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Procalcitonin and Interleukin-6 as Prognostic Markers in Intensive Care Unit Patients with Covid-19 in Minia University Hospital

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ABSTRACT

Background: A respiratory and systemic illness called COVID-19 has affected millions of people all over the world. A specific proportion of patients develop a very serious illness condition that necessitates intensive care and invasive ventilation.

Objective: To evaluate the predictive significance of procalcitonin (PCT) and interleukin-6 (IL-6) for the severity of illness and prognosis in COVID-19 patients hospitalised to the (ICU) at Minia University Hospital in Egypt.

Patients and Methods: The 90 participants in this study were separated into three groups: The P/F ratio (arterial PO_2 ("P") from the ABG divided by the FIO_2 ("F") - the fraction (percent) of inspired oxygen) was used to classify patients with ARDS according to severity. Group I (Patient group): included fifty (50) patients admitted to ICU diagnosed COVID-19 patients by PCR test and were further divided into three sub groups (group Ia; moderate cases; group Ib; severe cases; and group Ic. Group II (control group) consisted of forty seemingly healthy people who had the same age and sex.

Results: PCT, IL-6, and serum ferritin levels were all noticeably higher in the patient groups than in the control groups. A significant p value (p=0.0001) was found for each of the high positive correlations between IL-6 and ferritin, D-dimer, and CRP (r=0.722, 0.801, and 0.792, respectively) and there was moderate negative association between IL-6 and absolute lymphocytic count (r=-0.517). A significant p value (p=0.0001) was found for each of the strong positive correlations between procalcitonin and ferritin, D-dimer, and CRP (r=0.703, 0.721, and 0.711, respectively) and there was moderate negative association between procalcitonin and absolute lymphocytic count.

Conclusion: According to the study's findings, PCT and IL-6 levels are suitable prognostic indicators in COVID-19 patients who were hospitalized to the ICU, indicating a severe illness course and unfavorable outcome.

Keywords: COVID-19, ICU, Procalcitonin, IL-6.

INTRODUCTION

The COVID-19 epidemic, which started in Wuhan, Hubei Province, China, in December 2019 and quickly spread to the rest of the world, has been the largest threat the world has ever faced. It is characterized by symptoms resembling pneumonia, which could progress to significant hypoxia and many cardiovascular consequences [(1)]. Procalcitonin (PCT) is a well-known biomarker for predicting the likelihood of bacterial infection and the progression of disease. In individuals suffering from bacterial sepsis, suspected or confirmed lower respiratory tract infections, such as community-acquired pneumonia, acute bronchitis, and acute exacerbations of COPD, PCT can be a useful decision-making tool for antibiotic therapy. Furthermore, early results suggest that PCT may be a valuable tool for identifying COVID-19 patients who may be at risk for worsening and bacterial co-infection [(2)].IL-6 is a cytokine that regulates cell growth and differentiation as well as the immune response. Numerous cell types, including T cells, macrophages, endothelial cells, fibroblasts, and monocytes, release IL-6 [(3)]. It is believed that IL-6 is a crucial mediator of the cytokine storm that results in tissue damage and the development of COVID-19. Patients with COVID-19 have significantly higher serum IL-6 and IL-6 receptor levels [(4)].

The aim of this study was for assessment of the predictive significance of PCT and IL-6 in COVID-19 patients, who were admitted to the intensive care unit at Minia University Hospital in Egypt, for severe disease and outcome.

PATIENTS AND METHODS

The Clinical Pathology Department and the ICU Department at the Faculty of Medicine at Minia University in Egypt conducted this prospective cross-sectional study from May 2021 to March 2022. It was carried out on 90 patients.

The subjects included in the study were divided into:

Fifty (50) patients who were identified as COVID -19 patients by PCR test were included in **Group I (Patients group)**. Such a group was subsequently separated into three groups based on the P/F ratio: **Groups Ia and Ib** have moderate cases (thirty-five patients have P/F ratios under 300), Group Ic has critical cases (seven patients have P/F ratios under 100), and **Group Ic** has severe cases (eight patients have P/F ratios under 200). **Group II (Control group)** consisted of 40 people who appeared to be in good health and were of similar age and sex.

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When a patient is receiving supplementary oxygen, the P/F ratio is a potent objective measure for detecting acute hypoxemic respiratory failure at any time. The proportion (percent) of inspired oxygen that the patient is receiving, represented as a decimal (forty percent oxygen = FIO_2 of 0.40), is known as the P/F ratio and is equal to the arterial PO_2 ("P") from the ABG divided by the FIO_2 ("F") value. The P/F ratio, also known as acute lung injury in the setting of ARDS, has been validated and used for many years despite the fact that many doctors are not familiar with it [(5)].

Every participant in the study had a thorough history taking procedure that took into account factors including age, occupation, place of residence, length of the illness, smoking status, the existence of a fever, cough, or dyspnea, as well as co-morbid conditions like DM and high blood pressure. Each patient's clinical information, including temperature and oxygen saturation, was recorded. All of these clinical data were taken from the patient paper medical records and the hospital information system.

Patients under the age of eighteen, those with burns, autoimmune disorders, ICH, or people with concomitant bacteremia were all excluded from the study.

Methodology:

Blood sampling protocol:

Complete blood count (CBC) was performed using 5-part diff Celltac G, Nihon Kohden corporation, automated hematology analyser, Japan. [(6)] from suitable venous blood samples taken from each patient under fully aseptic conditions for routine blood culture using (BACTEC, Becton Dickinson Diagnostic Instrument Systems, Sparks, Md, USA) [(7)].

Using the auto-analyzer SELECTRA PRO XL, ELITech Group, clinical chemistry automation systems, Netherlands, random blood glucose, RFTs (blood urea nitrogen and serum cr), LFTs (ALT, AST and albumin) were carried out as per the manufacturer's instructions. According to the manufacturer's instructions, CRP was measured using a kinetic assay by GENRUI, Biotech Inc. in China. According to the manufacturer's instructions, PC and INR were assessed using the turbo densitometric method using the LABiTec coaDATA 4004 and PT-Reagent kit from the German company Biochemical Technology GmbH. According to the manufacturer's instructions, D-dimer assays were carried out using commercially available kits by GENRUI, Biotech Inc. in China. Clinical chemistry automation systems COBAS C311, ROCHE DIAGNOSTICS, and serum ferritin were used.

Before beginning antimicrobial medication, blood samples from each individual were taken, and they were then incubated aerobically at 37°C. This was done to rule out any related bacteremia. Every two days for a week, subcultures were performed on blood agar and MacConkey agar (aerobically at 36°C-1°C).

Procalcitonin and IL-6 levels were assessed using electrochemiluminescence (ECL) technology for immunoassay analysis using the Cobas e 411 clinical chemistry automation system from Roche Diagnostics in Mannheim, Germany. This method is based on the competition of the analyte in the sample with a ruthenium-labeled counterpart. Electrochemiluminescence signal is measured after application of voltage. using the kits that are available for purchase in accordance with the manufacturer's instructions [(8)].

Ethical approval:

Minia Faculty of Medicine, Minia Medical Ethics Committee approved this study. After getting all the facts, everyone gave their written consent. The entire process of conducting the study adhered to the Helsinki Declaration.

Statistical analysis

The statistical package software IBM SPSS (Statistical Package for the Social Sciences; Armonk, New York, USA) version 22.0 was used to analyse the data. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normal. In addition to frequency and percentage for qualitative data, non-parametric quantitative data were expressed as median (IQR). For non-parametric quantitative data between the four groups, the Kruskal-Wallis test was conducted, followed by the Mann Whitney test for each pair of groups. Comparing categorical variables was done using the chi square test. A p-value of 0.05 or less was regarded as significant. For the particular markers, Spearman's correlation was performed.

RESULTS

Regarding age and sex, there was no statistically significant difference between the groups under study (Table 1).

Table (1): Demographic data of all studied subjects

	Patient group no= 50	**Control group no= 40**	**p value**
Age (years): Median IQR	59 (48 – 67)	53 (34 – 64)	0.176
Sex (no %) Males Females	26 (52.0%) 24 (48.0%)	20 (50.0%) 20 (50.0%)	0.85

Considering O_2 saturation at the time of admission; it varied between the study groups in a statistically significant way. Regarding the length of stay in the ICU, there was a statistically significant difference between the patient groups under study (Table 2).

Table (2): O_2 saturation at time of admission and the L.O.S in ICU among the studied groups

	Group Ia no= 35	Group Ib no= 8	Group Ic no= 7	Group II no= 40	p value
O2 % saturation					
Median	65	65	88	99	**0.0001***
(IQR)	(60 – 72)	(50 – 84)	(80 – 90)	(98 – 99)	
L.O.S in ICU					
Median	17	17	9		
(IQR)	(12 – 19)	(9 – 25)	(7 – 15)	0	**0.0001***

L.O.S in ICU: length of stay in intensive care unit, *: Significant

CRP, serum ferritin, and D-dimer were significantly greater in the sick groups than the control group (Table 3).

Table (3): Comparison between studied groups regarding CRP, D-dimer and Ferritin

	Group Ia no= 35	Group Ib no= 8	Group Ic no= 7	Group II no= 40	p value
CRP mg/L					
(Range)	(17-156)	(6-160)	(48-179)	(1.0 - 4.0)	
Median	48	97	114	2.5	0.0001*
(IQR)	(24 – 96)	(48 – 140)	(57 – 175)	(2.0 – 3.0)	
Ferritin ng/mL					
(Range)	(118-1200)	(412-780)	(298-1000	(19-198)	
Median	312	461	690	72	0.0001*
(IQR)	(196 – 567)	(416 – 713)	(367 – 880	(59 – 125)	
D-dimer µg/mL					
(Range)	(0.2-16)	(1-16)	(1.5-14.5)	(0.1-0.6)	0.0001*
Median	1.7	3.4	7.9	0.3	
(IQR)	(0.8 – 4.9)	(2 – 6.5)	(3.3 – 14)	(0.2 – 0.4)	

Range, Median and IQR: non parametric test. *: Significant

Between the studied groups, there was a statistically significant differences in PC and IL-6 (Table 4).

Table (4): Level of procalcitonin and interleukin-6 among studied groups

	Group Ia no= 35	Group Ib no= 8	Group Ic no= 7	Group II no= 40	p value
PCT ng/Ml					
(Range)	(0.01 – 27.4)	(0.12 – 21.6)	(0.96 – 17.0)	(0.03 – 0.14)	
Median	0.1	1.9	5.2	0.05	0.0001*
(IQR)	(0.08 – 0.4)	(0.5 – 10.5)	(2.4 – 11.9)	(0.03 – 0.06)	
IL-6 pg/ml					
(Range)	(4.19 – 1308)	(40 – 2804)	(36.0 – 1642)	(2.3 – 19.0)	
Median	40	382	162	4	0.0001*
(IQR)	(10 – 68)	(71 – 1991)	(50 -546)	(3 – 6)	

Range, Median and IQR: nonparametric test. *: Significant

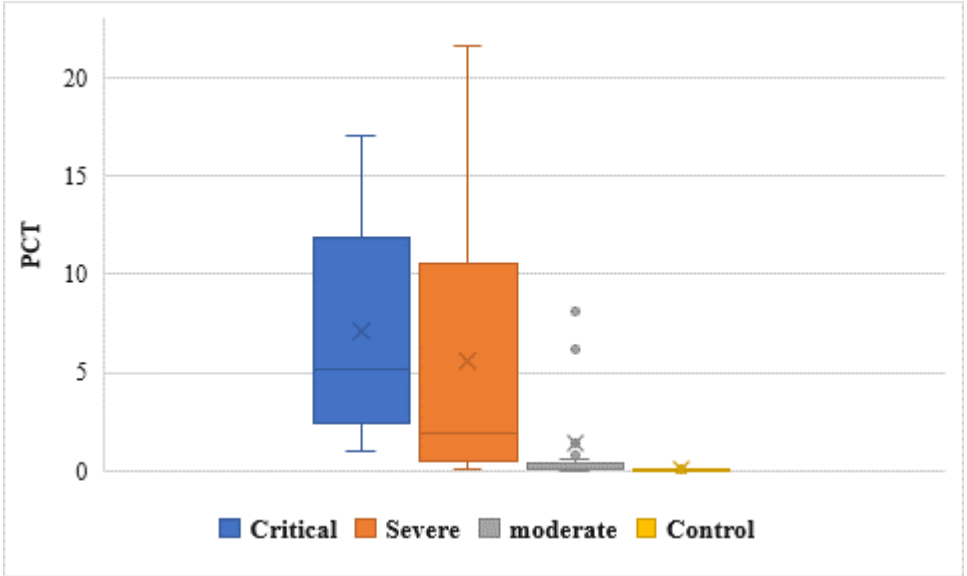

Figure (1): Boxplot of PCT for the 4 groups.

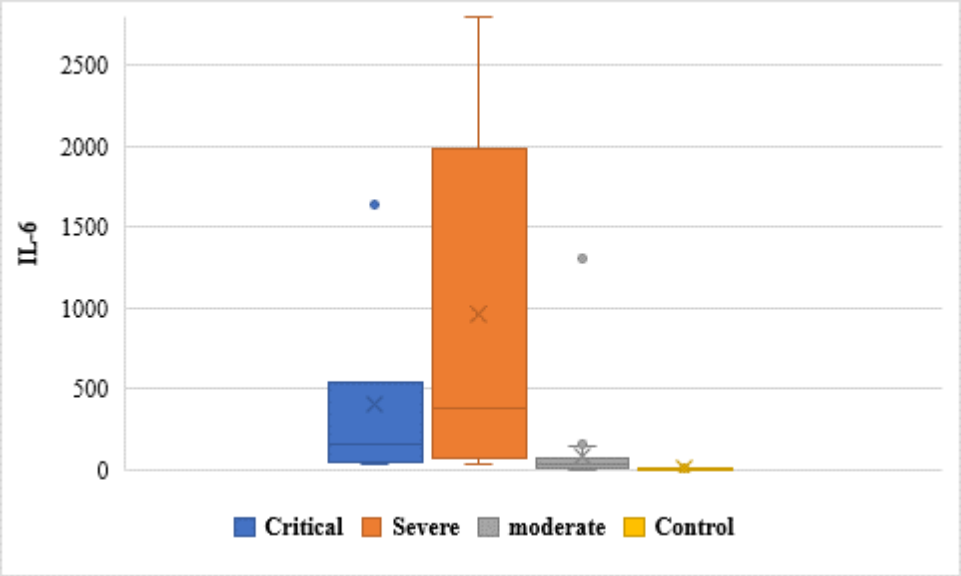

Figure (2): Boxplot of IL-6 for the 4 groups

With the exception of group Ib and Ic, there was a statistically significant difference in PCT and IL-6 between each patient group and the control, as well as between each patient group and each other (Table 5).

Table (5): Comparison of *p*-value between each two groups regarding PCT and IL-6

	Group Ia Vs Ib	Group Ia Vs Ic	Group Ib Vs Ic	Group Ia Vs II	Group Ib Vs II	Group Ic Vs II
PCT	0.003*	0.0001*	0.325	0.01*	0.0001*	0.0001*
IL-6	0.001*	0.004*	0.365	0.0001*	0.0001*	0.0001*

*: Significant

Procalcitonin (PCT) had a substantial strong positive connection with ferritin, D-dimer, and CRP. While PCT and absolute lymphocyte count had a moderately significant negative connection (Table 6).

Table (6): Correlation between PCT and (Ferritin, D- dimer, absolute lymph count and CRP)

	PCT	
	R	P
Ferritin	0.703	**0.0001***
D- dimer	0.721	**0.0001***
Absolute lymph count	-0.571	**0.0001***
CRP	0.711	**0.0001***

*: Significant

Interleukin-6 (IL-6) had a significant strong positive connection with ferritin, D-dimer, and CRP. While the absolute lymphocyte count had a significant moderately negative connection with IL-6 (Table 7)**.**

Table (7): Correlation between IL-6 and (Ferritin, D- dimer, Absolute lymph count and CRP).

	IL- 6	
	R	P
Ferritin	0.722	**0.0001***
D dimer	0.801	**0.0001***
Absolute lymph count	-0.517	**0.0001***
CRP titre	0.792	**0.0001***

*: Significant

DISCUSSION

The SARS-CoV-2-related coronavirus disease outbreak of 2019 (COVID-19) has developed into an ongoing worldwide health emergency. A progression of COVID-19 into a severe and critical stage may be indicated by changes in laboratory indicators, proinflammatory cytokines, and potential consequences **(9).** In this study, we aimed to evaluate the role of PCT and IL-6 as prognostic markers in COVID-19 patients.

This study found a statistically significant difference in PCT between the studied groups, as well as between each patient group and the control, and between patient groups themselves, with the exception of group Ib and Ic. This difference was higher in each patient group than the control and inversely correlated with the severity of each group.

According to **Mertoglu *et al.*** **(10)** admitted COVID patients had a greater PCT level than non-COVID patients, which was in conformity with what was said. According to **Malik *et al.*** **(11)**, who found that patients with severe COVID19 had higher PCT levels on average than those with a less severe course, patients with higher PCT were also more likely to experience a negative result.

This study demonstrated a statistically significant difference in the level of IL-6 between the patient groups and the control group, in addition to differences between the patient groups and each other in terms of severity. This was in agreement with **Santa Cruz *et al.*** **(12)** who found that higher levels of IL-6 correlate with the severity of the disease and are particularly good at identifying patients who progress to more severe stages of COVID-19. They also found that several patients who were moderately ill had very high IL-6 levels just before they became severely ill, 1 or 2 days later, suggesting that IL-6 may be a potential prognostic marker with patterns, as was also found by **Liu *et al.*** **(13).** This study demonstrated a statistically significant rise in IL-6 levels in the patient groups compared to the control group. It also agreed with **Cao *et al.*** **(14)**, who stated in their study that it is crucial to distinguish between various diseased groups according to severity using IL-6 and other markers for patient monitoring, resource management, or to support crucial clinical decisions like safely discharging patients.

Many additional studies, including those by **Santa Cruz *et al.*** **(12)** and **Milenkovic *et al.*** **(15)** in Italy and Serbia, respectively, looked at the predictive value of IL-6 on a number of clinical aspects of COVID-19 and discovered that the level of IL-6 at admission was useful to predict the risk of patients needing mechanical ventilation or high-flow oxygen during hospitalization. This is also in line with **Ruan *et al.*** **(16)** research, which discovered that individuals with COVID-19 who had elevated blood levels of the inflammatory marker IL-6 were more likely to die.

Studies like **Que *et al.*** **(17), and Saha *et al.*** **(18)** found that the phenomenon of (CRS) in COVID-19, which is a significant mechanism of morbidity and death in severely and critically ill patients, was used in the study to explain such a relationship between high levels of IL-6 in severe patients having severe progressive clinical courses. The therapeutic trials in which IL-6 inhibitors, such as anti-IL-6 monoclonal antibodies, had acted as immunomodulatory agents that directly targeted the cytokines involved in COVID-19 and helped relieve the hyper-inflammatory symptoms in severe cases, strongly supported the notion that IL-6 had a crucial role in such a phenomenon for COVID-19 patients. **(19).** According to the study's findings, procalcitonin showed a significant strong positive connection with ferritin, D-dimer, and CRP. This was in line with the findings of **Man *et al.*** **(20)**, who noted a favorable correlation between PCT, inflammatory markers including CRP, *and* serum ferritin as well as with the severity of the illness.

Our study findings on Interleukin-6 (IL-6) revealed a substantial positive correlation with ferritin, D-dimer, and CRP. This was in line with the findings of **Sayah *et al.*** **(21)** who observed that there was a substantial positive association between the level of IL6 and other immune-inflammatory markers such as PCT, CRP, and ferritin.

In the current study, the median length of ICU stay for patients in the moderate group was 9 days, compared to 17 days for each of the severe and critical groups. This was consistent with the findings of **Guan *et al.*** **(22)** who reported a median of 12 days for 1099 COVID-19 patients in China and **Grasselli *et al.*** **(23)**

who reported a median of 9 days for 1,591 ICU patients in Italian research.

Pijls *et al.* [(24)] reported that patients aged 70 years or older and men had higher rates of COVID 19 infection, disease severity, ICU hospitalisation, and death; however, this investigation did not find a statistically significant difference between the analysed groups regarding sex or age**.**

CONCLUSION

Overall, the findings of this study indicated that PCT and IL-6 levels can be regarded as appropriate prognostic markers in Covid-19 patients that were admitted to ICU predicting severe disease course and adverse outcome.

RECOMMENDATIONS

1- Assess the role of PCT and IL-6 and advise focusing of screening them besides routine investigation in ICU patients to predict prognosis and outcome.
2- Serial measurements of both PCT and IL-6 for early prediction of deteriorating disease course.

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Competing interests: Nil.

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