ORIGINAL ARTICLE

Prognostic value of Procalcitonin and Interleukin 6 in COVID-19 patients

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ABSTRACT

Background: *The inflammatory response plays a critical role in (COVID-19), and inflammatory cytokine storm increases COVID-19 infection severity.* ***Objective:*** *To investigate the ability of interleukin-6 (IL-6) and procalcitonin (PCT) to predict COVID-19 disease severity.* ***Methodology:*** *Cross sectional analytic study included 55 patients diagnosed with COVID-19 Clinically, radiologically and confirmed by PCR, who were admitted in the Intensive Care Units of Al Kasr Al Ainy Isolation Hospitals from July 2020 to March 2021. The study population was divided into two groups according to disease severity: a moderate group (n=25) and a severe group (n=30). Data on the clinical characteristics, demographic characteristics, IL-6 and PCT levels were carefully collected.* ***Results:*** *Among our 55 patients, IL-6 and PCT levels were increased in 100 % and 27.3% of the patients respectively. The proportion of patients with elevated PCT levels was significantly high in the severe group when compared to the moderate group. Cox proportional hazard model demonstrated that PCT can be a significantly better method to detect the severity COVID 19 infection more than IL-6 (AUC (95% CI), P value = 0.696 (0.52- 0.87), 0.025 vs. 0.611 (0.461- 0.762), 0.201) respectively.* ***Conclusion:*** *IL-6 and PCT levels can be considered effective markers in the determination of COVID-19 severity and disease progression.*

INTRODUCTION

COVID-19 presents an important and urgent threat to global health. Since the outbreak in early December 2019 in the Hubei province of the Republic of China, more than 1.2 million people have died from covid-19 till the 3rd of November 2020.[1]

Although public health responses aimed at containing the disease and delaying the spread, several countries have been challenged with a critical care crisis. To lessen the burden on the healthcare system, efficient diagnosis and information on the prognosis of the disease are needed. [2]

Much of the critical illness associated with SARS-CoV-2 infection is believed to be due to a hyper-inflammatory process referred to as a "cytokine storm". [3] Cytokine storm is mainly characterized by raised plasma concentration f interleukin 6 IL-6.[4]

Recently, several studies demonstrated that high levels of PCT are positively associated with COVID-19 severity, it was suggested that these high levels may be because of the bacterial co-infection that is causing increased severity. [5]

The aim of our work is to investigate possible associations between different inflammatory and hematological markers, mainly Interleukin 6 and procalcitonin and COVID-19 severity over a period of 9 month from Juy 2020 till March 2021.

METHODOLOGY

Study Design:

We conducted a Cross sectional analytic study on 55 patients diagnosed with COVID-19 clinically, radiologically and confirmed by PCR who were admitted in the Intensive Care Units at Kasr Al Ainy Isolation Hospitals from July 2020 till March 2021.

Data Collection:

The following data were carefully collected from patients with COVID-19 infection: name, age, sex, location of admission and unit, clinical picture, laboratory findings, radiological confirmation, duration of hospitalization, time of hospital discharge, co-morbidities and complications. All patients were carefully monitored in the ICU. Demographic and clinical informations were obtained from medical records, and informed consent was obtained from all the participants. The patients were classified into two groups in terms of the disease severity; there was a moderate group (consisting of 25 patients) and the severe group (consisting of 30 patients). Patients were classified according the four-classification system made

by Daegu Medical Association for fast classification of patients with COVID-19.[6]

Study Subjects:

A total number of 55 patients with COVID-19 infection were confirmed as positive cases by SARS CoV-2 nucleic acid RT-PCR. Specimens were obtained by oropharyngeal swabs, before or during hospitalization.

Sampling Techniques:

Ten ml of venous blood were collected from each participant in the morning a day after their admission and distributed into four vacationer tubes; (one EDTA tube, two serum tubes and one coagulation tube) and then analyzed within 2 hours. Routine blood tests; Complete Blood Count, CRP, D-dimer, Ferritin, LDH, PCT and IL-6 were done..

Assessment of Serum PCT and IL-6 levels

Serum samples were centrifuged first at 4000 RCF (g) for 3 minutes to separate the plasma.

Both PCT and IL6 were measured using the principle of electrochemiluminescence immunoassay "ECLIA" via the Cobas e 801 immunoassay analyzer using the Elecsys BRAHMS PCT assay kits and Elecsys IL-6 kits, respectively.

Routine investigations

Ferritin, LDH and CRP were all assayed by the electrochemiluminescence principles via the Cobas 6000 analyzer, while D dimer was measured by the Stago (STA-Max) through the immunoturbidimetric assay.

Complete blood count was detected from the EDTA tubes using the 5part differential hematology analyser (Sysmex XN-1000) via the Fluorescence Flow Cytometry principle.

Radiological assessment

The Dutch Radiological Society established the Coronavirus disease 2019 (COVID-19) Reporting and Data System (CO-RADS) based on other efforts for standardization, such as the Lung Imaging Reporting and Data System. CO-RADS assesses the suspicion for pulmonary involvement of COVID-19 on a scale from 1 (very low) to 5 (very high). The system was done and used in patients with moderate to severe symptoms of COVID-19. [7]

Statistical analysis:

Based we analyzed the data using Statistical Package for Social Science (SPSS) version 24. Qualitative data are expressed in terms of frequencies and percentages. Numerical data are expressed in terms of mean and standard deviation in case of numerically distributed and median and interquartile range if non normally distributed. Shapiro-Wilk test was used to detect the normality of distribution of data. Chi-square test was used to test the association between categorical variables. For numerical variables, we used independent sample t test to test the association between numerical variables if normally distributed and Mann Whitney test if not normally distributed. For testing the difference between numerical variables with more than 2 categories, one-way Anova test was used. P values less than 0.05 were considered statistically significant.

RESULTS

The 55 patients of our study were classified into 2 groups; 25 patients (45.5%) were classified as moderate group and 30 patients (54.5%) were classified as severe group. Among them there were 40 (68.1%) discharged patients and 15 (31.9%) arrested.

On comparing the sociodemographic characteristics between severely and moderately symptomatized patients, we found that age was not a significant indicator for severity of symptoms on admission (p=0.953). Among the moderate group, 14 patients (82.4%) had Co-morbidities while in the severe group 31 patients (81.6%) had Co-morbidities (p=1.000) as shown in **table 1.**

Table 1: **Difference in sociodemographic findings between the moderate and severe groups**

Variable	Severity		P value
	Moderate (n=25)	Severe (n=30)	
Age	60 ± 12.56	60.24±14.3	0.953[a]
Co-morbidities	14 (82.4%)	31 (81.6%)	1.000[b]
[a] Independent sample T test [b] Chi-square Test			

Out of the 25 patients of the moderate group 12 patients (48%) were CORADS 4 and the remaining 13 patients (52%) were CO-RADS 5. On the other hand all the patients in the severe group were CO-RADS 5 (P=<0.001) as shown in **table 2.**

Table 2: Difference in radiological findings between the moderate and severe groups:

Variable	Severity		P value
	Moderate (n=25)	Severe (n=30)	
CT Findings			
▪ **CO-RADS 4**	12 (48%)	0	<0.001[b]
▪ **CO-RADS 5**	13 (52%)	30 (100%)	
[a] Independent sample T test [b] Chi-square Test			

Among our study population, patients in the severe group had significantly lower levels of oxygen saturation than the moderate group (74.4±15.1 vs 87.47±8.8, respectively. P=0.002). The TLC, Ferritin and CRP median levels were extremely elevated in the severe group in comparison to the moderate group (p=0.01, p=0.001, p= 0.012, respectively) as shown in **table 3**

PCT median level was significantly higher among the severe group compared to the other group (P=0.019). On the other hand, the IL-6 greatly differed between the two groups but it was non-significant. (P=0.201) as shown in **table 3.**

Table 3: Differences in laboratory findings between the moderate and severe groups of patients:

Variable	Severity		P value
	Moderate (n=20)	Severe (n=35)	
SO_2 (room air)	87.47 ± 8.8	74.4 ± 15.1	0.002[a]
TLC	7.9 (6.93 – 11.21)	11.75 (9.66 – 18.98)	0.01[b]
Ferritin	695.8 ± 496.81	1279.45 ± 720.47	0.001[a]
CRP	51 (19.3 – 100.85)	139 (48.95 – 174.73)	0.012[b]
D-dimer	1.35 (0.55 – 6.88)	1.4 (0.8 – 4)	0.766[b]
LDH	372.94 ± 205.41	561.85 ± 291.43	0.024[a]
PCT	0.1 (0.03 – 0.5)	0.31 (0.17 – 0.82)	0.019[b]
IL-6	59.35 (24.3 – 104.3)	101 (29.65 – 417.5)	0.201[b]

[a] Independent sample T test
[b] Mann-Whitney Test

Among the moderate group, 21 patients (84%) were discharged after complete resolution and 4 patients (16%) died. While in the severe group, 19 patients (63.3%) survived and 11 patients (36.7%) arrested (p= 0.13).

When comparing the outcomes of the patients, we found that oxygen saturation level was a significant indicator of patient's death. Patients with low oxygen saturation were highly susceptible to death (P=0.009). The TLC was significantly elevated among patients arrested compared to those discharged (P=0.002) as shown in **table 4.**

The ferritin level also significantly differed between both groups. It was significantly elevated in mortality group compared to the other one (P=0.03). CRP serum levels were also higher among people who arrested (P=0.002).

PCT and IL-6 levels were higher in arrested patients but it wasn't significant (P=0.117, P=0.189, respectively) as shown in **table 4.**

Table 4: Association between laboratory findings and the outcomes of the studied patients:

Variable	Outcome		P value
	Discharge (n=40)	Arrest (n=15)	
SO_2 (room air)	84.06 ± 8.96	67.47 ± 20.67	0.009[a]
TLC	10.7 ± 5.48	17.38 ± 7.2	0.001[a]
Ferritin	828 (478 – 1678)	1875 (760 – 2000)	0.06[b]
CRP	55.6 (23.6 – 132.25)	144 (138 – 199)	0.002[b]
D-dimer	0.96 (0.58 – 2.95)	3.8 (1.05 – 9.92)	0.036[b]
LDH	404.21 ± 276.9	619 ± 219.51	0.015[a]
PCT	0.2 (0.06 – 0.48)	0.3 (0.13 – 5.8)	0.117[b]
IL-6	58.6 (24 – 139.7)	321.4 (27.76 – 839)	0.189[b]

[a] Independent sample T test
[b] Mann-Whitney Test

By comparing sociodemographic characteristics in the discharged and the arrested patients we found that both ages and presence of comorbidities were not significant indicators of patients mortality (P=0.817, P=0.697, respectively). On reviewing the CT findings, patients with CO-RADS 4 had a good outcome. Most of them were discharged. Whereas, in patients with CO-RADS 5, 30 patients (69%) were discharged while 13 (30.2%) patients died as shown in table 5.

Table 5: Association between the outcomes, sociodemographic characteristics and the radiological findings of the studied patients:

Variable	Outcome		P value
	Discharge (n=40)	arrest (n=15)	
Age	60.6 ± 13.76	61.6 ± 13.92	0.817 [a]
Co-morbidities	25 (65.8%)	13 (34.2%)	0.697 [c]
CT Findings			0.477[c]
▪ **CO-RADS 4**	10 (83.3%)	2 (16.7%)	
▪ **CO-RADS 5**	30 (69.8%)	13 (30.2%)	

[a] Independent sample T test
[c] Fissure exact Test

For testing the accuracy of both IL-6 and PCT in detecting COVID-19 severity of infection we developed ROC curve analysis and found that:
PCT can be a significantly better method to detect the severity of COVID19 infection more than IL-6 (AUC (95% CI), P value = 0.696 (0.52- 0.87), 0.025 vs. 0.611 (0.461- 0.762), 0.201) respectively as shown in figure 1.

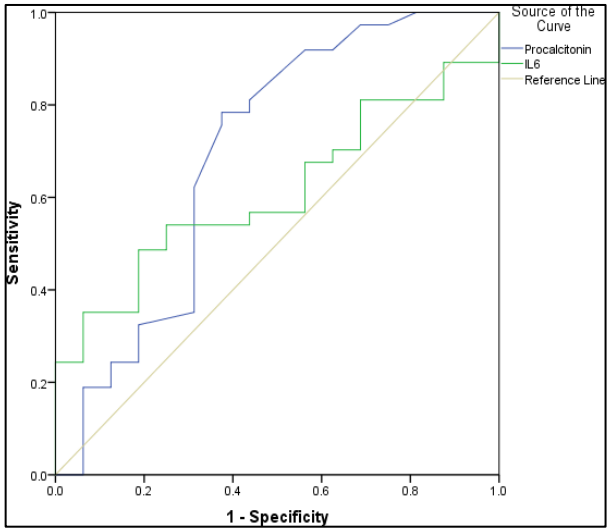

Fig. 1: ROC curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig	95% CI	
				Lower Bound	Upper Bound
Procalcitonin	.696	.090	.025	.520	.872
IL6	.611	.077	.201	.461	.762

DISCUSSION

Coronavirus disease 19 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in Wuhan, China, in December 2019. It spreads globally and resulted in a pandemic with more than 55 million cases and more than 1.6 million deaths by November 2020.[8]

Clinical and laboratory findings that can deliver a reliable COVID-19 prognosis will help in evaluating the risk of some patients to develop serious disease. It will also provide guidance for the best possible management of health resources.[9] The identification of laboratory parameters that can be used as predictor of severity or the mortality risk will facilitate appropriate treatment planning. [10]

Our present study included 55 samples from COVID-19 patients admitted in the ICU of Kasr Al Ainy Isolation Hospitals from July 2020 to March 2021. Patients were diagnosed clinically, radiologically and confirmed by PCR.

The 55 patients in the current study were categorized into 2 groups: 25 moderate cases (45.5%) and 30 severe cases (54.5%). Patients were classified according to the four-classification system made by Daegu Medical Association for fast classification of patients with COVID-19.[6]

In our current study, the moderate group had oxygen saturation mean 87.47 ± 8.8 while in severe group it was 74.4±15.1. This agrees with a study done by Aalinezhad et al, [11] where the mean blood oxygen saturation was 89.65±8.09.

The significant lower level of oxygen saturation in the severe group compared to the moderate group was similar to a study reported by Rubin et al, [12] which found that lower oxygen saturation at presentation was significantly related to measures of disease severity and thus may be used as a useful indicator of potential disease progression.

In our study population, TLC level in the moderate group was 7.9 (6.93 – 11.21) and in severe group was 11.75 (9.66 – 18.98) which is statistically significant (p=0.01). This result is similar to a prospective study reported by Schöning et al, [8] where TLC values were significantly difference in severe group (median values: 10.60 (7.83, 17.55)) and non- severe group (median value: 5.92 (4.70, 7.77)) with (p= <0.02), and a meta-analysis done by Feng et al, [13] that revealed a significant increase in number of WBC in severe COVID-19 group.

Among our study population, ferritin levels were 695.8±496.81 ng/l and 1279.45±720.47 ng/l in the moderate and severe groups respectively. There is a significant difference in ferritin level between patients in our two groups (p=0.001) which is similar to the study reported by Sun et al, [14] where ferritin level was significantly elevated in both severe and critically ill groups.

In the current study, CRP levels in the moderate group were 51 (19.3 – 100.85) mg/L while in the severe group were 139 (48.95–174.73) mg/l which is statistically significant (p=0.012).

Several studies have reported the importance of CRP level as a predictor of COVID-19 severity which agree with our study, such as the study conducted by LiuF et al, [15]where the percentage of cases with increased levels of CRP was significantly higher among the severe group than in the mild group.

Among the 55 patients in our present study, the median value of LDH level was 461 (297.3 – 663). There was difference between the LDH levels in our two groups with the median value in the moderate group 372.94 and in the severe group 561.85 which was statistically significant (p=0.024).

These results agree with the study of Han et al, [16] which proved a strong correlation between LDH, lung damage and disease severity of COVID-19 cases with (P= <0.001) and also agree with the study done by Sun et al; [14]which stated that LDH has a significant positive correlation to the disease severity (p=0.01).

In our study population, the median values of D-dimer was 1.4 (0.7 – 4.7) ml/l. Its median value in the moderate group was 1.35 (0.55 – 6.88) while in the severe group was 1.4 (0.8–4) ml/l showing no statistical significance.

Like a study conducted by Sun et al,[14] D-dimer did not reach statistical significance, in contrast a study conducted by Odabasi et al, [10] which reported that the D-dimer is level correlated with the disease severity.

Among all the 55 patients in the present study, PCT level was significantly higher among the severe group compared to the second group (P=0.019) with median values of 0.1 (0.03 – 0.5) and 0.31 (0.17 – 0.82) in the moderate and severe groups respectively. High PCT levels among the severe group indicate its effect on the disease progression and indicate that patients could have concomitant bacterial infections.

These results agree with results of many previous studies as the study performed by Odabasi et al, [10] who demonstrated that PCT value was related to the disease severity and the study done by LiuF et al, [15] where there were significant differences regarding the PCT level between the mild and severe groups with (p=0.025).

In our present work although there were differences between IL-6 levels in the 2 patient groups, with a median value in the moderate group [59.35 (24.3–104.3) pg/ml] and in severe group [101 (29.65 – 417.5) pg/ml], it wasn't statistically significant. This could be because of the close proximity of the symptomatology and the laboratory results between both groups.

These results come in contrast to a study performed by Chen et al, [4] where sharply increased IL-6 level was observed among critically ill cases, it was almost 10 times that of severe patients, although the median IL-6 levels in the moderate and severe groups were 10.4 (3.8–31.0) and 5.8 (3.1–16.9) pg/ml respectively, while in the critically ill cases it was 64.0 (25.6–111.9) pg/ml. It also comes in contrast to the study conducted by LiuF et al, [15] where the proportion of cases with elevated IL-6 levels was significantly higher among the severe group than the moderate group (P < 0.001).

In the current study, according to the COVID‑19 Reporting and Data System (CO-RADS), the percentage of patients classified as CO-RADS 5 was 78.2% (43 patients) while the rest of patients 21.8% (12 patients) were classified as CO-RADS 4. This is agreed with the study performed by Azab et al, [17] where the majority of cases were classified as CO-RADS 5 with 43%.

In the present study population, all the cases in the severe group were classified as CO-RADS 5 while in the moderate group 12 patients (48%) were CORADS 4 and 13 patients (52%) are CO-RADS 5. These results agree with the results of a study done by Özel et al [18] where of the CO-RADS 5 patients, 57% were from the medical floor (less severe patients), 61% were from ICU who were transferred from the medical floor, and 92% were from the ICU, which indicates that the more severe patients had the CORADS 5 CT images.

Out of the 55-study population, 68.1% (40 patients) were discharged from the hospital and 31.9 % (15 patients) died. Among the moderate group, 84% (21 patients) were discharged after complete resolution. Whereas 36.7% of the severe group arrested (11 patients).

Other studies have found a lower incidence of mortality as in the study of Borobia et al, [19] where 20.7% of the cases died while 79.3% of them were discharged and the study performed by Odabasi et al, [10] where only 8.56 % of our study population died, most of them (51.35%) were from the group of patients who had the more severe symptoms and admitted to the ICU.

In our current study, the levels of oxygen saturation, TLC, Ferritin, CRP, D-dimer and LDH were significantly higher among the patients who died than the survivors with (p=0.009, p=0.001, p=0.06, p=0.002, p=0.036 and p=0.15) respectively.

These results agreed with the results of the meta-analysis performed by Huang et al, [20] which showed that elevated serum CRP, Ddimer, and ferritin were correlated with a bad outcome in COVID-19 in addition, another study conducted by Borobia et al, 2020 [19]who stated that D-dimer, ferritin, LDH and CRP are higher in the patients with fatal outcomes.

In our work, there was a nonstatistical significance between PCT level and the patients' death although PCT levels were lower in the survivors. This disagree with the study done by Huang et al, [20] who reported a t higher PCT levels were associated with poor outcomes.

Although the levels of IL-6 differed greatly between the discharged and the arrested patients with median levels of 58.6 (24 –139.7) ng/ml and 321.4 (27.76 – 839) ng/ml respectively, it wasn't statistically significant. These results disagree with the results in the meta-analysis performed by Aziz et al, [21] which demonstrated that increasing mean IL-6 on admission was associated with an increased likelihood of mortality.

In the present study, we developed ROC curve analysis and demonstrated that PCT can be a significantly better method to detect the severity of COVID-19 infection more than IL-6 (AUC (95% CI), P value = 0.696 (0.52- 0.87), 0.025 vs. 0.611 (0.461-0.762), 0.201) respectively.

These results disagree with the results conducted by LiuF et al,[15] where both IL-6 ($P < 0.001$) and PCT ($P=0.002$) are considered independent factors for predicting the severity of infection with COVID-19.

CONCLUSION

Our study was conducted at Kasr Al Ainy Hospitals during a period of 9 months from July 2020 to March 2021. Levels of IL-6 and CRP were elevated in all of the ICU cases which indicated their effect on the severity.

PCT, ferritin and LDH levels were significantly higher among the severe group than the moderate group which indicated their effect on progression and prognosis of the disease.

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