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Original Article

The Significance of Interleukin 6 in Predicting Severity of Covid -19 Infection in Egyptian Patients

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Background:
Covid-19 infection is a highly infectious illness with high mortality especially among elderly patients with chronic illnesses . During the pandemic of Covid-19 infection , it is necessary to find a screening method to predict the patients at high risk for developing severe disease with increased risk of mortality. increased interleukin-6 (IL-6) is a key factor contributing to the cytokine storm syndrome involved in clinical manifestations of Covid-19.

Aim of the work: to determine the significance of Interleukin- 6 as a predictive factor of Hypoxemia and the severity of Covid-19 infection .

Subjects and Methods: Case - Control study was done at Abassia Fever hospital and Ain Shams University Isolation Hospitals on 75 persons (50 patients with different grades of severity for Covid-19 disease and 25 controls) during 6 months duration from September 2021 to March 2022 .

Results: we found a statistically significant difference as regard serum IL-6 between critically severe , mild and control groups with more increased levels of IL-6 between died patients than survived patients .

Conclusion: Neutrophil-Lymphocyte Ratio , CRP , ESR , Ferritin and Albumin were associated with increased disease severity and worse clinical outcome but IL-6 was found to be better than ferritin ,NLR, albumin, CRP and ESR in predicting disease severity and adverse outcome . the level of IL-6 > 12.6 pg/mL at the initial presentation before hospital admission had excellent sensitivity and good specificity and predicted the development of hypoxia demanding hospitalization . IL-6 might serve for early identification of moderate to severe Covid- 19 patients in need of hospitalization with better outcome . Further larger studies with large number of patients are needed to predict the significance of IL-6 as an effective screening method for the severe Covid-19 disease .

Keyword: Covid-19; Hypoxemia; Interleukin 6 .
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Introduction

Majority of patients with Covid-19 have selflimiting illness , but 20% of cases progress to severe pneumonia which might lead to Adult Respiratory Distress Syndrome (ARDS) with marked hypoxemia with resulting Acute Respiratory Failure. The overall mortality rate was found to be below 1% which could occur at any age even in children and young adults. [(1)]

There are several patient factors as demographic, clinical, immunologic,hematological, biochemical and radiographic findings that may be important for physicians to predict Covid -19 morbidity and mortality as age > 55 years, pre-existing co-morbidities, hypoxia at initial presentation , CT findings of extensive pulmonary involvement, severe laboratory test abnormalities, and markers of end-organ failure.[(2)]

The Co-morbidities most commonly associated with rising risk of death due to Covid-19 were Cardiovascular diseases, Diabetes Mellitus and obesity. the mortality rate among such patients aged over 80 years old was 15%. [(3)]

The rapid spread of infection in LTCF (Long Term Care Facility) always significantly increases the health care system burden with high morbidity and mortality so, early intervention is always necessary to identify patients at risk of deterioration to reduce such morbidity and mortality. Such intervention usually includes early identification of cases at risk ,initiation of infection control measures with daily follow up of patients. [(4)]

Such patients usually need close follow up with early hospitalization for rapid management. These necessitates the importance of use of biomarkers that signify severe Covid-19 infection.

Those inflammatory biomarkers as C-reactive protein (CRP), Ferritin , D-dimer , Fibrinogen , and Interleukin 6 (IL-6) are associated with severe infection . IL-6 was found to be more significant than CRP and other inflammatory biomarkers in predicting ARDS in severe disease . IL-6 was considered as the most significant factor of immune dysfunction and ARDS in such pandemic. [(5)]

Covid-19 induced severe pneumonia may be aggravated by dysregulated inflammatory response with massive cytokine storm and macrophage activation syndrome (MAS) that might can lead to end system failure , ARDS and mortality in patients with severe infection. CRP and IL -6 were increased in this hyper-inflammatory state which are associated with ARDS and death .[(6)]

IL-6 usually increases the permeability of pulmonary vasculature with developing pulmonary edema and ARDS and also initiate the coagulation cascade with developing micro-thrombi in pulmonary vasulature with developing pulmonary embolism which may be massive. [(6)]

The level of IL-6 > 12.6 pg/mL at medical presentation had excellent sensitivity and good specificity and usually predicted the occurence of hypoxia demanding hospital admission better in ICU . so , IL-6 is an important factor for the occurrence of the severe pulmonary infection that needs immediate early intervention for saving lives. [(7)]

AIM OF THE WORK

To signify the importance of Interleukin- 6 as a predictive factor for Hypoxemia and Covid-19 severity

SUBJECTS AND METHODS

Technical design:

Study design:

-It is a Case - Control study.

Setting:

- This study was done at Abassia Fever hospital and Ain Shams University Isolation Hospitals.

Time of the study: 6 monthes period from September 2021 till March 2022.

Target population:

- We included 75 participants (50 patients with Covid-19 disease and 25 healthy control) that attended Abbasia Fever Hospital and Ain Shams University Isolation Hospitals over 6 months period from September 2021 till March 2022. Diagnosis of Covid -19 was confirmed by PCR for the SARS-COV-2 viral gene by using naso and oro-pharyngeal swabs done prior to hospitalization , all patients underwent at least one High Resolution CT Chest for assessment of pulmonary infiltrates . The criteria of recovery included: resolution of fever, resolution of respiratory symptoms , two negative PCR with 24 hours apart.

Inclusion criteria:

- ❖ All patients followed the definition of confirmed cases based on the Egyptian national protocol for Covid -19 issued by Ministry of Health Protocol .
- ❖ Subjects age more than 15 years old.

- Classification of patients were based on symptoms and signs , clinical examination , results of chest radiography, laboratory investigations into 2 groups:
- Non severe cases: mild symptoms (fever, anorexia, cough, expectoration, sore throat, runny nose, myalgia, nausea, anorexia and other GIT symptoms) and absence or mild changes in the CT Chest (multiple small patches with changes in the peripheral and subpleural zones).
- Severe cases: characterized by occurence of any one of the following : tachypnea with respiratory rate more than 30 /minute, hypoxia with SO2 at resing state <93%, partial pressure of oxygen/fraction of inspired oxygen (PaO2)/FiO2) <300 mmHg in the arterial blood gases (ABG) and respiratory or other organ failure requiring ICU admission and treatment with shock.

Exclusion criteria:

- Age less than 15 years .

Sampling technique: on accessability sample .

Sample size:

Sample size was measured by using MedCalc Statistical Software version 15.8 the type-1 error (α) at 0.05 and the power (1-β) at 90%. Results of last study [5] showed that the ROC analysis for IL-6 in differentiating non hypoxic from hypoxic Covidc-19 cases had an area under the curve of 0.91. Therefore, a sample size of 25 hypoxic and 25 non hypoxic cases will needed assuming a null hypothesis AUC value equal to 0.7.

Method:

- All study participants were classified into two groups:-
- **Group Severe Cases (A1):** 25 Patients with hypoxia.
- **Group Mild Cases (A2):** 25 Patients without hypoxia.
- **Group Control (B):** 25 healthy subjects without Covid-19.

1. Clinical assessment:

a) History: full personal history with pressure on age , gender , place of residency, occupation, history of smoking and smoking index, complains, nausea , abdominal pain, presence of comorbid diseases as DM or HTN or cardiac disease .

b) Clinical Examination: general examination including vital data with Body Mass Index, chest, cardiological and abdominal examination.

Investigations:

- **Lab investigation:** The amount of blood needed for laboratory investigations were 6 cm , CBC, Neutrophil Lymphocyte Ratio (NLR) , inflammatory markers as Erythrocyte Sedimentation Rate (ESR) , C-Reactive Protein (CRP) , liver enzymes as Alanine Transaminase (ALT) , Aspartate Transaminase (AST) , Albumin, Bilirubin (Total and Direct), Creatinine , Urea, Ferritin, D-Dimer.
- PCR for SAR-COV 2 performed by oral and naso-pharyngeal swab.
- High Resolution Chest CT for better assessment of the extent of the pulmonary disease.
- Arterial Blood Gases (ABG) .
- Detection of IL-6 by ELISA.

Study Tools:

- Study Tools Laboratories and Radiology Departments of Abassia Fever hospital and Ain Shams University Isolation Hospitals.

Statistical analysis

Analysis of data was performed using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative values were illustrated in the form of mean and standard deviation. Qualitative variables were illustrated as number and percent. In order to compare quantitative values between two groups, Student t test was done . Qualitative values were compared using chi-square (X_2) or Fisher's exact test when frequencies were below five. Pearson correlation coefficients assess the association between two normally distributed values. When a value was not normally distributed, A P value < 0.05 is considered significant.

RESULTS

Table 1: Comparison between Critical (A1) and Mild (A2) cases as regard personal and medical history :

		Group				**P**	**Sig**
		Critical (A1)		**Mild (A2)**			
		Mean	**±SD**	**Mean**	**±SD**		
Age		62.68	10.46	56.12	16.21	0.096‡	NS
Gender	Male	16	64.0%	15	60.0%	0.771*	NS
	Female	9	36.0%	10	40.0%		
Smoking	No	20	80.0%	16	64.0%	0.208*	NS
	Yes	5	20.0%	9	36.0%		
Diabetes	No	5	20.0%	13	52.0%	0.018*	**S**
	Yes	20	80.0%	12	48.0%		
Hypertension	No	2	8.0%	14	56.0%	0.0001*	**HS**
	Yes	23	92.0%	11	44.0%		
IHD	No	13	52.0%	21	84.0%	0.015*	**S**
	Yes	12	48.0%	4	16.0%		
Chest diseases	No	24	96.0%	24	100.0%	1.0**	NS
	Yes	1	4.0%	0	0.0%		
Liver disease	No	22	88.0%	18	72.0%	0.157*	NS
	Yes	3	12.0%	7	28.0%		
Hemorrhagic or ischemic stroke	No	25	100.0%	25	100.0%	-------	------
	Yes	0	0.0%	0	0.0%		
Malignancies	No	23	92.0%	25	100.0%	0.49**	NS
	Yes	2	8.0%	0	0.0%		
CKD	No	24	96.0%	24	96.0%	1.0**	NS
	Yes	1	4.0%	1	4.0%		

*Chi-Square Tests
**Fisher exact test
‡ Student t test

Table (1): There was no significant difference between Critical (A1) and Mild (A2) cases as regard personal and medical data except for DM, hypertension and IHD with higher percentage of cases with DM , hypertension and IHD (80.0% , 92.0% , 48.0% respectively) was present among Critical cases when compared to Mild cases (48.0% , 44.0% , 16.0% respectively).

Table 2: Comparison between Critical (A1) and Mild (A2) cases as regard clinical data :

		Group				P	Sig
		Critical (A1)		Mild (A2)			
		Mean	±SD	Mean	±SD		
O2% saturation		80.84	7.04	96.72	1.54	0.001‡	**HS**
Fever	No	13	52.0%	3	12.0%	0.002*	**HS**
	Yes	12	48.0%	22	88.0%		
Fatigue	No	15	60.0%	10	40.0%	0.157*	NS
	Yes	10	40.0%	15	60.0%		
Bony aches	No	10	40.0%	1	4.0%	0.002*	**HS**
	Yes	15	60.0%	24	96.0%		
Anosmia	No	23	92.0%	19	76.0%	0.247**	NS
	Yes	2	8.0%	6	24.0%		
Loss of taste	No	23	92.0%	19	76.0%	0.247**	NS
	Yes	2	8.0%	6	24.0%		
Nausea	No	19	79.2%	19	76.0%	0.791*	NS
	Yes	5	20.8%	6	24.0%		
Vomiting	No	19	76.0%	16	64.0%	0.355*	NS
	Yes	6	24.0%	9	36.0%		
Diarrhea	No	23	92.0%	19	76.0%	0.247**	NS
	Yes	2	8.0%	6	24.0%		
Abdominal pain	No	17	68.0%	11	44.0%	0.087*	NS
	Yes	8	32.0%	14	56.0%		
Sore throat	No	0	0.0%	3	12.0%	0.235**	NS
	Yes	25	100.0%	22	88.0%		
Cough	No	0	0.0%	1	4.0%	1.0**	NS
	Yes	25	100.0%	24	96.0%		
Dyspnea	No	0	0.0%	23	92.0%	0.001*	**HS**
	Yes	25	100.0%	2	8.0%		
Hospitalization	Ward	0	0.0%	25	100.0%	0.001*	**HS**
	Intermediate	11	44.0%	0	0.0%		
	ICU	14	56.0%	0	0.0%		
Hypoxia	No	0	0.0%	25	100.0%	0.001*	**HS**
	Yes	25	100.0%	0	0.0%		
CT >50%	No	0	0.0%	17	68.0%	0.001*	**HS**
	Yes	25	100.0%	8	32.0%		
Outcome	Cured	15	60.0%	25	100.0%	0.001*	**HS**
	Died	10	40.0%	0	0.0%		

*Student t test
*Chi-Square Tests
**Fisher exact test

Table(2): There was a highly significant difference between Critical (A1) and Mild (A2) cases as regard O2% saturation, fever, bone ache, dyspnea, site of hospitalization either ICU or Intermediated care unit or ward , hypoxia , CT finding >50% of lung parynchma and outcome.

Table 3: Comparison between three study groups (A1 , A2 , B) as regard lab parameters :

	Group						P	Sig
	Critical (A1)		Mild (A2)		Control (B)			
	Mean	±SD	Mean	±SD	Mean	±SD		
IL-6	119.39	153.25	5.84	3.40	2.23	1.23	0.0001**	**HS**
CRP	76.17	36.8	22.93	13.84	5.92	.76	0.0001**	**HS**
AST	44.68	37.25	30.16	14.44	22.20	8.80	0.012**	**S**
ALT	36.24	23.90	27.68	24.55	24.68	8.02	0.105**	NS
T. Bilirubin	0.98	0.67	1.69	2.39	0.65	0.31	0.34**	NS
D. Bilirubin	0.38	0.37	0.81	1.21	0.18	0.13	0.01**	**S**
Albumin.	3.26	0.49	3.91	0.64	4.18	0.39	0.001*	**HS**
Urea	49.72	17.58	52.04	27.39	30.36	7.97	0.0001**	**HS**
Creatinine	1.11	0.39	1.13	0.52	0.49	0.40	0.0001**	**HS**
Ferritin	826.62	359.01	466.00	180.20	64.10	29.40	0.0001*	**HS**
D-dimer	1.39	2.22	0.56	0.23	0.24	0.23	0.001**	**HS**
Hb	12.47	2.00	12.43	1.70	13.24	1.45	0.184*	NS
MCV	82.21	4.53	81.23	10.22	83.68	3.73	0.445*	NS
MCH	36.84	6.22	34.36	4.53	30.50	5.23	0.0001*	**HS**
TLC	11.59	4.39	8.49	3.95	7.58	2.56	0.0001*	**HS**
Lymphocytes	12.02	5.24	18.83	10.50	38.36	14.86	0.0001*	**HS**
Neutrophils	80.31	15.86	74.75	18.83	53.08	14.19	0.0001*	**HS**
NLR	8.13	4.43	6.22	6.18	1.72	0.98	0.0001*	**HS**
Platelets	262.76	142.59	220.00	128.71	281.40	84.21	0.192*	NS
ESR	77.08	24.71	59.88	28.73	17.72	9.51	0.0001*	**HS**
PH	7.41	0.14	7.43	0.05			0.479‡	NS
CO2	38.43	14.32	38.10	5.44			0.915‡	NS
HCO3	23.55	5.11	27.87	14.83			0.175‡	NS

*ANOVA test

**Kruskal Wallis test

‡ Student t test

Table(3): There was high statistically significant difference between Critical (A1) , Mild (A2) and Control (B) groups as regard serum IL-6, CRP, Albumin , Urea , Creatinine , Ferritin , D-dimer , ESR and NLR and statistically significant difference between the three groups as regard AST and Direct Bilirubin.

Table 4: Comparison among severe patients (A1) according to site of hospitalization, and disease outcome as regard IL-6 :

		SERUM IL-6. pg/mL					P	Sig
		Mean	±SD	Median	IQR			
Hospitalization	Intermediate	123.03	153.58	58.7	23.1	212.0	0.935*	NS
	ICU	116.54	158.72	61.2	31.6	83.3		
Outcome	Cured	55.21	54.12	31.9	24.3	79.1	0.028*	**S**
	Died	215.67	202.24	149.8	73.0	350.0		

*Mann Whitney test

Table(4): There was a statistically significant difference between survived and died cases among critical cases groups as regard serum IL-6 with higher level among died cases than survived patients.

Table 5: Correlations between serum IL-6 and liver and kidney function tests among cases :

		AST	ALT	T. Bilirubin	D. Bilirubin	Albumin. g/dL	Urea	Creatinine
IL-6. pg/mL	**r***	.136	.302*	.138	-.116-	-.356	-.020-	-.070-
	p	.345	.033	.338	.422	.011	.892	.628
	Sig	NS	**S**	NS	NS	**S**	NS	NS

*Correlation coefficient

Table(5): Among cases, there was a significant direct correlation between serum IL-6 and ALT, and a negative correlation between IL-6 and Albumin.

Table 6: Correlations between serum IL-6 and CBC findings among cases :

		TLC	Lymphocytes	Neutrophils	NLR
IL-6. pg/mL	**r***	.430**	-.323*	.244	.324*
	p	.002	.022	.088	.022
	Sig	**HS**	**S**	NS	**S**

*Correlation coefficient

Table(6): Among cases, there was a high statistical significant direct correlation between serum IL-6 and each of TLC and NLR , and a significant negative correlation between IL-6 and Lymphocyte count.

Table 7: Correlations between serum IL-6 and inflammatory markers among cases :

		Ferritin	D-dimer	CRP. mg/L	ESR
SERUM IL-6. pg/mL	**r***	.425**	-.042	.575**	.343*
	p	.002	.770	.001	.015
	Sig	**HS**	NS	**HS**	**S**

*Correlation coefficient

Table(7): Among cases, there was a statistical significant direct correlation between serum IL-6 and each of Ferritin, CRP, ESR .

Table 8: Correlations between serum IL-6 and Arterial Blood Gases parameters among cases :

		PH	CO2	HCO3	O2% sat
IL-6. pg/mL	**r***	.055	-.097-	-.141	-.684**
	p	.706	.501	.330	.0001
	Sig	NS	NS	NS	**HS**

*Correlation coefficient

Table(8): Among cases, there was a statistical significant negative correlation between serum IL-6 and arterial O2 saturation.

Table 9: ROC curve using IL6 for differentiation between mild (A2) and critical (A1) cases :

Cutoff level	AUC(CI)^	Sensitivity	Specificity	PPV*	NPV**	Accuracy	P(Sig)
Il-6 ≥12.4	0.978 (0.890 to 0.9)	92.0%	96.0%	95.8%	92.3%	97.8%	<0.001

^ Area under curve (confidence interval)
*Positive predictive value
**Negative predictive value

Table(9): Using ROC curve, IL-6 could discriminate between mild (A2) and critical (A1) Covid -19 cases at a cutoff level ≥12.6 with 92% and 96% sensitivity and specificity respectively

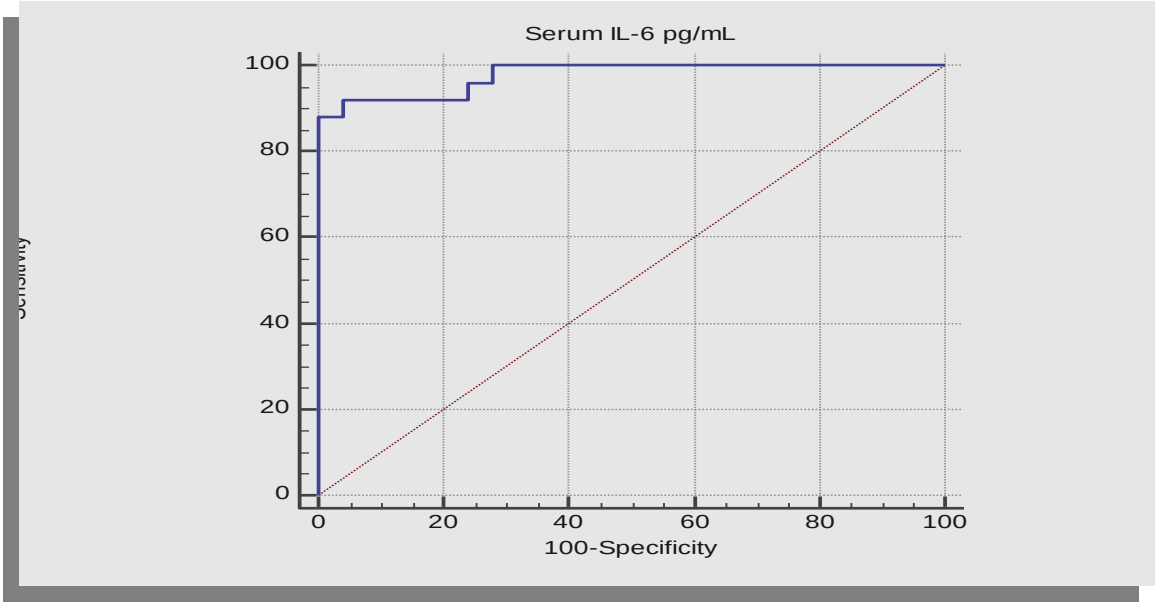

Figure 1: ROC curve using IL6 for differentiation between mild and critical cases

Table 10: Comparison between Mild (A2) and critical (A1) cases according to IL6, ESR, Ferritin, NLR, albumin and CRP:

Cutoff level	Sensitivity	Specificity	Accuracy	P	Sig
Il-6 ≥12.4	**92.0%**	**96.0%**	**97.8%**	0.0001**	**HS**
ESR ≥50	**88.00%**	**52.00%**	**67.4%**	0.001**	**HS**
Ferritin ≥650	**76.0%**	**84.0%**	**83%**	0.029*	**S**
NLR ≥2.86	**100.0%**	**40.0%**	**67.4%**	0.0001*	**HS**
Albumin ≤3.3	**60.00%**	**92.00%**	**78.0%**	0.001*	**HS**
CRP>30	**88.0%**	**76.0%**	**91.7%**	0.0001**	**HS**

*Student t test

*Chi-Square Tests

**Fisher exact test

Table(10): Using ROC curve , Ferritin, NLR, Albumin, CRP and ESR were associated with increased disease severity and worse clinical outcome but IL-6 was better than Ferritin, NLR, albumin, CRP and ESR predicting disease severity and adverse outcome.

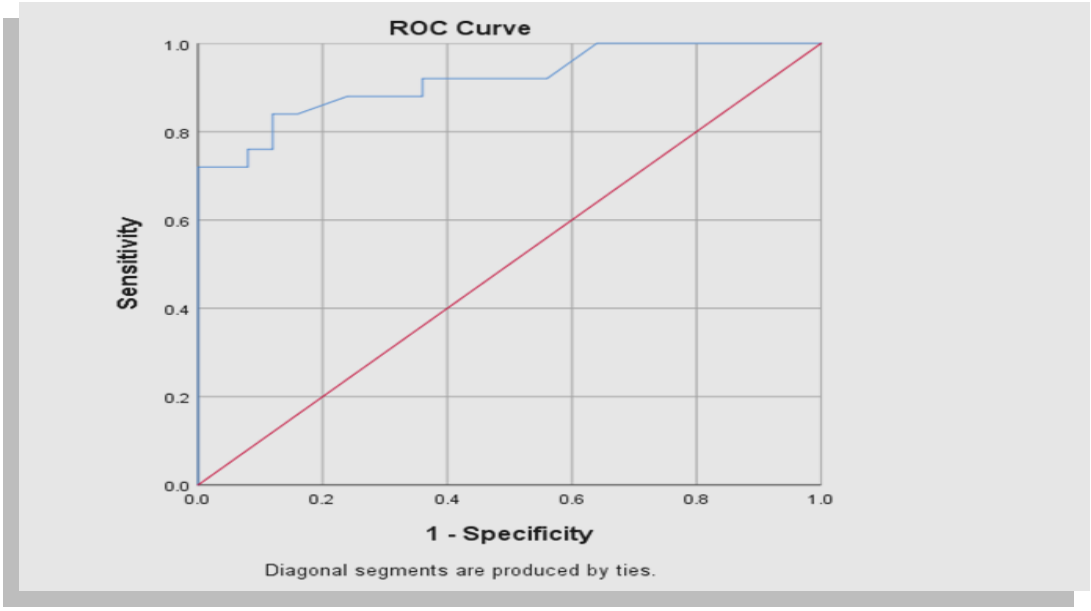

Figure 2: ROC curve using Il-6, ESR, ferritin, NLR, albumin, CRP for differentiation between mild and critical cases**.**

DISCUSSION

Covid-19 infection is a rapidly distributed pandemic , affecting millions of persons which is more infectious than Influenza virus with a relatively longer incubation period with increased hospital admission rate with higher morbidity and mortality. The virus usually spreads through the droplet transmission .[8]

Although majority of cases recover sponatanously being self -limiting disease or mild curable disease by medicines while others with moderate in severity specially with high risk as elderly people (more than 60 years old), obesity, and associated co-morbidities as DM , Cardiac disease can rapidly deteriorate and become severe with life threatening illness with increasing hospital particularly ICU care with a rising morbidity and mortality . So , early diagnosis of moderate to critical patients is so vital for ameliorating disease severity even at early stage .[9]

Cytokines play a significant role in the regulation of immunological and inflammatory pathways of such pandemic and in the pathogenesis of life threatening cytokine storm that can lead to multi-organ failure in patients with severe disease . One of them is IL-6 levels which were pro-

ved to be a significant predictor of severity of infection and hypoxemia. **(10)**

Inflammatory biomarkers as C-reactive protein (CRP) and interleukin (IL)-6 were increased in such hyper-inflammatory state. IL-6 is associated with direct widespread cytotoxicity of lymphocytes by natural killer cells (NK) with impaired T lymphocytes function with resultant lymphopenia . **(11)**

The aim of this study is to assess the significance of Interleukin- 6 as a predictive factor of Hypoxemia and its relation with the Severity of Covid-19 infection .

In this study , 31 males (62 %) and 19 females (38 %) were included with the mean age 56.12 to 62.68 . Of all included patients , 16 males and 9 females were critical cases (A1) , 15 males and 10 females were mild cases (A2) . There was non significant relation between Severe (A1) and Mild (A2) cases as regard personal and medical data except for DM, hypertension and IHD with higher percentage of cases with DM , hypertension and IHD (80.0% , 92.0% , 48.0% respectively) was present among Critical cases when compared to Mild cases (48.0% , 44.0% , 16.0% respectively).

These results agreed with **Taha et al. 2020**. **(12)** study which included 85 Covid -19 patients , 48 (56.5%) patients were males, and 37 (43.5%) patients were females with the median age of 55 years (42 – 65). 54.1% of all included study patients were non-severe cases while 45.9% were severe cases . HTN (40.0%) and DM (36.5%) were the most common co-illnesses in their study .

Also, in **Aykal et al. 2021**. **(13)** study**,** 46 patients were females (40%) and 69 (60%) were males. 24 patients were considered as mild, 52 patients as moderate, and 39 patients as severe. There were no statistical significance in the sex ratio between the patients (p=0.566). It was found that the severity was more severe with rising age (p=0.008). 66.9% of patients study had at least one co-morbidity with Hypertension (31.3%) was the most common co-morbidity.

Also , in **El-Shabrawy et al. 2021**. **(14)** study which included 116 Covid-19 patients . severe patients were 14.7% and non-severe patients were 85.3% . The severe group had increasing age and smoking percent with more co-illnesses in relation to mild group .

Additionally , **Guo ., 2020** .**(15)** study revealed that high smoking index was positively related with increased disease severity. Diseases as HTN , DM , CVS , Renal , Hepatic , and Pulmonary diseases were widely spread in severe cases than mild cases which agreed with study of **Yang et al. 2020**. **(16)**

ACE2 receptors are the cellular entry points for the Covid-19 which has a higher affinity for ACE2 receptors . ACE2 are expressed in respiratory and renal systems which signify the most common emergency conditions: ARDS and ARF .

Uncontrolled Hypertension are involved in increased development of vascular remodeling and , which may lead to adverse outcome and mortality .

Digestive symptoms are usually not serious and has no significant difference between mild and critical cases. A possible explanation of GIT symptoms is that the virus in the sputum of patients is swallowed to the gastro-intestinal tract , but the virus is degraded into fragments by different digestive enzymes , so , the virulence of the virus is decreased that cause only mild gastrointestinal damage.

In this study, smoking has no significant difference between critical and mild cases which is related to the decreased number of smokers in patients included in our study.

In this study, we found a high statistical signifycance between critical and mild cases as regard O2% saturation, fever, bone ache, dyspnea, site of hospitalization (ward or ICU), CT findings and adverse outcome in which fever was significantly higher in mild cases which agreed with **Zheng et al. 2020**. **(17)** study who found that fever was higher in the mild group than critical group .

Additionally, **Shi et al. 2020**. **(18)** study showed no significant relation between fever and Covid mortality risk factors so, dyspnea more than fever is a prognostic factor of severity of the disease .

Also, **El-Shabrawy et al. 2021**. **(14)** study found that the most common symptoms were constitutional symptoms as fever, anorexia , bone ache and cough . The critical patients were more dyspneic and hypoxic than in mild patients.

Moreover, **Taha et al. 2020** .**(12)** stated that there was a statistical significance in the admitted

patients to Intensive Care Unit (ICU) among mild, moderate and critical groups . Cough (58.3%), dyspnea and hypoxia (43.5%) and pyrexia (79.72%) were the most prevalent symptoms, while fatigue (16.5%), gastrointestinal symptoms (anorexia , diarrhea, vomiting, nausea etc., 10.4%) and sore throat (7.8%) were uncommon with Significant differences between the study groups as regards dyspnea , hypoxia and myalgia .

Ali et al. 2021 [19] found that hypoxia and dyspnea were the most common symptoms between severe group (87.5%) with statistical significance , While fever in the severe group was (68.8%) without statistical significance as compared with mild group (59%) .

Omran et al. 2021 [20] found that critical patients were associated with lower SO2 and PO2 ($p<0.001$).

In our study, there was a statistical significance between severe, mild and control groups as regarding serum IL-6, CRP, AST, Albumin, Urea, Creatinine, Ferritin, D-dimer, TLC, Lymphocytes, Neutrophils, NLR and ESR.

This agreed with **Omran et al. 2021**. [20] who found that severe patients had higher CRP ($p<0.001$), Ferritin ($p = 0.003$), WBCS ($p<0.001$), INR ($p<0.001$), HCO3 ($p = 0.029$), and Moreover, total bilirubin ($p<0.001$), direct bilirubin ($p<0.001$), albumin ($p = 0.001$), ALT ($p = 0.008$), AST ($p<0.001$), and creatinine ($p = 0.007$) were higher in severe patients.

Also, **El-Shabrawy et al. 2021**. [14] found that the severe patients had higher serum levels of IL-6, CRP with lower serum levels of albumin.

Ghweil et al. 2020 [21] found that there were significantly higher lymphopenia, increased CRP, ALT, and AST among severe in comparison to mild to moderate patients ($p<0.05$).

Also , **Ali et al. 2021**. [19] found that a statistical significant higher results of NLR, CRP, Ferritin, and D-dimer in severe group compared to non-severe group.

In our study , IL-6 and CRP have statistical significance higher results in severe cases than in mild and control groups.

Liu et al. 2021. [22] found that the initial IL-6 level is statistically significant higher results in severe cases than in mild or moderate cases.

Aykal et al. 2021. [13] found that the IL-6 levels were higher significantly in the severe group than those in the mild group ($p=0.04$) while there was no statistical difference in the initial IL-6 levels between the mild and moderate group ($p=0.223$).

Zhao, 2020. [23] found a significantly significant higher IL-6 in severe patients than mild patients based on 9 studies by meta-analysis.

In our study , there was a statistical significance between cured and died patients among critical cases groups as regard serum IL-6 with much higher level among died cases.

El-Shabrawy et al. 2021. [14] found that non-survivors had significant higher values of IL-6 than survivors (87.5% and 31.5% respectively; $P = 0.001$).

Taha et al. 2020. [12] found that serum levels of CRP and IL-6 were significantly higher in severe patients and dead patients than mild patients and survivors.

Among our cases, there was a significant positive relation between serum IL-6 and ALT and a negative relation between IL-6 and albumin**.**

This agreed with **Liu et al. 2021**. [22] who found that the elevated IL-6 at initial presentation in severe cases was positively related with the body temperature and with the rise of CRP , ALT ($P < 0.001$).

Direct virus cytopathic effects could play a vital role in liver function tests abnormalities .also during critical disease , inflammatory mediators decrease albumin synthesis with increased synthesis of acute phase reactants which increase vascular permeability with albumin escape which may contribute to hypoalbuminemia.

Our study had statistical significant positive relation between serum IL-6 with TLC and NLR and statistical significant negative relation between IL-6 and lymphocyte count.

This agreed with **Taha et al. 2020**. [12] who found statistical significant negative relation between IL-6 and lymphocyte count with the Lymphocyte / IL-6 ratio was lower in severe patients .

In our study , there was statistical significant direct relation between IL-6 levels and both ferritin and ESR.

This agreed with **Liu et al. 2021**. [22] who found that the markedly increased IL-6 in severe patients at initial presentation was positively correlated with increased Ferritin and D-dimer .

Using ROC curve, IL-6 could discriminate between mild and critical Covid -19 subjects at a

cutoff value ≥12.6 with 92% and 96% sensitivity and specificity respectively.

Our study results agreed with **Chen et al. 2021**. **(24)** who found that IL6 was elevated in 13.4% of moderate patients , 27.1% of severe patients and 86.2% of critical patients suggesting a significant relation between increased IL-6 and severity of disease with the critical patients having significantly higher IL-6 than moderate and severe patients .

Taha et al. 2020. **(12)** found a good and diagnostic and prognostic value of IL-6 for disease severity with a sensitivity (87.8%) and specificity (52.4%).

Aykal et al. 2021. **(13)** found that the AUC for IL-6 level was 0.864 (95% CI 0.765–0.963, p<0.001) . increased IL-6 above 28.44 pg/mL was sufficient to identify patients who had severe infection demanding hospial; admission .

Also, **Han et al. 2020** .**(25)** concluded that IL-6 was the best predictor of severe hypoxia demanding hospital admission with bad prognosis.

El-Shabrawy et al. (2021) .**(14)** found that CRP was a sensitive and non specific marker of inflammation, and tissue damage. During the acute inflammatory responses, the CRP level rises rapidly. So, CRP was as an effective biomarker in assessing disease severity and inflamematory process .

Our study showed that high CRP level was associated with increased disease severity and adverse outcome , But IL-6 and CRP/albumin ratio were better than CRP in predicting disease severity. So, IL-6 could be considered as an independent significant predictor of disease severity.

This study has small number of patients , so , a large sample size helps to get a more comprehensive understanding of the disease , however, this study permits an early assessment of the severe hypoxic Covid-19 pneumonia in Egypt.

CONCLUSION

The level of IL-6 more than 24 pg/mL predicted the development of significant hypoxia demanding hospitalization even in ICU with good sensitivity and specificity. So , IL-6 can be considered as a significant predictor for the development of the severe hypoxic disease and help for early identification of patients in need of hospitalization. Further larger studies are needed to evaluate the significance of IL-6 as useful screening method for predicting the severe course of Covid-19.

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