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Association between Interleukin 6 Serum Level and Severity of Disease among Pediatrics with Covid-19

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ABSTRACT

Background: Most studies quantify IL-6 only at patient admission, a strategy that may not be appropriate to accurately predict the outcome or to guide treatment due to the dynamic inflammatory process occurring during infection with SARS-CoV-2.

Objective: This study aimed to investigate the association between interleukin-6 serum level and severity of disease among pediatrics with covid-19.

Patients and methods: A cross-sectional study was conducted on 130 children with COVID-19. All children were divided into 4 groups according to WHO criteria as asymptomatic, which included 20 children, mild included that 60 cases, moderate that included 40 cases and severe, which included 10 cases. All cases were admitted to Benha Teaching Hospital, with a diagnosis of COVID-19 during the period study from February 2020 to December 2020.

Results: Interleukin-6 serum level was significantly increased with severe than other severity features groups. ROC curve analysis showed that procalcitonin and interleukin-6 were the best markers for early prediction of severity of disuses among children with covid-19. The sensitivity of interleukin-6 was 87.9% and specificity was 63.5%, at AUC of 0.640 with cut-off of 7.41.

Conclusion: Children at any age seem to be susceptible to COVID-19, and even though their symptoms are milder, they still present a diverse range of clinical presentations. Interleukin-6 was the best marker for determining the severity of disease among pediatrics with covid-19.

Keywords: COVID-19, Interleukin-6, Pediatrics, Disease severity.

INTRODUCTION

A novel coronavirus was identified following a cluster of cases of pneumonia in Wuhan, China, in December 2019 [1].

It rapidly spread as an outbreak there. A limited human-to-human transmission mainly within families was recorded, and the World Health Organization (WHO) announced this on January 22, 2020. On the 23rd of January, it was announced that the outbreak constituted a public health emergency of international concern [2].

WHO designated the disease as coronavirus disease 2019 (COVID-19) and that the causative agent was severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in February 2020 [3].

A few weeks later, the virus spread was recorded worldwide and was announced as a pandemic by WHO on March 11, 2020 [4]. The global spread included Egypt, and the first case was recorded in Egypt on February 14, 2020 [5].

The total number of confirmed cases on May 1, 2020, was 5895, with a case fatality rate of 6.9%. Children were affected like other age groups, but the total incidence was less than 10%. Confirmed cases among health care workers were 11% of the total confirmed cases [6].

Considering the challenge of controlling virus transmission, and the lack of an unquestionably effective antiviral treatment, a therapeutic strategy of immunomodulation has been advocated [7]. This strategy particularly relevant gave the excessive production of proinflammatory cytokines recognized as crucial in the pathophysiologic process of severe COVID-19 [8]. In these cases, the loss of negative feedback in the immune response caused excessive production of inflammatory cytokines, leading to deleterious effects and poor prognosis [9].

A large group of cytokines has been recognized as significantly increased in severe COVID-19 patients: interleukin-1β (IL-1β), IL-1RA, IL-2, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-17, IL-18, tumor necrosis factor (TNF-α), interferon-gamma (IFN-gamma), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1 (MIP-1alpha/CCL3), monocyte chemoattractant protein-1 (MCP-1/CCL2), interferon gamma-induced protein 10 (IP-10/CXCL10), and fibroblast growth factor (FGF) [10]. Most importantly, some of them (IL-6, IL-8, and TNF-α) were regarded as independent markers of the severe disease [11].

A deeper knowledge of the SARS-CoV-2-induced cytokine storm, including its triggering mechanisms, molecular components, and kinetics, is necessary for a better understanding of the pathological process in COVID-19 and therefore for the identification of the most adequate therapeutic targets and timing of drugs administration. So far, several studies have been published on the potential effects of specific (anti-IL-6, anti-IL-1, anti-GM-CSF, and anti-TNF-α) and non-specific therapies (corticosteroids) [12]. Of all the upregulated cytokines that may represent selective therapeutic targets, IL-6 has been regarded as particularly important in the COVID-19 pathogenesis and may be antagonized by existing drugs. IL-6 is an inflammatory interleukin mainly produced by

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macrophages and T lymphocytes in response to pathogens and is pivotal to controlling several viral infections [13]. While homeostatic values of IL-6 contribute to the resolution of infections and tissue lesions, its exacerbated production contributes decisively to cytokine storms [14]. In COVID-19, IL-6 has been positively correlated with disease stages and radiologic changes [15]. Furthermore, the potential prognostic value of IL-6 has been explored regarding the need for mechanical ventilation, mortality, or both, when considered alone or in combination with other variables [16]. Yet, most studies quantify IL-6 only at patient admission, a strategy that may not be appropriate to accurately predict the outcome or to guide treatment due to the dynamic inflammatory process occurring during infection with SARS-CoV-2. Of all the available drugs that specifically inhibit IL-6 pathway, only tocilizumab (an IL-6 receptor antagonist) has, so far, a reasonable body of evidence in COVID-19 [17]. Recently published meta-analysis on the efficacy of tocilizumab in those patients found that cumulative evidence from randomized controlled trials (RCTs) suggests a risk reduction of mechanical ventilation but no effect on mortality, while cumulative evidence from cohort studies suggests an association between tocilizumab and lower mortality [18]. However, only 3 of the 19 cohort studies and none of the 5 selected RCTs, used elevated IL-6 levels as an inclusion criterion. This fact suggests that tocilizumab and other IL-6R antagonists may be further exploited [19].

So, the purpose of the present study is to describe the distribution of baseline IL-6 levels and its kinetics among different stratifications of COVID-19 pediatric patients. Thus, the aim of the current study was to evaluate the association between interleukin-6 serum level and severity of disease among pediatrics with covid-19.

PATIENTS AND METHODS

A cross-sectional study was conducted on 130 children with COVID-19 who were admitted to Benha Teaching Hospital with a diagnosis of COVID-19 during the period from February 2020 to December 2020. All pediatrics included in this study were divided into 4 groups according to WHO criteria as follows: Asymptomatic that included 20 children infection identified during screening or contact tracing without symptoms, mild included 60 children with fever and/or fatigue and/or upper airways symptoms without radiological/ultrasound findings, moderate included 40 children with fever and/or fatigue and/or upper airways symptoms and/or poor feeding and/or pneumonia identified with chest X-ray or ultrasound and severe, which included 10 cases with fever and/or fatigue and/or upper airways symptoms and/or poor feeding and/or pneumonia identified with chest X-ray or ultrasound, fever and cough, plus at least one of: Oxygen saturation on finger pulse, severe respiratory distress, cyanosis, intermittent apnea, fast breathing and systemic symptoms like drowsiness, lethargy, seizures and dehydration.

Ethical consent:

An approval of the study was obtained from Benha Teaching Hospital Academic and Ethical Committee. Written informed consent was taken from parent of every participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: pediatrics with COVID-19 their age between 3-18 years. **Exclusion criteria** included children less than 3 years or more than 18 years.

All included children were subjected to the following: Name, age, sex & residence. Family history & history of contact. Present history of illness including fever, cough, sputum production, sore throat, running nose, dyspnea, diarrhea, vomiting, fatigue and abdominal pain.

Clinical features: Including asymptomatic, mild, moderate and severe.

Symptoms: including fever, cough, dyspnea, runny nose, sore throat, vomiting, diarrhea, fatigue and headache.

Signs: Including tachypnea, intercostal retraction, grunting, cyanosis and abdominal rigidity. Complete blood count, hepatic and renal function tests, C-rp, erythrocyte sedimentation rate, serum ferritin assay, D dimer assay, interloukin-6 assay for Covid-19.

Radiography: Including plain chest x-ray and CT whenever indicated. **Symptomatic and treatments:** including symptomatic, antibiotic, oxygen supplementation, mechanical ventilation and intravenous immune globulin.

Statistical analysis

Results were collected, tabulated, statistically analyzed by IBM personal computer and statistical package SPSS version V.25. Descriptive statistics included percentage (%), mean (x) and standard deviation (SD). Analytic statistics included Chi-Squared (χ^2), ANOVA F test and Mann-Whitney test. ROC curve analysis included sensitivity, specificity and positive and negative predictive values. P value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 130 children included in this study were divided into 4 groups their age and family contact were significantly increased among asymptomatic than mild, moderate, and severe clinical features groups. While, the duration of fever was significantly increased among severe than mild, moderate, and asymptomatic clinical feature groups ($p < 0.05$). There were no significant

differences between the studied groups regarding sex and residence (Table 1).

Table (1): Demographic data of the studied groups in relation to severity of Covid-19

Variable	Severity (N=130)								F	P value
	Asymptomatic (N=20)		Mild (N=60)		Moderate (N=40)		Severe (N=10)			
Age (years) Mean ± SD Range	14.00 ± 2.05 12.00-16.00		11.10 ± 4.46 3.50-17.00		6.04 ± 4.99 2.00-14.00		5.90 ± 4.61 1.00-17.00		28.13	<0.001*
Duration of fever (days) Mean ± SD Range	0.00±0.00 0.00-0.00		3.41±1.28 2.00-7.00		4.35±1.53 2.00-6.00		4.45±1.47 2.00-7.00		12.34	<0.001*
Sex Male Female	N	%	N	%	N	%	N	%	X^2= 5.98	0.098
	10 10	50.0 50.0	51 9	85.8 14.2	13 27	32.5 67.5	7 3	65.0 35.0		
Residence Urban Rural	10 10	50.0 50.0	34 26	57.5 42.5	29 11	72.5 27.5	4 6	40.0 60.0	46.65	0.084
Family contact No Yes	0 20	0.0 100.0	5 55	7.5 92.5	14 26	35.0 65.0	2 8	20.0 80.0	19.37	<0.001*

X^2: Chi square, F**:** ANOVA f test, *Significant

Also, a significant differences were found among the studied groups regarding fever, cough, dyspnea, running nose, sore throat, vomiting, diarrhea, fatigue, headache, tachypnea, cyanosis, abdominal rigidity and associated disease (Table 2).

Table (2): Clinical presentation of the studied groups in relation to severity of Covid-19

Variable	Severity (N=130)								X^2	P-value
	Asymptomatic (N=20)		Mild (N=60)		Moderate (N=40)		Severe (N=10)			
	N	%	N	%	N	%	N	%		
Common symptoms										
Fever										
No	20	100.0	4	6.7	0	0.0	0	0.0	13.684	<0.001*
Yes	0	0.0	56	93.3	40	100.0	10	100.0		
Cough										
No	20	100.0	21	35.8	0	0.0	1	10.0	6.021	<0.001*
Yes	0	0.0	39	64.2	40	100.0	9	90.0		
Dyspnea										
No	20	100.0	56	93.3	0	0.0	3	35.0	14.311	<0.001*
Yes	0	0.0	4	6.7	40	100.0	7	65.0		
Runny nose										
No	20	100.0	42	70.8	20	50.0	7	75.0	16.468	<0.001*
Yes	0	0.0	18	29.2	20	50.0	3	25.0		
Sore throat										
No	20	100.0	22	35.8	13	32.5	5	50.0	17.225	<0.001*
Yes	0	0.0	38	64.2	27	67.5	5	50.0		
Respiratory symptoms										
Vomiting										
No	20	100.0	22	36.7	20	50.0	6	55.0	8.304	<0.001*
Yes	0	0.0	38	63.3	20	50.0	4	45.0		
Diarrhea										
No	20	100.0	18	29.2	27	67.5	5	50.0	30.740	<0.001*
Yes	0	0.0	42	70.8	13	32.5	5	50.0		
Fatigue										
No	20	100.0	4	6.7	6	15.0	0	0.0	12.938	<0.001*
Yes	0	0.0	56	93.3	34	85.0	10	100.0		
Headache										
No	20	100.0	4	6.7	20	50.0	3	25.0	55.071	<0.001*
Yes	0	0.0	56	93.3	20	50.0	7	75.0		
Signs										
Tachypnea										
No	20	100.0	55	92.5	7	17.5	7	65.0	48.176	<0.001*
Yes	0	0.0	5	7.5	33	82.5	3	35.0		
Intercostal retraction										
No	20	100.0	55	92.5	40	100.0	8	85.0	03.181	0.066
Yes	0	0.0	5	7.5	0	0.0	2	15.0		
Grunting										
No	20	100.0	60	100.0	40	100.0	10	100.0	NA	---
Yes	0	0.0	0	0.0	0	0.0	0	0.0		
Cyanosis										
No	20	100.0	60	100.0	27	67.5	3	35.0	62.184	<0.001*
Yes	0	0.0	0	0.0	13	32.5	7	65.0		
Abdominal rigidity										
No	20	100.0	60	100.0	34	85.0	9	90.0	14.313	<0.001*
Yes	0	0.0	0	0.0	6	15.0	1	10.0		
Associated disease										
No	20	100.0	60	100.0	34	85.0	5	45.0		
Diabetic	0	0.0	0	0.0	0	0.0	1	15.0	48.107	<0.001*
Cardiac	0	0.0	0	0.0	6	15.0	3	25.0		
Cerebral palsy	0	0.0	0	0.0	0	0.0	1	15.0		

Regarding interleukin-6, serum level was significantly increased with severe than with other severity features groups (Table 3).

Table (3): Interleukin serum level in relation to severity of Covid-19

Variable	Clinical features N=200				KW	P value
	Asymptomatic (N=20)	Mild (N=60)	Moderate (N=40)	Severe (N=10)		
Interleukin 6 Mean ± SD	0.47±0.03	1.94±0.67	9.27±1.78	14.97±3.85	29.941	<0.001*

KW: Kruskal Wallis test *Significant

There were no significant relations between d-dimer and interleukin-6 serum level with fever, cough, dyspnea, running nose and sore throat. Also, there were no significant relations between procalcitonin with running nose and sore throat. Also, there were no significant relations between interleukin-6 with chest-X ray (opacity). Also, there were no significant relations between interleukin-6 with CT findings (ground glass opacity) (Table 4).

Table (4): Interleukin 6 serum levels in relation to common symptoms, chest X ray and CT findings of the studied groups

Variable	**Interleukin 6** Median (IQR)	*U test*	*P value*
Fever			
No	11.63(56.45)	-1.982	0.053
Yes	14.24(65.28)		
Cough			
No	12.63(53.36)	-1.710	0.089
Yes	14.24(65.28)		
Dyspnea			
No	12.63(53.36)	-1.901	0.061
Yes	73.96(119.78)		
Chest X-ray (opacity)			
Abnormal	73.96(118.26)	1.136	0.264
Normal	12.63(53.36)		
CT findings (ground glass opacity)			
Abnormal	68.00(118.47)	1.201	0.233
Normal	12.63(53.36)		

U: Mann-Whiteny U test

ROC curve analysis showed that procalcitonin and interleukin-6 were the best markers for early prediction of severity of disuses among children with covid-19. The sensitivity of interleukin-6 was 87.9% and specificity was 63.5% at AUC of 0.640 with cut off of 7.41 (Table 5 & Fig 1).

Table (5): ROC curve of Interleukin 6 serum level for early detection of severity among children with covid-19

Variables	AUC	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval		Cutoff	Sens	Spec
				Lower Bound	Upper Bound			
Interleukin 6	0.640	0.042	0.0145*	0.231	0.965	7.41	87.9	63.5

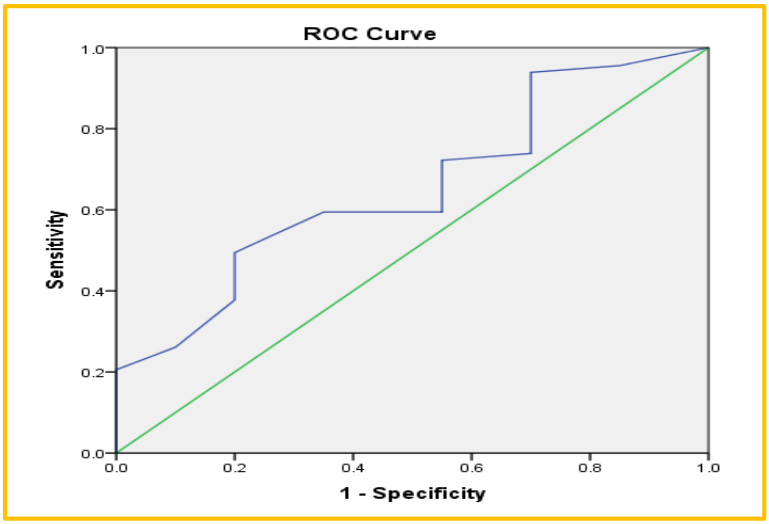

Figure (1): ROC curve of interleukin 6 of detection of different presentation, clinical and laboratory finding among children with covid-19

DISCUSSION

In pediatric patients, clinical findings are not typical and relatively milder than those in adult patients. While these patients are mostly asymptomatic or have upper respiratory symptoms, their clinical findings and prognosis are generally good [20]. The laboratory findings data in children with COVID-19 is still limited, with poor number of studies and reports. Laboratory tests usually show lymphopenia and leukocytosis [21]. The aim of the work was to study different presentations, clinical and laboratory findings among children with COVID-19.

Our results showed that age was significantly increased among asymptomatic clinical feature than mild, moderate and severe groups. In the same line **Shoaib *et al.*** [22] reported that the PCR positive group was stratified into three categories, i.e., asymptomatic, mild symptoms, and severe symptoms. There was a clear association of symptom severity with age. Our analysis revealed that the highest proportion (61%) of individuals developing severe symptoms were aged 50 or above. Within the severe symptoms group, only 5% of the individuals were in their 20s. The participants below the age of 20 were either asymptomatic or developed only mild symptoms. Also, **Zhang *et al.*** [23], **Rubin *et al.*** [24], **Riccardo *et al.*** [25] and **Petrilli *et al.*** [26] indicated that higher age is one of the major risk factors for a severe course of COVID-19.

Our results showed that interleukin-6 did not show any significant difference. While, **Bayramoğlu *et al.*** [27] reported that procalcitonin was significantly increased among mild and moderate to severe groups than asymptomatic clinical feature. The mild group had similar laboratory findings to the asymptomatic group in terms of both inflammation and calcium metabolism markers.

Also, we found no significant differences between the studied groups regarding Interleukin 6. While, **Liu *et al.*** [28] found that IL-6 was the most type of cytokine released by activated macrophages that rises sharply in severe manifestations of COVID-19. However, it is difficult to extrapolate if the rise is significant enough to cause the manifestations seen in severe forms. Similarly, **Coomes and Haghbayan** [29] showed that mean IL-6 concentrations were 2.9-fold higher in patients with complicated COVID-19 compared to those with non-complicated disease. Since the proportionate rise of IL-6 is correlated with disease severity, this study can prove ground-breaking. Although clinicians can use this to identify severity earlier and commence oxygen therapy sooner, the varying outcomes makes it somewhat difficult to ascertain what level of IL-6 corresponds to what negative outcome. Furthermore, many studies recruited participants from the same center, giving rise to the potential of selection bias [30].

ROC curve analysis showed that procalcitonin and interleukin 6 were the best markers for early prediction of severity of disuses among children with covid-19. The sensitivity of interleukin-6 was 87.9% and specificity was 63.5%, at AUC of 0.640 with cut off of 7.41. In the same line **Sun *et al.*** [31] found that, IL-6 is closely associated with the degree of infection of SARS-CoV-2, and they investigated whether monitoring IL-6 levels in severely ill patients with COVID-19 could predict the development of critical illness. ROC curve analysis indicated that IL-6 was a good predictor of the clinical severity of COVID-19. Serum IL-6 concentrations ≥ 24.3 pg/ml were associated with a greater likelihood of progression to critical illness status. IL-6 may also play a key role in the development and progression of novel coronavirus pneumonia [28, 32]. Circulating IL-6 concentrations have been closely associated with the clinical severity of COVID-19. For example, serum IL-6 levels were found to be significantly higher in severely ill patients than in those with mild symptoms [33], suggesting that IL-6 levels are closely associated with the occurrence of severe COVID-19 and could predict the severity of illness in patients with COVID-19. IL-6 levels were also found to be significantly elevated in patients with respiratory insufficiency, suggesting that IL-6 plays an important role in lung injury due to SARS-CoV-2 infection [34].

This study's had limitations that included the small sample size, which limited the ability of our analysis to detect small differences between the groups in certain variables. In addition, some disease severity factors, such as the mortalities, nutritional status, socioeconomic status, and management were not used as comparative elements between patients.

CONCLUSION

Children at any age seem to be susceptible to COVID-19, and even though their symptoms are milder, they still present a diverse range of clinical presentation. Interleukin-6 was the best marker for determining severity of disease among pediatrics with covid-19.

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