta coronavirus SARS-CoV-2, which causes severe acute respiratory syndrome (SARS), first appeared in China at the end of 2019 and has since spread throughout the world. Globally, the disease would have caused over 6.7 million fatalities and over 662 million "confirmed" cases by January 15th, 2023 (2, 3).

Clinically speaking, 80% of COVID-19 cases either show no symptoms at all or only moderate patterns. However, about 15% of COVID-19-infected patients experience a severe form of illness that necessitates oxygen support, while only about 5% experience a form of that is life-threatening and is accompanied by fatal complications. These complications can include acute respiratory distress syndrome, respiratory failure, sepsis and septic shock, thromboembolism, as well as multiorgan failure (4, 5).

Cytokine storm was discovered to play a significant role in the pathophysiology of severe COVID-19 patients (6). Numerous viral and non-infectious disorders can start the cytokine storm (7), which can seriously harm many organs.

The spread of COVID-19 could place a considerable strain on the local healthcare system and dramatically increase mortality in the context

of the existing pandemic (8). The advancement of COVID-19 is correlated with a variety of biomarkers, particularly inflammatory markers such as C-reactive protein (CRP), ferritin, fibrinogen, D-dimer, and Interleukin 6 (IL-6) (9). One of the main causes of immunological dysregulation and ARDS in COVID-19 has been suggested to be IL-6 (10).

In order to determine the relationship between numerous clinical and laboratory factors, computerized CT chest findings, and the requirement for tocilizumab, the study's objective was to assess the blood level of IL-6 in hospitalized COVID-19 patients. Additionally, its predictive validity for the requirement for intensive care unit (ICU) admission, the requirement for mechanical ventilation, the occurrence of complications, and mortality.

2. PATIENTS AND METHODS

- **Study design:**

A multicentre prospective cohort study was conducted between January 2021 and September 2021 at three tertiary hospitals: New Kasr Al-Ainy Teaching Hospital and Internal Medicine Hospital, Cairo University, and Benisuef University Hospital. The Faculty of Medicine at Cairo University's institutional ethics commission (Ethical Commission Number 105-2020) gave its approval to the study.

- **Subjects:**

According to COVID-19 diagnosis and treatment recommendations from the Egyptian Ministry of Health (11), all admitted patients (n = 140) with PCR-positive COVID-19 were included in this study. They were split into two groups: group I, which included moderate cases (n = 44), and Group II, which included severe and critical cases (n = 96).

- Moderate cases: Patients with fever, respiratory symptoms, and radiological evidence of pneumonia, whether or not they also have one or more risk factors (such as obesity, pregnancy, active cancer, age > 65, chemotherapy, immunosuppressants, or uncontrolled co-morbidities).
- Severe cases: any of the following conditions in patients: breathing difficulty, breathing less than 30 times per minute, arterial oxygen saturation (SaO2) 92%, arterial oxygen pressure (PaO2) /oxygen concentration (FiO2) in arterial blood 300, and computerized tomography of the chest (CT-chest) affection >50% that has progressed in the prior 24-48 hours.
- Critical cases: Patients who experienced any of the conditions listed below: Mechanical ventilation is necessary due to respiratory failure. Admission to the intensive care unit (ICU) due to shock and/or severe organ dysfunction.

Upon admission, all participants in the study provided the following information:

- History taking including age, sex, smoking history, and the presence of co-morbidity.
- Full clinical examination.
- Imaging: CT-chest
- Laboratory analysis: Complete blood count (CBC), C-reactive protein (CRP), procalcitonin, kidney function tests, liver function tests, serum ferritin, lactate dehydrogenase (LDH), D-dimer.
- Arterial oxygen saturation.
- Measurement of serum level of IL-6 using enzyme linked immune sorbent assay (ELISA) for the patients on the 1st day of hospital admission.
- Pharmacological therapy was recorded. All patients were monitored for improvement of dyspnea, fever, improvement of oxygen saturation, the need for intensive care, and/or mechanical ventilation, and the occurrence of complications.

STATISTICAL METHODS

IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA) was used for the statistical analysis. The right way to express numerical data was using the mean, standard deviation, or median and range. Frequency and percentage were used to display qualitative data. The Mann-Whitney test (non-parametric t-test) was adopted to compare two groups of quantitative data with non-normal distribution. The Kruskal-Wallis test (a non-parametric ANOVA) was used to compare the three groups, and the postdoc test was performed to compare two groups based on the Kruskal-Wallis distribution. To examine the correlation between numerical variables, the Spearman-rho method was applied.

The area under the curve (AUC) for the IL6 and cut-off values were calculated using the Receiver Operating Characteristic (ROC) curve. By assessing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy, the predictive value of IL6 was evaluated. The Kaplan-Meier method for survival analysis was used, and the log-rank test was used to compare the two survival curves. To calculate the hazard ratio (HR) and its 95% confidence interval (CI), a Cox-proportional hazard regression model was utilized.

Odds ratios (ORs) and 95% confidence intervals (CIs) were generated for the evaluation of the relationships between high IL-6 levels and outcomes using univariate and multivariate logistic regressions. The following hierarchical regression models were employed successfully: Model 1 was not calibrated. Model 2 was gender- and age-adjusted. Model 3 was modified for gender, age, and co-morbid conditions such as diabetes, chronic renal disease, chronic obstructive lung disease,

hypertension, and cardiovascular disease. Procalcitonin and the variables from Model 3 were combined to create Model 4. D-dimer was included in Model 5 along with variables from Model 4. Variables from Model 5 and CRP were added to Model 6 to alter it.All tests were two-tailed. A p-value > 0.05 was considered significant.

3. RESULTS

Table 1 highlights both the demographic and co-morbidity data of all cases (before the onset of COVID-19). Their age ranged from 28 to 84 years with a mean age of 58.4±11.9 years. Fifty-nine cases were females (42.1%). The commonest co-morbidity was hypertension (n=50 patients, 35.7%).

Table (1): Demographic & co-morbidity data (before the onset of COVID-19)

Demographic data	
Age (mean ± SD) years	58.4±11.9
Gender: number (%) *female* *male*	 59 (42.1%) 81 (57.9%)
Smoking	59 (42.1%)
Co-morbidity: number (%)	
Hypertension	50 (35.7%)
Diabetes Mellitus	46 (32.9%)
Coronary heart disease	15 (10.7%)
Cancer	7 (5%)
Chronic respiratory disease	36 (25.7%)
Renal disease	7 (5%)
Hepatic disease	7 (5%)

Table 2: The clinical picture, diagnosis, and consequences of COVID-19 in the individuals that were included are described in Table 2 below. Dyspnea was the most prevalent COVID-19 symptom (129 cases; 92.1%), while vascular thrombosis was the most prevalent consequence in 51 cases (36.4%). According to radiology, the majority of the cases—81 or 57.9%—had more than 50% lung affection in their chest CT scans due to the presence of ground glass opacities or consolidation.

Table (2): The clinical picture, diagnosis, and complications of COVID-19

COVID-19	**Number (%)**
COVID-19 manifestations	
Fever	108 (77.1%)
GIT symptoms	19 (13.6%)
Dyspnea	129 (92.1%)
Cough	125 (89.3%)
COVID-19 complications	67 (47.9%)
Thrombosis	51 (36.4%)
Septic shock	8 (5.7%)
Renal failure	4 (2.9%)
cardiogenic shock	4 (2.9%)
Liver cell failure	5 (3.6%)
Invasive mechanical ventilation	14 (10%)
CT result (lung involvement)	
Less than 50%	59 (42.1%)
More than 50%	81 (57.9%)
laboratory data	
Haemoglobin (g/dL) (mean ± SD)	12.2± 1.7
Total leukocyte count x10^3/ml (median, Min-Max)	8.2 (2.0-33.90)
Platelet (median, Min-Max)	233.5 (7.0-559.0)
Neutrophil number (median, Min-Max)	6.3 (1.8-30.6)
Lymphocytes (median, Min-Max)	1.13 (0.11-6.78)
Neutrophil/lymphocyte ratio (median, Min-Max)	5.3 (1.2-31.3)
O2 saturation % on room air (median, Min-Max)	82.0 (0.75-96.0)
O2 saturation on oxygen (mean ± SD)	85 ± 4.0

*ALT (U/L) (median, Min-Max) **	34 (8.0-221)
Creatinine (mg/dl) (median, Min-Max)	1.05(0.9-6.2)
Urea (mg/dl) (median, Min-Max)	43 (1-200)
Ferritin (ng/ml) (median, Min-Max)	548.5 (60.2-6595.0)
D-dimer (ng/ml) (median, Min-Max)	520.0 (30.0- 9500.0)
*CRP (mg/dL) (median, Min-Max)**	54 (0.5-230)
*LDH U/L(median, Min-Max)**	545.5(193-1932)
Procalcitonin ng/mL (median, Min-Max)	0.10 (0.01-24.0)
IL-6 pg/mL(median, Min-Max)	32.5(0-4678.0)

*Abbreviations: Min: Minimum, Max: Maximum, ALT, Alanine transaminase, CRP, C reactive protein, LDH, Lactate dehydrogenase

All of the cases were hospitalized, as shown in Table 3. 96 cases (68.6%) were admitted to the intensive care unit (ICU) because they were severely or dangerously unwell. Regarding the COVID-19 results, the majority of patients (n=80, 57.1%) were released without oxygen, while 40 cases (28.6%) were released with it. The hospital stay lasted for 8.5 (2-30) days. 20 patients passed away (14.3%).

Table (3): Management and Outcome of COVID-19 Patients

COVID-19	**number (%)**
Place of management	
Ward(moderate)	44 (31.4%)
ICU (severe/critically ill)	96(68.6%)
Oxygen treatment	
No Oxygen	2 (1.4%)
Low flow oxygen	36 (25.7%)
High-flow oxygen reservoir	32 (22.9%)
High-flow nasal cannula	13 (9.3%)
Non-invasive ventilator	42 (30%)
Invasive ventilator	15 (10.7%)
Need for systemic steroids	
No steroids	1 (0.7%)
<0.5 mg/kg/day	6 (4.3%)
0.5-1 mg/kg/day	47 (33.6%)
1-2 mg/kg/day	86 (61.4%)
Other medications for COVID-19	
Ivermectin	47 (33.6%)
Hydroxychloroquine	22 (15.7%)
Favipiravir	30 (21.4%)
Remdesivir	78 (55.7%)
Tocilizumab	66 (47.1%)
Need for anticoagulant	
No	54 (38.6%)
Prophylactic	63 (45%)
Therapeutic	23 (16.4%)
Need for plasma exchange	3 (2.1%)
ECMO*	2 (1.4%)
Outcome of COVID-19	
Discharged without O2	80 (57.1%)
Discharged on O2	40 (28.6)
Death	20 (14.3%)
Duration till recovery	
Number of days (median, Min-Max)	8.5 (2.0-30.0)

*Abbreviation: ECMO, extracorporeal membrane oxygenation

Table 4. highlighted that there was a statistically significant disparity in serum level of IL-6 and the following variables (gender, complications, thrombosis, lung affection in chest CT, the place of management, oxygen treatment, need for tocilizumab, need for anticoagulation, and outcome of COVID-19.

Table (4): Relation between IL-6 and variables of COVID-19 disease

Variables	**IL-6 level *pg/mL* Median (Min-Max)**	**P-value**
Descriptive data		
Age < 60 years ≥ 60 years	 31.7 (0.03-227) 34.2 (1.5-4678)	0.530
Gender Male Female	 43.00 (1.7-1550) 15.00 (0.3-4678)	**0.001**
Smoking Yes No	 37.79 (1.7-1550) 30.00 (0.03-4678)	0.365
Co-morbidities Yes No	 43.00 (0.03-4678) 22.9 (1.5-227)	0.340
COVID-19 manifestations		
Fever Yes No	 24.05 (0.03-4678) 42.5 (1.5-193.2)	0.493
GIT symptoms *Yes* *No*	 37.8 (2.7-146) 32 (0.03-4678)	0.650
Dyspnea *Yes* *No*	 34.29 (0.03-4678) 16.7 (1.7-51)	0.750
Cough *Yes* *No*	 34.2 (0.03-4678) 25.1 (2.35-95.9)	0.450
COVID-19 complications **Yes** **No**	 45.0(0.03-4678) 17.8 (1.5-1550)	**0.002**
Thrombosis *Yes* *No*	 45.0 (0.03-4678) 25.0(1.5-1550)	**0.020**
Septic shock *Yes* *No*	 45.03 (7.60-227) 31.85 (0.03-4678)	0.492
*Renal failure** Yes No	 53.50 (44.06-65.00) 30.85 (00.03-4678)	
*Cardiogenic shock** Yes No	 77 (51-200) 30.85 (00.03-4678)	
Liver cell failure *yes* no	 13.7 (9.30-44.06) 34.2 (0.03-4678)	0.370
Invasive mechanical ventilation *Yes* *No*	 39.18 (8.23-140.8) 29.08 (0.03-4678)	0.179
CT chest		
Less than 50% *More than 50%*	16.7 (0.03-193.2) 43.0 (2.35-4678)	**<0.001**
Place of management		
Ward (moderate) *ICU (severe/critically ill)*	10.63 (1.5-4678) 43.0 (0.03-1550)	**<0.001**
Oxygen treatment		
No oxygen + Low flow nasal bronge/mask	10.09(0.03-189)	**<0.001**
High flow oxygen reservoir	24.75(1.5-164)	
High flow nasal canula	89.0(6.3-1550)	
Non-invasive ventilator	46.94(1.8-4678)	
Invasive ventilator	44.06(8.23-140.8)	
Need for systemic steroids**		
No steroids + low dose 0.5mg prednisolone/Dexamethasone	51.0 (4.80-713.80)	0.309
Dexamethasone 8mg once daily	17.8 (1.7-4678)	
Methylprednisolone 1-2mg/kg	36.04 (0.03-1550)	
Other medications for COVID-19		
Ivermectin		0.453

Yes *No*	42 (1.7-227) 25.1 (0.03-4678)	
Hydroxychloroquine *Yes* *No*	 24.55 (2,35-109.1) 33.6 (0.03-4678)	0.610
Favipiravir *yes* no	 20.15 (2.5-189) 36.35 (0.03-4678)	0.267
Remdesivir *Yes* *No*	 36.35 (0.03-1550) 26.05 (1.5-4678)	0.248
Tocilizumab *Yes* *No*	 52.5 (6.2-4678) 11.68 (0.03-227)	**<0.001**
Need for anticoagulant		
No	14.98 (1.5-227)	**0.023**
Prophylactic	39.00(0.03-4678)	
Therapeutic	43.00 (5-200)	
Need for plasma exchange* Yes No	 100 (22-110) 32 (00.03-4678)	
ECMO* Yes No	 61.45 (22.90-100) 32.50 (00.03-4678)	
Outcome of COVID-19		
Discharged without O2	15 (0.03-1550)	**<0.001**
Discharged on O2	48.25 (2.1-713.8)	
Death	47.50 (8.23-4678)	

Abbreviation: Min: minimum, Max: maximum.
* No p-value because a small number of patients in the subgroup

According to Table 5: there were statistically significant inverse correlations between IL-6 levels and the percentage of lymphocytes, oxygen saturation on room air, and oxygen saturation. The levels of IL-6 and the following laboratory indicators (neutrophils percentage, N/L ratio, ferritin, D-dimer, LDH, and urea) showed statistically clear positive correlation.

Table (5): Correlations between IL-6 and other variables of COVID-19 disease

Variables	Spearman's coefficient (r)	P-value*
Age(years)	0.121	0.154
O2 sat % on room air	-0.346	**<0.001**
O2 sat % on oxygen	-0.337	**<0.001**
HB	-0.035	0.683
PLT	-0.071	0.405
TLC	0.119	0.162
Neutrophils number	0.161	0.058
Neutrophils%	0.222	**0.008**
Lymphocyte number	-0.111	0.193
Lymphocyte%	-0.247	**0.003**
N/L ratio	0.248	**0.003**
CRP	0.153	0.071
Ferritin	0.188	**0.026**
D-dimer	0.273	**0.001**
Procalcitonin	-0.006	0.946
LDH	0.195	**0.021**
Urea	0.179	**0.035**
Creatinine	0.069	0.420
ALT	0.065	0.448
AST	0.109	0.201

*Significant p-value < 0.05

The recovery period's median length was 8.5 days, ranging from 2 to 30 days. The possibility of survival at two weeks in cases with low IL-6 levels (≤ 22.19 pg/ml) was more than in patients with higher IL-6 level (>22.19 pg/ml (85.7% versus 81.9% respectively), with no statistical significance.

According to Table 6, the following variables (lung affection, ICU hospitalization, need for tocilizumab, need for anticoagulation, need for systemic steroids, and death) had cut-off values of IL-6 that were statistically noticed. However, because a mechanical ventilator was required, it was statistically unmarked.

Table (6):IL-6 cut-off values for some important COVID-19 variables:

	IL6 cut-off	P value	OR (95% CI)	Sensitivity	PPV	specificity	NPV	Accuracy	AUC**
Lung affection*	26.75	<0.001	4.12 (2.02-8.41)	67.9%	73.3%	66.1%	60.0%	67.2%	0.692
ICU admission	22.19	<0.001	5.79 (2.64-12.67)	70.8%	84.0%	70.5%	52.5%	70.7%	0.712
Need for tocilizumab	26.75	0.000	13.5 (5.91-30.83)	83.3%	73.3%	73.0%	83.1%	77.9%	0.815
Need for anticoagulant	27.57	0.02	2.22 (1.11- 4.45)	60.5%	70.3%	59.3%	48.5%	50.0%	0.635
Need for systemic steroids	22.19	0.01	2.45 (1.22-4.94)	66.3%	70.4%	55.6%	50.8%	62.1%	0.564
Need for IMV	34.24	0.394	1.67 (0.56-4.99)	60.0%	13.2%	52.8%	91.7%	53.5%	0.631
Mortality	44.03	0.01	3.44 (1.27-9.30)	65.0%	23.6%	65.0%	91.8%	65.0%	0.662

* Presence of ground glass opacities or consolidation by radiology

** AUC area under the curve

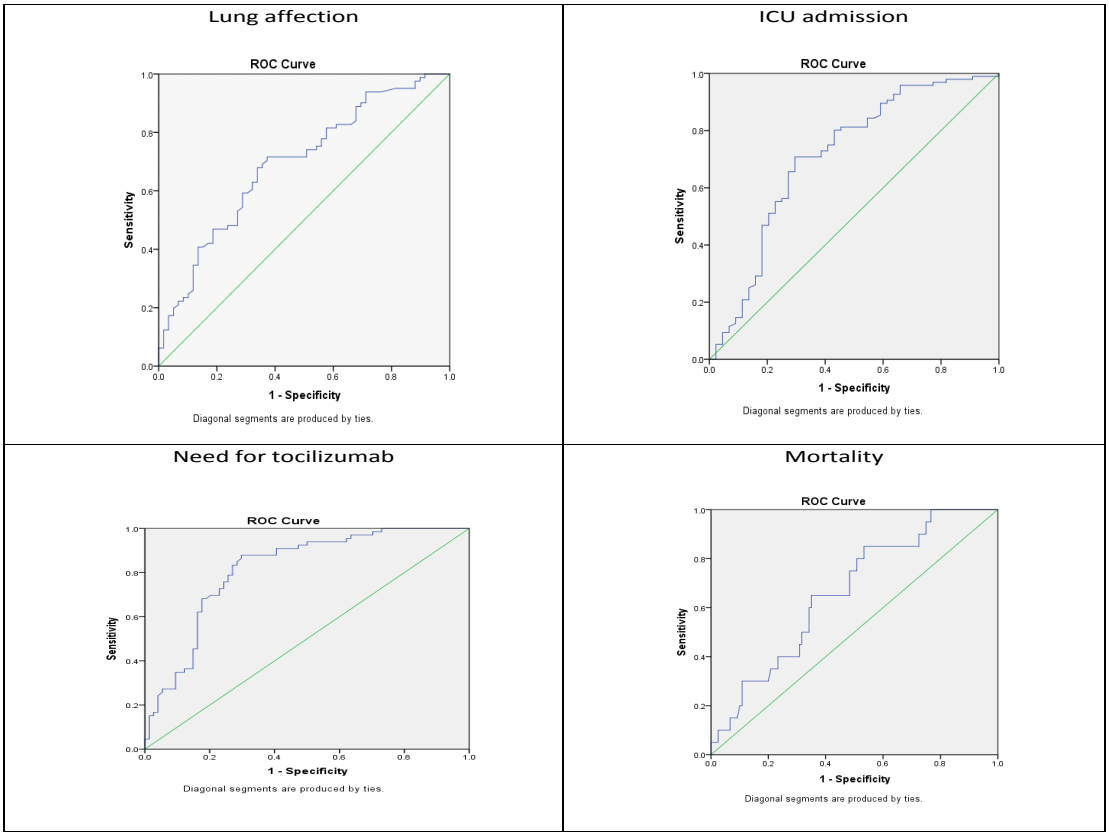

Figure 1: ROC curves for IL6 level cut-off value and different variables

According to univariate logistic modelling, there is a 1.6-times greater risk of ICU admission for every unit rise in IL-6 [(95% CI = (1.2-2.1) and (P-value= 0.002)]. After adjusting for age, sex, co-morbidities, procalcitonin, D-dimer, and CRP in multivariate logistic regression, IL-6 continues to be an independent predictor for admission to the intensive care unit (ICU) (table 7).

Table (7): Univariate and multivariate logistic regression analysis of (log) serum IL-6 for ICU admission

ICU admission	IL-6		
	OR	95% CI	*P*-value
Model 1	1.591	1,188-2.129	0.002
Model 2	1.698	1.242-2.323	0.001
Model 3	1.726	1.255-2.374	0.001
Model 4	1.726	1.254-2.375	0.001
Model 5	1.640	1.197-2.247	0.002
Model 6	1.649	1.196-2.276	0.002

Model 1 was basic (unadjusted), Model 2 was adjusted for age and sex, and Model 3 was adjusted for co-morbidities like diabetes, chronic renal disease, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease; Model 4 was modified using Model 3 variables plus procalcitonin, while Model 5 was adjusted using Model 4 variables plus D-dimer. Variables from Model 5 and CRP were added to Model 6 to alter it. Confidence interval and odds ratio are also adopted.

4. DISCUSSION

The present study shows the relationships between serum IL-6 levels in 140 hospitalized moderate to critical COVID-19 cases and the complications and outcomes of this infection. This is due to the reported unique role of IL-6 in the cytokine storm, which is important in the pathogenesis of severe cases of COVID-19.

According to earlier research, there are 1.5 times as many men as women who have COVID-19 (12–13), and men are 50% more likely to be hospitalised (5). These findings are almost identical to our findings (table 1). Males account for a greater proportion of critically ill patients in several cohorts around the world (up to 75 percent in early cohorts from China) (14–16); however, some cohort studies have suggested that the proportion of critically ill males and females is more evenly distributed (17–18). In the current investigation, men had considerably higher median IL6 levels than women (15 pg/ml vs. 43 pg/ml; P-value< 0.001) (table 4).

According to COVID-19 (19-20), death and the severity of the clinical state were both attributed to old age as the main risk factor. According to a prior study, age and different COVID-19 problems were positively linked with blood IL-6 concentrations (21). Cases older than 60 years old in the current cohort have greater IL-6 levels, but there is no statistically significant difference (table 4).

Additionally, serum IL-6 concentration was greater in patients with COVID-19 problems, but only thrombosis was statistically noticeable; this may be due to the small number of patients who had renal failure and cardiogenic shock as complications.

The majority of the cases (57.9%) exhibited more than 50% lung involvement with ground glass opacities or consolidation on the CT of their chests (table 4). With a cut-off value of 26.75pg/ml, the serum IL-6 content was significantly positively correlated with lung ailment (table 6, figure1). Other earlier investigations (12–13) revealed findings that were similar to these.

In accordance with earlier research (22-23), forty patients (28.6%) who were discharged on oxygen had substantially higher serum IL-6 levels than those who were discharged without oxygen (48.25 pg/ml, 15 pg/ml; P-value<0.001) (table4).

Regarding the laboratory variables, there were statistically significant negative correlations between IL-6 level and oxygen saturation on room air, oxygen saturation on oxygen and lymphocytes percentage. While there were statistically significant positive correlations between IL-6 level and neutrophils percentage, N/L ratio, ferritin, the D-dimer , LDH and urea (table5).

According to several studies, individuals with COVID-19 infection had higher serum IL-6 levels, and these levels were strongly connected with the disease's severity and death (19, 24). The current study suggested some cut-off values of serum IL-6 concentrations which can significantly predict; the need for ICU admission (22.19pg/ml), the need for anticoagulation (27.57 pg/ml), the need for systemic steroids (22.19 pg/ml), the need for tocilizumab, a monoclonal antibody which blocks IL-6 receptors (26.75 pg/ml), and mortality (44.03 pg/ml) (table 6, figure1).

Based on a research population of 140 patients with mild to severe illnesses, the cut-off value of IL-6 for death prediction in a prior study was 26.09 pg/ml (21) and serious sequelae were more likely to occur in COVID patients with IL-6 > 32.1 pg/ml (25). According to a different study, IL-6 may serve as a biomarker for the development of COVID-19 (26). While a different study group identified the IL-6 cut-off value as 86.95 pg/ml as the predictive value for a worse outcome (27).

Critical and fatal COVID-19 are linked with markedly raised levels of inflammatory markers, such as D-dimer and ferritin, as well as elevated levels of pro-inflammatory cytokines, such as IL-6 (28). By blocking the inflammatory pathway, the disease may not proceed. In a previously published meta-analysis of tocilizumab's effectiveness in these patients, it was discovered that cumulative

evidence from randomised controlled trials (RCTs) suggested a reduction in the risk of mechanical ventilation but no effect on mortality, whereas cumulative evidence from cohort studies suggested an association between tocilizumab and lower mortality (29). In our investigation, the levels of IL-6 were considerably higher in the sixty-six patients (47.1%) who got tocilizumab (table3) compared to the controls (52.5 pg/ml and 11.68 pg/ml, respectively; P-value <0.001) (table4, figure1).

On univariate logistic regression, we found that for each unit increase of IL-6 there are 1.6 times risk of ICU admission with 95% CI of (1.2-2.1) (P-value = 0.002). As ICU admission may be affected by other factors such as age, sex, co-morbidities, procalcitonin, D-dimer, and CRP, we adjusted all these factors using multivariate logistic regression and found that IL-6 an independent factor for admission to ICU (table7).

IN CONCLUSION, IL-6 is a crucial indicator of inflammation and plays a crucial role in COVID-19's cytokine storm. Critical illness, ICU hospitalisation, the need for anticoagulation, the need for systemic steroids, the need for tocilizumab, and mortality were all related with elevated serum IL-6 levels. As IL-6 has shown to be an independent predictor for admission to the intensive care unit (ICU), some cut-off levels of IL-6 upon hospital admission can be utilised as a good predictor for the development to a severe condition and can be an appropriate marker for monitoring poor outcomes. Therefore, by intervening with the appropriate treatment at the right time, severe morbidity and fatality rates can be decreased.

AUTHORS' CONTRIBUTIONS:

Concept of the study: SafyKaddah, Nasser Keshar ,Samah Selim, Naglaa Bakry Ahmed, Amira Ismail, Aml Ibrahim

Data collection: Nasser Keshar, SafyKaddah, Waleed Ramadan

Data analysis: Marwa Ahmed Abdo, El KhateebAlkemary, Naglaa Bakry Ahmed, Nasser Keshar, Samah Selim

Writing the original draft: El KhateebAlkemary, Marwa Ahmed Abdo.,Nasserkeshar , Amira Ismail, Aml Ibrahim, Samah Selim

All authorsparticipated in reviewing and editing the final paper.

5. REFERENCES

1. Channappanavar R, Perlman S. Pathogenic human corona virus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. (2017) 39: 529–39. doi: 10.1007/s00281-017-0629-x
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel corona virus from patients with pneumonia in China, 2019. N Engl J Med. (2020) 382:727–33. doi: 10.1056/NEJMoa2001017.
3. World Health Organization (WHO): Corona virus Disease (COVID-19) Pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed January 19, 2023).
4. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC.Pathophysiology, transmission, diagnosis, and treatment of corona virus disease 2019 (COVID-19): a review. J Am Med Assoc2020; 324:782–93.506
5. Aykal G, Esen H, Seyman D and Çalışkan T: Could IL-6 predict the clinical severity of COVID-19? Turkish Journal of Biochemistry, 2021: 46(5). https://doi.org/10.1515/tjb-2021-0020
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective,observational study. Lancet Respir Med. 2020 May; 8(5): 475-481. doi: 10.1016/S2213 2600(20)30079-5.
7. Gu Y, Hsu AC, Pang Z, et al. Role of the innate cytokine storm induced by the influenza A virus. Viral Immunol. 2019 Jul/Aug; 32(6):244–251. doi:10.1089/vim.2019.0032.
8. Kim G, Wang M, Pan H, et al. A health system response to covid-19 in long term care and post-acute care: a three-phase approach. J Am Geriatr Soc.2020. https://doi.org/10.1111/jgs.16513 [published online ahead of print, 2020 Apr 28].
9. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci.2020:1–11. https://doi.org/10.1080/10408363.2020.1770685 [published online ahead of print, 2020 Jun 5].
10. Han H, Ma Q, Li C, et al. profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect.2020; 9(1):1123–30. https://doi.org/10.1080/22221751.2020.1770129.
11. Masoud H, Elassal G, Zaky S, Baki A, et al. Management Protocol for COVID-19 Patients Version 1.4/30th May 2020 Ministry of health and population (MOHP), Egypt. http://www.mohp.gov.eg/JobsDetails.aspx?job_id=3061.

12. Liu, Z. et al. Dynamic Interleukin-6 Level Changes as a Prognostic Indicator in Patients With COVID-19. Front. Pharmacol. 11, 1–11 (2020).
13. Liu, T. et al. The role of interleukin- 6 in monitoring severe case of coronavirus disease 2019. EMBO Mol. Med. 12, 1–12 (2020).
14. Bhatraju, P. K. et al. Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. N. Engl. J. Med. 382, 2012–2022 (2020).
15. Grasselli, G. et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA - J. Am. Med. Assoc. 323, 1574–1581 (2020).
16. Guan, W. et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N. Engl. J. Med. 382, 1708–1720 (2020).
17. Bin, S. Y. et al. Environmental Contamination and Viral Shedding in MERS Patients during MERS-CoV Outbreak in South Korea. Clin. Infect. Dis. 62, 755–760 (2015).
18. Livingston, E. & Bucher, K. Coronavirus Disease 2019 (COVID-19) in Italy. Jama 323, 1335 (2020).
19. Liu, B., Li, M., Zhou, Z., Guan, X. & Xiang, Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. 111, 102452 (2020).
20. Li, X. et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J. Allergy Clin. Immunol. 146, 110–118 (2020).
21. Jiali Zhou†, Wenbo He†, Jingyu Liang, Lang Wang, Xiaomei Yu, Mingwei Bao, and H. L. Association of interleukin-6 level with morbidity and mortality in patients with coronavirus disease 2019 (COVID-19).Jpn J Infect Dis. 293–298 (2021) doi:10.7883/yoken.JJID.2020.463.
22. Herold, T. et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J. Allergy Clin. Immunol. 146, 128-136.e4 (2020).
23. Liu, T. et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. doi:10.15252/emmm.202012421.
24. Coperchini, F., Chiovato, L., Croce, L., Magri, F. &Rotondi, M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 53, 25–32 (2020).
25. Liu, F. et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J. Clin. Virol. 127, 104370 (2020).
26. Ulhaq, Z. S. & Soraya, G. V. Interleukin-6 as a potential biomarker of COVID-19 progression. Med. Mal. Infect. 50, 382–383 (2020).
27. Santa Cruz, A. et al. Interleukin-6 Is a Biomarker for the Development of Fatal Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. Front. Immunol. 12, 1–10 (2021).
28. Mehta, P. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395, 1033–1034 (2020).
29. Tleyjeh, I. M. et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin. Microbiol. Infect. 27, 215–227 (2021)..