Original article

Value of Interleukin 6 in Assessment of the Disease Severity in Patients with COVID-19 Infection without Preexisting Comorbidities

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Abstract

Background: In December of 2019, Wuhan, a new coronavirus-caused pandemic of atypical pneumonia was reported by China. **This study** determined IL-6 value in disease severity assessment of COVID-19 patients without preexisting pathologies. **Methods:** This cross-sectional study was conducted on 100 participants. They were classified into group A included 25 patients classified as mild or moderate cases, group B included 25 patients classified as severe cases, group C included 25 patients classified as critical ill cases and all was positive PCR COVID-19 and group D (Control Group) included 25 healthy individuals. Participants were subjected to history taking, Serum IL-6 measurement using ELISA, laboratory investigations and imaging. **Results**: IL-6 significantly differed between the studied groups ($P < 0.001$). IL-6 showed significant positive correlations with age ($r = 0.338$, $P = 0.003$), SBP ($r = 0.288$, $P = 0.012$), temperature ($r = 0.262$, $P = 0.023$), respiratory rate ($r = 0.729$, $P < 0.001$), D-dimer ($r = 0.704$, $P < 0.001$), ferritin ($r = 0.791$, $P < 0.001$), CRP ($r = 0.592$, $P < 0.001$), and severity ($r = 0.821$, $P < 0.001$). Multinomial logistic regression analysis revealed that IL-6 was a significant predictor for mild to moderate covid (OR = 7.66, 95% CI = 2.212 – 26.528, P = 0.001), severe covid (OR = 17.727, 95% CI = 4.545 – 69.141, P < 0.001), and critically ill patients (OR = 24.345, 95% CI = 6.135-96.604, P < 0.001). **Conclusion:** IL-6 can significantly predict COVID-19 severity (mild to moderate, severe and critically ill) and mortality.

Keywords: Interleukin 6; COVID-19; Severity; Comorbidities

Introduction

In December of 2019 in Wuhan, China, a novel coronavirus produced an outbreak of atypical pneumonia. WHO subsequently identified this as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its related sickness as Coronavirus Disease-2019 (COVID-19) (1). The majority of COVID-19 individuals suffer a moderate, self-limiting illness. Up to 20% of COVID-19 cases are linked to severe pneumonia, that can result in acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure. Note that deadly outcomes may occur at any age, including in children and adolescents (2). Age > 55, many underlying comorbidities, hypoxia, particular computed tomography results suggesting substantial lung involvement, numerous laboratory test abnormalities, and signs of end-organ failure are related with higher disease severity and/or fatality (3). Effective and prompt medicines are important to prevent morbidity and death during the COVID-19 outbreak. Identifying those at risk for serious disease or death requires a reliable screening method (4).

Following exposure to the COVID-19, IL-6 is a naturally occurring pleiotropic cytokine which has significant impact on respiratory failure and multiorgan dysfunction. This condition mimics cytokine release syndrome (CRS) or "cytokine storm," which may cause a range of severe side consequences (5). Multiple biomarkers, including inflammatory markers such as ferritin, CRP, D-dimer, and IL-6, are related to COVID-19 development. IL-6 seems to have an effective role in ARDS and dysregulation of immunity in COVID-19 (6).

Maximal level of IL-6 is a useful marker that has high accuracy in detecting imminent respiratory failure and mechanical ventilation need. This highlights the feasibility of utilizing IL-6 levels to guide therapy intensification in COVID-19-associated hyperinflammatory syndrome patients (7).

The purpose of this research was to establish value of Interleukin 6 in disease severity assessment in COVID-19 patients without pre-existing comorbidities.

Patients and methods

This observational comparative cross-sectional study was carried out on 100 participants (75 patients with COVID-19 disease manifestation and 25 controls) at

Benha university hospital from May 2021 to September 2022.

Inclusion criteria:

- 18 years and older.
- Patients with positive COVID-19 infection by Molecular testing (PCR) with deep nasal swab.
- Patients who haven't or on treatment for chronic diseases detected by history, clinical examination and routine investigations.

Exclusion criteria:

- Age less than 18 years
- Patients who had other comorbidities in the form of chronic liver diseases, cardiac diseases, chronic kidney diseases and chest diseases.

All parents of the participants gave their agreement in a written consent. Benha Faculty of Medicine's research ethics committee authorized the project.

Classification of patients were based on Scoring of the Covid-19 severity according to protocol for COVID-19 patients issued by Egyptian Ministry of Health and Population (8). **Mild Case**: Patient with mild symptoms (Fever, general weakness/fatigue, cough, malaise, myalgia, sore throat, headache, anorexia/nausea/vomiting, diarrhea, loss of taste and smell), No hypoxia and Normal imaging (No pneumonia). **Moderate Case**: Patient has pneumonia manifestations on radiology associated with symptoms &/or leucopenia or lymphopenia without hypoxia ($SpO_2 \geq 92\%$). **Severe Case**: Patient that has any of the following criteria: $SpO_2 < 92\%$ at room air, $PaO_2/FiO_2 <300$, Respiratory rate > 30 breaths/min and/or Chest radiology showing lung infiltrates $> 50\%$ or progressive lesion within 24 to 48 hrs. **Critically ill Case**: patient with severe disease is considered critically ill if: $SpO_2 <92\%$, **or** RR>30/min and PaO_2/FiO_2 ratio < 200 despite Oxygen Therapy and/or additional organ dysfunction.

Eligible patients are categorized into Four groups according to MOHP protocol 2021 (8); group A included 25 patients positive PCR COVID-19 classified as mild or moderate cases, group B: included 25 patients positive PCR COVID-19 classified as severe cases, group C included 25 patients positive PCR COVID-19 classified as critical ill cases and group D (Control Group) included 25 control apparently healthy individuals

All patients were subjected to personal history, past history, complaint, clinical examination including general appearance,

vital Signs, chest examination (as wheezing, decreased breath sounds, or crackling by auscultation, dullness on percussion). Human IL-6 ELISA Kit from SHANGHAI KORAIN BIOTECH CO., LTD., Shanghai, China was used to detect IL-6 in all patients' serum, blood plasma, and other connected biological liquids. Biotin double antibody sandwich technology-based enzyme-linked immune sorbent test (ELISA), this kit assays quantity of Human IL-6 in ng/l. Laboratory tests involving ALT, CBC, serum Albumin, AST, serum bilirubin, INR, prothrombin concentration, serum creatinine and urea, serum ferritin, CRP, D-Dimer and ABG and imaging.

COVID-19 is based on PCR for the SARS-COV-2 gene using nasal or pharyngeal swabs taken prior to admission, all patients underwent at least one chest CT scan after admission. RT-PCR for detection of COVID-19 was performed by deep nasal swab.

Imaging:

All patients have been undergone non-contrast-enhanced chest computed tomography (CT) in the radiology department for better assessment of the disease extent utilizing COVID-19 Reporting and Data System (CO-RADS) scheme which is a CT-based method evaluates the possibility of COVID-19 pulmonary involvement (9).

CO-RADS Categories: Based on a normal CT scan, CO-RADS 1 implies a very low suspicion for COVID-19 lung involvement (negative for pneumonia), Based on CT abnormalities that are incompatible with COVID-19 in the lungs, CO-RADS 2 supports a low suspicion for COVID-19 involvement in the lungs (atypical appearance), CO-RADS 3 reveals ambiguous evidence for COVID-19 involvement in the lungs depending on CT findings in the lungs that can be found in other viral pneumonias (indeterminate appearance), CO-RADS 4 indicates a high degree of suspicion for pulmonary involvement by COVID-19 based on CT abnormalities that are characteristic of COVID-19 but exhibit overlap with other pneumonias, Based on usual CT results, CO-RADS 5 shows a high degree of suspicion for COVID-19 lung involvement (typical appearance) and CO-RADS 6 shows that COVID-19 has been confirmed by an RT-PCR test.

All Eligible patients have been followed up during hospital stay while receiving therapy

(Anti-viral, anti-inflammatory and anticoagulant) according to the Egyptian MOHP protocol, Identify ICU admission for moderate and severe cases and determine outcome (Cure or Death). Study Tools laboratories and radiology of Abassia fever hospital.

Sample Size Calculation:

The sample size was estimated using G* power version 3.1.9.2 with test family (t-tests) and from previous study Sabaka et al (2021), type of power analysis (A priori: Compute required sample size - given α , power and effect size), input parameters, effect size= 0.8, α error= 0.05, power(1- β)= 0.95, resulting output parameter was total sample size of 84 patients.

Statistical analysis

Version 28 of SPSS was utilised for data management and statistical analysis (IBM, Armonk, New York, United States). Using the Shapiro-Wilk test and approaches for direct data visualisation, the normality of quantitative data was established. On the basis of normality testing, the numerical data were presented as means and standard deviations or medians and ranges. Percentages and numbers were utilized to represent the categorical data. Comparing

quantitative data across study groups via one-way ANOVA or the Kruskal-Wallis test on normally and non-normally distributed quantitative variables, respectively, was performed. The Bonferroni method was applied to post hoc analysis. To compare categorical data, the Chi-square test or Fisher's exact test was utilised. ROC analyses were done for interleukin 6. Correlations were done using Spearman's correlation. Interleukin-6 was evaluated by test of Mann-Whitney U based on several research criteria. Multinomial logistic regression analysis was performed to predict COVID-19 severity using interleukin 6. Calculations of odds ratios and 95 percent confidence intervals were conducted. Each statistical test was bilateral. P values less than 0.05 were deemed statistically critical.

Results

Age showed a significant difference between the studied groups (P < 0.001), while gender did not significantly differ (P = 0.1). Significant differences between the studied groups were reported regarding AST (P = 0.006), albumin (P < 0.001), d-dimer (P < 0.001), ferritin (P < 0.001), CRP (P < 0.001), and PO2 (P < 0.001). No significant differences were reported regarding creatinine, ALT, total bilirubin, PH, PCO2,

and HCO3. IL-6 significantly differed among groups (P < 0.001). It was considerably lower in group A (median = 4) than in groups B (median = 10) and C (median = 23). Furthermore, it was substantially lower in group D (median = 2) than in groups B and C (Table 1).

IL-6 showed significant positive correlations with age (r = 0.338, P = 0.003), temperature (r = 0.262, P = 0.023), respiratory rate (r = 0.729, P < 0.001), D-dimer (r = 0.704, P < 0.001), ferritin (r = 0.791, P < 0.001), CRP (r = 0.592, P < 0.001), CORADS (r = 0.419, P < 0.001), and severity (r = 0.821, P < 0.001) (Table 2).

ROC analysis was done for using interleukin-6 in distinguishing patients of COVID-19 from healthy controls and revealed a critical AUC of 0.950 with a 95 percent CI ranging between 0.910 and 0.990 (P < 0.001). The best cutoff point was > 3 ng/l, at which specificity and sensitivity were 96% and 86.7%, respectively. Also, it was done for using interleukin-6 to distinguish critically ill patients from other patients and revealed a critical AUC of 0.930 with a 95% CI ranging between 0.866 and 0.994 (P < 0.001). The best cutoff point was > 12 ng/l, at any specificity and

sensitivity were 82% and 88%, respectively. Analysis of ROC was done for using interleukin-6 to distinguish critically ill patients from severe patients. It revealed a critical AUC of 0.878 with a 95% CI ranging between 0.780 and 0.977 (P < 0.001). The best cutoff point was > 14.5 ng/l, at which specificity and sensitivity were 96% and 72%, respectively (Figure 1).

Interleukin-6 was significantly higher in those with fever (P = 0.024), sore throat (P < 0.001), dyspnea (P < 0.001), altered mental status (P = 0.005), ICU admission (P < 0.001), and mortality (P < 0.001). No significant differences were reported in interleukin-6 regarding sex, cough, anosmia, diarrhea, vomiting, and loss of taste (Table 3).

Analysis of multinomial logistic regression was performed for using IL-6 in predicting COVID-19 severity. It revealed that interleukin-6 was a significant predictor for mild to moderate patients (OR = 7.66, 95% CI = 2.212 – 26.528, P = 0.001), severe patients (OR = 17.727, 95% CI = 4.545 – 69.141, P < 0.001), and critically ill patients (OR = 24.345, 95% CI = 6.135-96.604, P < 0.001), controlling for age and gender (Table 4).

Table 1: General characteristics, Interleukin 6 (ng/L) and Laboratory findings of the studied groups

	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)	Group D (n = 25)	P-value
Age (years)	51 ±14 [3, 4]	59 ±14 [4]	66 ±10 [1, 4]	39 ±16 [1, 2, 3]	< 0.001*
Sex					
Males	14 (56)	6 (24)	12 (48)	13 (52)	0.1
Females	11 (44)	19 (76)	13 (52)	12 (48)	
Interleukin 6 (ng/L)	4 (2-7) [2, 3]	10 (3-17) [1, 4]	23 (4-64) [1, 4]	2 (2-4) [2, 3]	<0.001*

Laboratory findings	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)		P-value
Creatinine (mg/dl)	0.9 ±0.3	0.8 ±0.3	0.9 ±0.3		0.324
ALT U/L	25 (6-110)	22 (10-76)	25 (4-118)		0.201
AST U/L	21 (10-122)	36 (7-80) [4]	30 (7-88) [4]		0.006*
Albumin (g/dl)	4.1 ±0.6 [2, 3]	3.7 ±0.5 [1, 4]	3.4 ±0.5 [1, 4]		<0.001*
Total bilirubin (mg/dl)	0.4 (0.1-1.2)	0.4 (0.2-1.2)	0.4 (0.2-1.1)		0.278
D- dimer (g/ml)	0.3 (0.2-0.5) [2, 3]	0.5 (0.3-0.9) [1, 4]	0.8 (0.5-1.4) [1, 4]		<0.001*
Ferritin (ng/ml)	48 (12-184) [2, 3]	410 (45-1120) [1, 4]	820 (418-1580) [1, 4]		<0.001*
CRP (mg/L)	16 (8-32) [2, 3]	32 (16-64) [1, 4]	64 (16-128) [1, 4]		<0.001*
PH	7.4 ±0.1	7.4 ±0.1	7.4 ±0.1		0.129
PO_2 (mmHg)	37 (20-101) [4]	47 (15.9-122) [4]	45.7 (14-97) [4]		<0.001*
PCO_2 (mmHg)	36.7 ±5.9	35.7 ±11.4	40.2 ±13.8		0.255
HCO_3 (mmol/L)	24.2 ±2.6	23.5 ±4.2	24.6 ±6		0.748

Data were presented as median (min-max) or number (percentage); * Significant; 1: Significantly different from group A; 2: Significantly different from group B; 3: Significantly different from group C; 4: Significantly different from group D

Table 2: Correlation between interleukin-6 and other parameters in the studied patients

	Interleukin 6 (ng/L)	
	r	**P**
Age (years)	.338*	0.003
O_2 Saturation (%)	-.620*	<.001
Pulse (b/min)	0.184	0.115
Temperature ©	.262*	0.023
Respiratory rate (breath/min)	.729*	<.001
Creatinine (mg/dl)	0.054	0.643
ALT (U/L)	0.115	0.324
AST (U/L)	0.106	0.364
Albumin (g/dl)	-.369*	0.001
Total Bilirubin (mg/dl)	0.039	0.737
D-dimer (g/ml)	.704*	<.001
Ferritin (ng/ml)	.791*	<.001
CRP (mg/L)	.592*	<.001
PH	-0.109	0.351
PO_2 (mmHg)	0.177	0.129
PCO_2 (mmHg)	0.009	0.941
HCO_3 (mmol/L)	0.052	0.657
CORADS	.419*	<0.001
Severity	.821*	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C reactive protein. r= person correlation coefficient *: statistically significant as P value <0.05

**Table 3: Interleukin-6 according to different study parameters**

		Interleukin 6 (ng/L)	P-value
Sex	**Males**	8.5 (2-64)	0.953
	Females	8 (2-64)	
Fever	**Yes**	13 (2-64)	0.024*
	No	7 (2-64)	
Sore throat	**Yes**	5 (2-17)	<0.001*
	No	12.5 (2-64)	
Cough	**Yes**	8 (2-64)	0.141
	No	4 (3-5)	
Dyspnea	**Yes**	13 (2-64)	<0.001*
	No	4.3 (2-7)	
Anosmia	**Yes**	4 (3-5)	0.141
	No	8 (2-64)	
Diarrhea	**Yes**	6.8 (2-64)	0.627
	No	8 (2-64)	
Vomiting	**Yes**	21 (2-64)	0.094
	No	7.5 (2-64)	
Altered mental status	**Yes**	37 (10-64)	0.005*
	No	7 (2-64)	
Loss of taste	**Yes**	4 (3-5)	0.141
	No	8 (2-64)	
ICU admission	**Yes**	14.5 (3.5-64)	<0.001*
	No	5 (2-13)	
Outcome	**Cure**	7 (2-46)	<0.001*
	Death	36 (13-64)	

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C reactive protein. *: statistically significant as P value <0.05

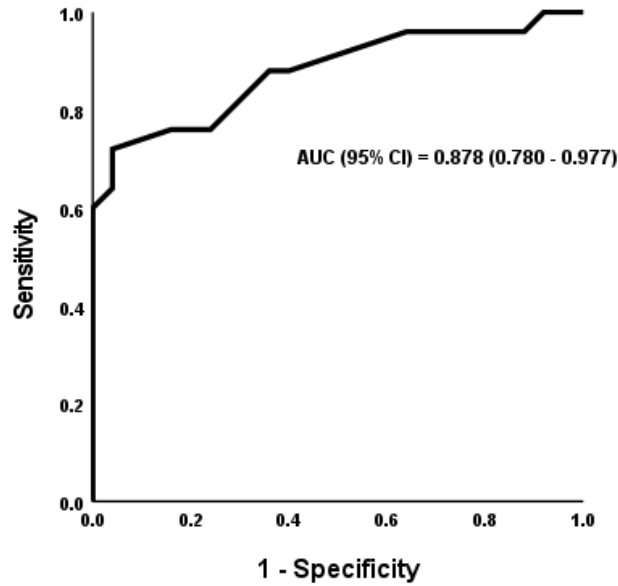**Table 4:** Multinomial logistic regression analysis for prediction of covid severity using interleukin 6

Interleukin 6 (ng/L)	OR (95% CI) **	P-value
Group A	7.66 (2.212-26.528)	0.001*
Group B	17.727 (4.545-69.141)	<0.001*
Group C	24.345 (6.135-96.604)	<0.001*

Group D is the reference; * Significant; ** Adjusted for age and gender; OR: odds ratio; 95% CI: 95% confidence interval
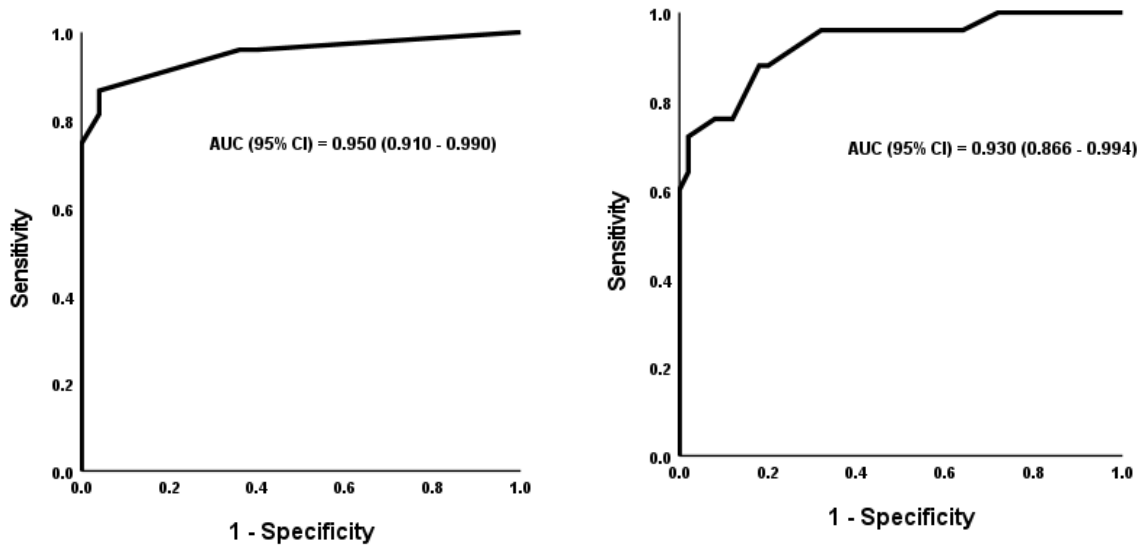
Figure 1: (A) ROC analysis of interleukin-6 in distinguishing covid patients from healthy controls (B) ROC analysis of interleukin-6 in distinguishing critically ill patients from other patients (C) ROC analysis of interleukin-6 in distinguishing critically ill patients from other patients

Discussion

COVID-19 is now infecting millions of people worldwide. Seasonal flu is less infectious than 2019 coronavirus illness, with a shorter incubation period, and associated with a less risk of hospitalization and total fatality. coronavirus rapidly spreads through the respiratory system causing terrible illness and may cause death (10). CRP and IL-6 are raised in this hyperinflammatory disease, and IL-6 is related to lymphopenia leading to widespread death of lymphocytes. According to a different study, COVID-19 patients with high levels of serum IL-6 had reduced NK- and T-cell cytotoxicity (11).

At this investigation, we demonstrated a very substantial difference between the analyzed groups and patients' symptoms, including fever, sore throat, cough, dyspnea, diarrhea, and altered mental status. In which fever, cough and dyspnea was considerably higher in severe and critical ill patients.

A similar result was found in a study done in 2021 (12), they found that the most common symptoms included fever, cough, fatigue, and bone ache. Moreover, a recent study done in 2022 (13) The ratio of inpatient clinics to intensive care units differed significantly across the mild, moderate, and severe categories (p<0.001). 43.5 percent shortness of breath, 79.72 percent fever and 58.3 percent Cough were the most prevalent symptoms, while 10.4 percent gastrointestinal symptoms (diarrhea, vomiting, etc.,), 7.8 percent sore throat and 16.5 percent exhaustion were less frequent.

In this study, there was a statistically substantial variation between investigated groups in terms of CRP, AST, Ferritin and D-dimer where they were elevated in severe group and the highest was among the critically ill group and the albumin, which was the lowest among the critically ill group, no significant differences were reported regarding creatinine, ALT, total bilirubin, PH, PCO_2, and HCO_3.

Additionally, a new study (13) found that compared to the non-severe group, severe patients had substantially higher values of CRP (p $\leq$ 0.001), and CRP/alb (p $\leq$ 0.001). And considerably lower values of albumin (p $\leq$ 0.001). In another study (14) regarding the categorical analysis of anomalies of the observed hematological and biochemical parameters, no statistically significant

variations were discovered (p>0.05) between COVID-19 severity categories in terms of frequency percentage of leucopenia, anemia, serum creatinine or elevated ESR, albumin or low serum total protein. Severe COVID-19 had considerably higher rates of ALT, increased CRP, AST, and lymphopenia than mild to moderate COVID-19 (p<0.05) for all four measures.

In this study, Interleukin-6 significantly differed between examined groups (P < 0.001). It was considerably lower in mild and moderate patients (median = 4) than in severe patients (median = 10) and critically ill patients (median = 23). Our elevated IL-6 serum levels are consistent with a study's findings (15) in which of moderate patients were 13.4 percent, severe patients were 27.1%, and critical patients were 86.2 percent had concentrations of serum IL6 higher than the reference concentration [7pg/mL], Critical patients had considerably higher IL-6 readings than moderate and severe patients, demonstrating a connection between IL-6 and COVID-19 severity[P < 0.001].

In this study ROC analysis was done for using interleukin-6 to distinguish critically ill patients from other patients. It revealed a critical AUC of 0.930 with a 95 perecnt CI

ranging between 0.866 and 0.994 (P < 0.001). The best cutoff point was > 12 ng/l, at which specificity and sensitivity were 82% and 88%, respectively.

Also, a study (16) found that As a predictor of the severe clinical state, the AUC for IL-6 was 0.864 (95 percent CI 0.765–0.963, p<0.001). It was discovered that even somewhat high levels of IL-6, such as those more than 28.44pg/mL, were adequate to identify individuals with COVID-19 infection accompanied with severe pneumonia.

Using ROC analysis in this study for IL-6 in predicting mortality, it revealed a significant AUC of 0.929, with a 95% CI ranging from 0.861-0.998. The best cutoff was > 24 ng/L, at which specificity and sensitivity were 96.8% and 76.9%, respectively.

Also, in another study (17) they found that IL-6 levels of non-survivors were substantially greater than those of survivors ($p < 0.0033$ and $p = 0.0131$; for survivors' group 1 and survivors' group 2, respectively).

Conclusion

Interleukin-6 can distinguish COVID-19 patients from healthy controls, it also can

distinguish critically ill patients from other patients. By using multinomial logistic regression analysis, Interleukin-6 can significantly predict COVID-19 severity (mild to moderate, severe and critically ill) and also mortality.

Drawbacks of this study

Changes in the levels of the markers over the disease progression were not part of this study design.

It was a single-center study.

The validity of interleukin-6 needs to be further investigated.

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