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ORIGINAL ARTICLE

The Value of Interleukin-6 Among Several Inflammatory Markers as a Predictor of Respiratory Failure in COVID-19 Patients

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Abstract

Background: **The severe acute respiratory syndrome coronavirus, often known as SARS-CoV-2, can lead to severe pneumonia and hypoxia. Some studies have shown that interleukin-6 (IL-6) can indicate respiratory failure in COVID-19 patients.**

Aim of the work: **To determine if the laboratory marker IL-6 has the ability to predict respiratory worsening in COVID-19 patients 3 days after hospital admission.**

Patients and methods: **The last 100 consecutive COVID-19-infected individuals as determined by a positive reverse transcription real-time polymerase chain reaction (rt RT-PCR) test of their respiratory tract swabs were included in this retrospective study. Patients were separated into two groups based on the highest FiO_2 they needed in the first 3 days after admission; group with low FiO_2 and group with high FiO_2.**

Results: **In comparison to the low FiO_2 group, the high FiO_2 group had considerably greater serum IL-6 levels. In comparison to the low FiO_2 group, the non-survivors' percentage was much higher in the high FiO_2 group. In addition, in both low and high FiO_2 groups, serum IL-6 was considerably lower in survivors compared with non-survivors. According to the ROC curve, IL-6 displayed an AUC of 0.82 with a strong significance at a cutoff value of 41.2 pg/mL. Sensitivity, specificity, PPV, and NPV were 88.2%, 79.8%, 52.2%, and 96.4%, respectively.**

Conclusion: **In COVID-19 patients who have been admitted to the hospital, serum IL-6 is a potent indicator of early respiratory failure. Elevated IL-6 levels are linked to mortality and the requirement for mechanical ventilation (MV).**

Keywords: COVID-19, Interleukin-6, Respiratory failure

1. Introduction

In Wuhan, Hubei province, China, SARS-CoV-2 was found during a pneumonitis outbreak in December 2019. The World Health Organization (WHO) proclaimed the virus to be pandemic in March 2020.[1] Furthermore, the virus has been shown to cause severe respiratory diseases with a fatality rate of 2.9%.[2] Some coronavirus disease 2019 (COVID-19) patients may develop respiratory deterioration for variable periods of time during their clinical course, making it crucial to identify those who are more likely to experience substantial symptoms as early as conceivable.[3]

Abbreviations: ALT, Alanine transaminase; AST, Aspartate aminotransferase; AUC, Area under the curve; BMI, Body mass index; CBC, Complete blood count; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; FiO_2, Fraction of inspired oxygen; Hb, Hemoglobin; HRCT, High-resolution computed tomography; ICU, Intensive care unit; IL, Illinois; IL-6, Interleukin-6; LDH, Lactate dehydrogenase; MV, Mechanical ventilation; NPV, Negative predictive value; PPV, Positive predictive value; RBS, Random blood sugar; ROC, Receiver-operating characteristic; rpm, Revolutions per minute; rt-RT-PCR, Reverse transcription real-time polymerase chain reaction; SARS-Cov-2, Severe acute respiratory syndrome coronavirus 2; SD, Standard deviation; SO_2, Oxygen saturation; USA, United States of America; WHO, World Health Organization.

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The capacity of various inflammatory cytokines in COVID-19 patients, such as IL-6, to distinguish between varying degrees of disease severity was examined. Accordingly, COVID-19's radiologic alterations and illness stages are positively correlated with IL-6.[4]

Furthermore, it has been proposed that IL-6, either alone or in combination with other indicators, has predictive significance in foreseeing the need for invasive mechanical ventilation, mortality, or both.[5]

This study's goal was to assess the laboratory marker IL-6's predictive significance for respiratory deterioration in COVID-19 patients within 3 days of hospital admission.

2. Patients and methods

Data from the most recent 100 consecutive COVID-19-infected individuals who satisfied our inclusion criteria and did not meet our exclusion criteria at the time this study was launched were included in this retrospective analysis. All patients were admitted at the COVID-19 isolation sector in Bab Al-Sha'eria and Al- Hussein University Hospitals, after being diagnosed by positive (rt RT-PCR) test of their respiratory tract swabs.

Inclusion criteria: Adult patients who tested positive for COVID-19 by rt-RT-PCR and underwent positive high-resolution computed tomography (HRCT) for signs of pneumonia.

Exclusion criteria: Patients who had any of the following conditions were totally excluded from the study: age <18 years, negative PCR for COVID-19, normal HRCT on chest, advanced chronic chest illness, known fixed radiologic lesions mimicking those occur in COVID-19 pneumonia, uncompensated vital organ disease which may cause hypoxemia, e.g., cardiac, hepatic or renal failure, neuromuscular disorders, history of recent steroids intake or regular inhaled/systemic steroids therapy.

2.1. Sample size

Epi-Info STATCALC was used to calculate the sample size by considering the following assumptions: 95% two-sided confidence level, with a power of 80% and an α error of 5%; odds ratio calculated = 1.215. The final maximum sample size taken from the Epi-Info STATCALC output was 95. Thus, the sample size was increased to 100 for more accuracy.

2.2. Methods

The following data were obtained and registered using the medical records of included patients:

Personal/demographic data: age, sexual orientation, and smoking behavior. Patients' body mass indices (BMIs) were computed using the formula: BMI = weight (kg)/squared height (m^2).

Clinical data: including symptoms, signs, and comorbidities, e.g., DM, hypertension, COPD, chronic kidney disease, etc.

Laboratory values measured at admission: CBC, CRP, ESR, random blood sugar (RBS), AST, ALT, serum creatinine, blood urea, IL-6, LDH, ferritin, and D-dimer.

IL-6 levels were measured in serum after blood sample centrifugation at 3000 rpm for 5 min using RayBiotech IL-6 ELISA kit (RayBiotech Life, Inc., 3607 Parkway Lane, Georgia, USA), which is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human IL-6 in cell culture supernatants, plasma, serum, and lysate samples.

Received medications during or before admission: including supplemental oxygen, steroids e.g., dexamethasone, antiviral drugs e.g., favipiravir and remdesivir, biological treatment e.g., tocilizumab and invasive mechanical ventilation.

Clinical outcome: as survivor and non-survivor.

Patients groups: According to the greatest oxygen fraction (FiO_2) needed to acquire 94% oxygen saturation (SO_2) (or the highest SO_2 that could be reached) within the first 3 days of hospital admission, patients were divided into two groups: **Low FiO_2 group (LFG):** which included 80 patients with the maximum FiO_2 required was <0.4. **High FiO_2 group (HFG):** which included 20 patients with the maximum FiO_2 required was ^{3}0.4.

For patients not submitted for invasive mechanical ventilation, FiO_2 was estimated using the following table[6]:

Oxygen delivery device	Flow rate (L/min)	Approximate FiO_2
Nasal cannula	1–6	0.24–0.44 FiO_2 = 20+4n (n = number of L/min)
Simple face mask	5–8	0.40–0.60
Partial rebreathing mask	6–10	0.60–0.80
Non-rebreathing mask	10–15	0.90–1.00
Venturi mask	2–15	0.24–0.60

FiO_2, fraction of inspired oxygen.

Ethical considerations: The study's procedure received approval from the Al-Azhar University Ethics Committee. The signed, verified consent criteria was waived as a result of the study's retrospective design. However, all patients' privacy was protected, and data were gathered anonymously.

2.3. Statistical analysis

The entire data collection, processing, and analysis were done using the Statistical Package for the Social Sciences (SPSS), version 14.0 (IBM corp., Chicago, IL, USA). The χ^2 test was used to evaluate a big collection of qualitative data. To present the qualitative data, frequencies and relative percentages were used. Minor qualitative frequencies were more accurately evaluated using Fisher's exact test (>20% of cells are 5). For parametric data, the mean and SD (standard deviation) were used, then tested using independent sample *t*-test, while for nonparametric data, the median and range were obtained followed by analysis using the Mann–Whitney test. The *P* value cutoff was chosen at 0.05 to indicate a significant difference, and at 0.001 to indicate a highly significant difference in all two-tailed statistical comparisons.

3. Results

As shown in Table 1, there were no statistically significant differences in age, sex, BMI, or smoking, diabetes, and hypertension between the groups under study.

There were statistically significant differences between the studied groups considering receiving of supplemental oxygen and administration of steroids, whereas there were statistically highly significant variations as regards requiring invasive mechanical ventilation, antiviral drugs, and anti-IL-6 antibodies (Table 2).

As clarified in Table 3, TLC, neutrophil count, ESR, CRP, D-dimer, serum ferritin, LDH, and IL-6 were significantly higher in high FiO_2 group compared with the low FiO_2 group, while Hb, RBS, serum creatinine, blood urea, AST, and ALT did not differ greatly between the studied groups.

Table 1. Demographic and common comorbidities distribution in the studied groups.

Demographic data	Low FiO_2 ($n = 80$)	High FiO_2 ($n = 20$)	Statistical test	*P*
Age (years) Mean ± SD	57.64 ± 12.45	59.13 ± 10.71	$t = 0.491$	0.624
BMI (kg/m^2) Mean ± SD	26.53 ± 2.37	27.12 ± 2.84	$t = 0.956$	0.341
Smoking	30 (37.5%)	11 (55%)	$\chi^2 = 2.03$	0.155
Sex				
Female	34 (42.5%)	7 (35%)	$\chi^2 = 0.372$	0.542
Male	46 (57.5%)	13 (65%)		
Comorbidity				
Diabetes mellitus	18 (22.5%)	6 (30%)	$\chi^2 = 0.493$	0.482
Hypertension	32 (40%)	12 (60%)	$\chi^2 = 2.59$	0.107

χ^2, Chi square; FiO_2, fraction of inspired oxygen; SD, standard deviation; t, independent sample *t*-test.

Table 2. Required medications during hospital admission in the studied groups.

Required medication	Low FiO_2 ($n = 80$)	High FiO_2 ($n = 20$)	*P*
Invasive mechanical ventilation	2 (2.5%)	7 (35%)	<0.001[b]
Supplemental oxygen	58 (72.5%)	20 (100%)	0.0054[a]
Steroids	56 (70%)	20 (100%)	0.0028[a]
Antiviral drugs	52 (65%)	20 (100%)	<0.001[b]
Anti-IL-6 antibodies	0 (0%)	9 (45%)	<0.001[b]

FiO_2, fraction of inspired oxygen; IL-6, interleukin-6.
NB: p is calculated using Fisher's exact test.
[a] statistically significant.
[b] statistically highly significant.

Non-survivor's percentage was significantly higher in high FiO_2 group compared with low FiO_2 group (Table 4).

IL-6 was significantly lower in survivors compared with non-survivors in both low and high FiO_2 groups (Table 5).

In COVID-19 patients, there were statistically significant correlations between a few inflammatory markers and early respiratory failure (within 3 days of hospital admission). For instance, IL-6 displayed an AUC of 0.82 with a very high significance at a cutoff value of 41.2 pg/mL. Sensitivity, specificity, PPV, and NPV, in that order, were (88.2%, 79.8%, 52.2%, and 96.4%). (Table 6), Fig. 1.

4. Discussion

Predicting abrupt clinical deterioration and the onset of respiratory failure in COVID-19 patients is still realistically challenging. Finding trustworthy markers that might foretell such hazardous circumstances in clinical settings is therefore of utmost importance.[7]

As a result, this study was designed with the goal of examining the laboratory marker IL-6's capacity to predict respiratory worsening within the first few days after COVID-19 patients' arrival. Considering demographic data, age, BMI, and sex variations across the studied groups were not statistically different. Similar to the results of the current study, Fujino et al.[4] found no statistically significant variations in age, sex, or BMI between the groups they looked at. With 16 patients in the high FiO_2 group and 65 patients in the low FiO_2 group, this study was analogous to the one we conducted.

However, we permit no intended selection of our patients, and the main parameter of patients' initial inclusion was the sequence of presentation and admission. These insignificant differences in demographic data between low FiO_2 and high FiO_2 groups add to the power of our results, as age, sex,

Table 3. Laboratory tests in the studied groups.

Laboratory test	Low FiO_2 ($n = 80$)	High FiO_2 ($n = 20$)	Z	*P*
Hb (g/dl) Mean ± SD	11.24 ± 1.63	11.11 ± 1.34	0.330	0.742
TLC ($x10^3$/l) Mean ± SD	6.41 ± 5.1	8.62 ± 2.92	2.6	0.011[a]
Neutrophil count ($x10^3$/l) Mean ± SD	4.99 ± 2.04	7.17 ± 2.52	4.007	<0.001[b]
RBS (mg/dl) Mean ± SD	237.78 ± 146.62	293.25 ± 122.55	1.56	0.122
Creatinine (mg/dl) Mean ± SD	1.13 ± 0.529	1.41 ± 0.904	1.81	0.074
Urea (mg/dl) Mean ± SD	43.16 ± 9.26	47.39 ± 11.8	1.73	0.088
ALT (U/l) Mean ± SD	24.38 ± 4.69	27.51 ± 15.78	1.54	0.127
AST (U/l) Mean ± SD	30.63 ± 7.03	32.55 ± 16.37	0.802	0.425
ESR (mm/h) Mean ± SD	40.1 ± 12.62	53.27 ± 28.29	3.13	0.002[a]
CRP (mg/l) Mean ± SD	57.23 ± 29.18	84.77 ± 34.41	3.64	0.001[a]
D-dimer (ng/ml) Mean ± SD	488.75 ± 375.71	780.22 ± 220.11	3.32	0.001[a]
Ferritin (μg/l) Mean ± SD	1125.75 ± 427.01	1386.97 ± 365.65	2.51	0.014[a]
LDH (IU/l) Mean ± SD	219.58 ± 93.66	341.63 ± 125.85	4.85	<0.001[b]
IL-6 (pg/ml) Median (range)	17 (8–61)	91 (55–145)	6.885	<0.001[b]

ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FiO_2, fraction of inspired oxygen; Hb, hemoglobin; IL-6, interleukin-6; LDH, lactate dehydrogenase; RBS, random blood sugar; SD, standard deviation; TLC, total leukocyte count; Z, the statistical score of Mann–Whitney test.
[a] Statistically significant.
[b] Statistically highly significant.

Table 4. Prognosis distribution in the studied groups.

Prognosis (outcome)	Low FiO_2 ($n = 80$)	High FiO_2 ($n = 20$)	*P*
Survivors	77 (96.25%)	16 (80%)	0.028[a]
Non-Survivors	3 (3.75%)	4 (20%)	

FiO_2, fraction of inspired oxygen.
NB: p is calculated using Fisher's exact test.
[a] statistically significant.

Table 5. Interleukin-6 levels in relation to prognosis in the studied groups.

Group	IL-6 (pg/ml) Survivors	IL-6 (pg/ml) Non-survivors	Z	*P*
Low FiO_2 group ($n = 80$)	Median (range) 15 (8–53)	Median (range) 43 (26–61)	2.624	0.0086[a]
High FiO_2 group *n*=(20)	Mean ± SD 87.06 ± 16.45	Mean ± SD 114.75 ± 22.74	2.626	0.017[a]

FiO_2, fraction of inspired oxygen; IL-6, interleukin-6; SD, standard deviation; Z, the statistical score of Mann–Whitney test.
[a] Statistically significant.

and BMI were shown to influence the severity of COVID-19 infection by the vast majority of literature.

Palaiodimos *et al.*[8] concluded that elderly, males, and morbidly obese patients infected with COVID-19 were more liable to develop clinical deterioration, ICU admission, invasive mechanical ventilation, and mortality.

Likewise, **Yamada *et al.*[9] and Li *et al.*[10]** found that the severity of COVID-19 was substantially correlated with both age and male sex. Furthermore, **Herold *et al.*[11]** found a significant relationship between the need for mechanical ventilation in COVID-19 patients with both older age and male sex but not BMI.

Alongside, **Popadic *et al.*[12]** showed that COVID-19 mortality was the same in males and females, while the liability of elder people to die from COVID-19 infection was significantly higher than middle-aged and young ones. The same results were reported by a large Spanish study.[13]

Taking into account the received medications during hospital admission in the studied groups, the high

Table 6. Some inflammatory markers as predictors of early respiratory failure in hospital-admitted COVID-19 patients.

Variable	Cutoff	AUC	SE	Sig.	95% CI	Sen.%	Spec.%	PPV%	NPV%
IL-6	41.2	0.82	0.05	<0.001[b]	0.723–0.918	88.2%	79.8%	52.2	96.4
CRP	62	0.756	0.061	<0.001[b]	0.637–0.876	86%	74.5%	45.7	95.5
LDH	245	0.75	0.058	<0.001[b]	0.637–0.863	82.5%	71.3%	41.8	94.2
D-dimer	638	0.676	0.062	0.014[a]	0.555–0.796	81.6%	68.7%	39.5	93.7
Ferritin	1200	0.67	0.06	0.014[a]	0.552–0.79	80%	67.2%	39.0	91.8

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; NPV, negative predictive value; PPV, positive predictive value; SE, standard error; Sen, sensitivity; Sig, significance; Spec, specificity.
[a] statistically significant.
[b] Statistically highly significant.

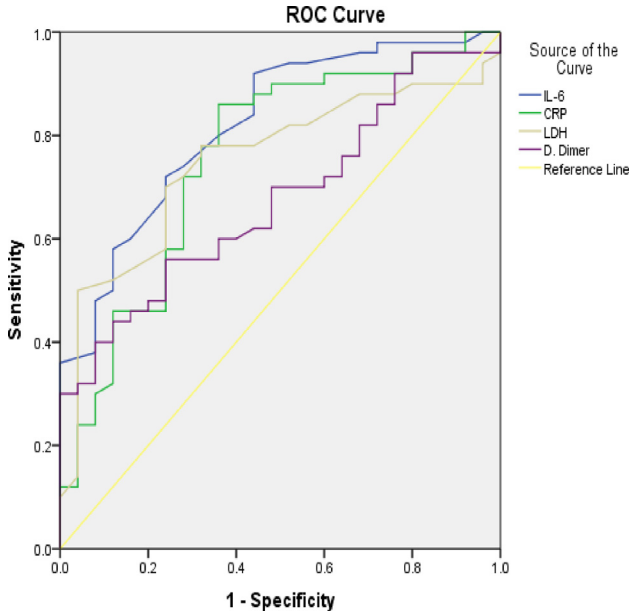

Fig. 1. Receiver-operating characteristic (ROC) curve of some inflammatory markers as predictors of respiratory failure within 3 days following hospital admission of COVID-19 patients.

FiO_2 group showed significantly more frequent indication of supplemental oxygen, steroids, antiviral drugs (remdesivir), anti-IL-6 antibodies (tocilizumab), and invasive mechanical ventilation when compared with the low FiO_2 group. Corresponding to the current study, **Fujino** *et al.*[4] reported significant differences between low and high FiO_2 groups regarding invasive mechanical ventilation and administration of steroids.

Regarding laboratory parameters done at hospital admission, our study showed that the high FiO_2 group had significantly higher levels of TLC, neutrophil count, D-dimer, ferritin, CRP, LDH, IL-6, and ESR compared with the low FiO_2 group. The levels of hemoglobin, random blood sugar, blood urea, serum creatinine, AST, and ALT did not significantly differ between the two groups. Our study is remarkably similar to that of **Yamada** *et al.*[9] as they discovered a strong correlation between the time spent on mechanical ventilation and the admission neutrophil count, levels of CRP, LDH, ferritin, D-dimer, and IL-6. An important difference in LDH, TLC, D-dimer, and IL-6 levels was also discovered by **Fujino** *et al.*[4] following hospital admission, with the higher values belonging to the high FiO_2 group. However, the former study reported a noticeably increased serum creatinine levels in the high FiO_2 group.

According to the **Herold** *et al.*[11] research, individuals with COVID-19 who had higher IL-6 levels required mechanical ventilation at the highest rates. **Ayanian** *et al.*[14] also came to the conclusion that increased IL-6 was significantly related to ICU admission. They both harmonized with our observations.

In the current study, non-survivors' percentage was significantly higher among the high FiO_2 group compared with the low FiO_2 group. This finding comes in agreement with **Fujino** *et al.*,[4] who detected a significantly higher mortality in high FiO_2 group in relation to low FiO_2 group.

Our results are also supported by **Perincek** *et al.*,[15] **Hajiahmadi** *et al.*,[16] and **Colombi** *et al.*,[17] as they all noted a strong association between low SO_2 and COVID-19 patient in-hospital mortality. The current study demonstrated the ability of this proinflammatory cytokine to predict death in COVID-19 patients by demonstrating that IL-6 was considerably lower in survivors compared with non-survivors in the low and high FiO_2 groups. These results concurred with those of **Ayanian** *et al.*[14] and **Popadic** *et al.*,[12] who found that IL-6 levels were markedly increased in COVID-19 non-survivors. Similar findings were made by **Marimuthu** *et al.*[18] and **Laguna-Goya** *et al.*,[13] who believed that greater levels of IL-6 were strongly linked to COVID-19 mortality.

In a binary logistic regression, **Santa Cruz** *et al.*[5] found that the non-survivors group's highest IL-6 level was the most important predictor of mortality, which is highly consistent with our findings. Our ROC curve investigation of some inflammatory markers permitted us to decide the most reliable indicators of respiratory failure in COVID-19 patients throughout the first three admission days. Accordingly, IL-6, CRP, LDH, and D-Dimer can be used to foresee early respiratory failure in COVID-19 patients. In the exact path with the current study, **Fujino** *et al.*[4] disclosed the validity of IL-6, CRP, and LDH for the same purpose, with the superiority of IL-6 among all.

Reciprocally, **Yamada** *et al.*[9] found that CRP levels were the best sign of respiratory distress happening 3 days after the confirmation of COVID-19 infection, trailed by ferritin, LDH, and IL-6 in order. The distinction in example size and the determination of the end limit for every marker might be the reason for this dissimilarity with our discoveries.

4.1. Limitations

Major limitations oppressing this study were: (1) it is a single-center retrospective observational study with a small sample size, (2) only six hematological inflammatory markers were tested, thus other sensitive indicators signalizing respiratory failure in COVID-19 patients may be still concealed, (3) focusing on FiO_2 and SO_2 only without affording more attention to other arterial blood gases

parameters, and (4) inability to perform regular follow-up of IL-6 levels due to shortage of resources.

4.2. Conclusion

In COVID-19 patients admitted to hospitals, serum IL-6 is a potent indicator of early respiratory failure. Elevated IL-6 levels are linked to mortality and the requirement for mechanical ventilation (MV).

Authorship

Each author made a major contribution to the study's conception and design, data gathering, data analysis and interpretation, article writing and critical revision. All authors have a substantial contribution to the article.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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Conflicts of interest

Authors reveal any business and personal connections with individuals or groups that might inadvertently influence their work.

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