Diagnostic utility of IL-6 and some biomarker correlated with the diseases severity of COVID-19 patients

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Abstract

Coronavirus disease 2019 (COVID-19) SARS-2 is a respiratory tract infection with a newly recognized coronavirus thought to have originated as a zoonotic virus that has mutated or otherwise adapted in ways that allow human pathogenicity. This study describe the association between IL-6, D-dimer, C-reactive protein (CRP, Ferritin, erythrocyte sedimentation rate (ESR), and hematological marker in a cohort of COVID-19 patients. The baseline characteristics of the studied samples according to age and gender with a comparison of significance in studied groups show that a total of 65 individuals were divided into three groups according to the severity of disease (17 milds, 24 moderates, and 24 severe). Moreover, no significant difference was reported in the current study according to age groups between male and female groups at P>0.05. The laboratory tests included hematological, biochemical detections, and inflammatory biomarkers. A significant increase in neutrophil counts, but decrease in lymphocyte count. While normal reading in platelet count, HB, and PCV. There were a significantly higher D-dimer and serum ferritin in the severe patient, farther increased in inflammatory marker C-reactive protein, erythrocyte sedimentation rate in moderate and sever patients ($p < 0.05$). Moreover, analysis of serum levels of Il-6 showed a highly significant difference in the mean value in patients groups. In Conclusion, serum IL-6 is important marker of inflammation identifying this elevated lies in the potential use of antibody against IL-6 that can guide the clinicians in recognizing patients with severe COVID-19 early in the disease. The potential risk factors of old age, high baseline of D-dimer, dynamic of ferritin, CRP, and ESR could help clinicians to identify and treat subjects with poor prognosis.

Keywords: *COVID-19, IL-6, CRP, ESR D-dimer, ferritin, hematological parameter, diseases severity.*

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الاهمية التشخيصية لـ IL-6 وبعض العلامات الحيوية المرتبطة بخطورة المرض لمرضى COVID-19

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الخلاصة

مرض فيروس كورونا 2019 (COVID-19) السارس 2 هو عدوى في الجهاز التنفسي مع فيروس كورونا تم التعرف عليه حديثًا يُعتقد أنه نشأ كفيروس حيواني المنشأ تحور أو تكيف بطريقة أخرى بطرق تسمح بالإصابة بالأمراض البشرية. تصف هذه الدراسة العلاقة بين البروتين التفاعلي IL-6 و D-dimer و C التفاعلي (CRP) و Ferritin ومعدل ترسيب كرات الدم الحمراء (ESR) وعلامة الدم في مجموعة من مرضى .COVID-19 الخصائص الأساسية للعينات المدروسة وفقًا بالنسبة للعمر والجنس مع مقارنة الدلالة في المجموعات المدروسة ، تبين أن إجمالي 65 فردًا تم تقسيمهم إلى ثلاث مجموعات وفقًا لشدة المرض (17 معتدل ، 24 معتدل ، 24)شديد .علاوة على ذلك ، لم تسجل أي فروق ذات دلالة إحصائية في الدراسة الحالية حسب الفئات العمرية بين مجموعات الذكور والإناث عند P> 0.05. تضمنت الاختبارات المعملية الكشف عن الدم والكيمياء الحيوية والعلامات الحيوية الالتهابية. زيادة معنوية في تعداد العدلات ، ولكن انخفاض في تعداد الخلايا الليمفاوية. أثناء القراءة الطبيعية في عدد الصفائح الدموية و HB و PCV. كان هناك ارتفاع ملحوظ في D-dimer و ferritin في المصل في المريض الشديد ، وزيادة أكبر في البروتين التفاعلي للعلامة الالتهابية C ، ومعدل ترسيب كرات الدم الحمراء في المرضى المعتدلين والشديد (P <0.05). علاوة على ذلك ، أظهر تحليل مستويات Il-6 في المصل فرقًا معنويًا للغاية في متوسط القيمة في مجموعات المرضى. في الختام ، يعتبر مصل IL-6 علامة مهمة للالتهاب الذي يحدد هذا المستوى المرتفع في الاستخدام المحتمل للأجسام المضادة ضد IL-6 التي يمكن أن توجه الأطباء في التعرف على المرضى المصابين بـ COVID-19 الحاد في وقت مبكر من المرض. يمكن أن تساعد عوامل الخطر المحتملة للشيخوخة ، وخط الأساس العالي لـ D-dimer ، وديناميكية الفيريتين ، و CRP ، و ESR الأطباء على تحديد وعلاج الأشخاص الذين يعانون من سوء التشخيص .

الكلمات المفتاحية : *كوفيد -19 ، انترلوكين -6 ، المؤشرات الحيوية الالتهابية ، المعلمات الدولية ، شدة المرض .*

Introduction

Coronaviruses are a large family of viruses that usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. However, three new coronaviruses have emerged from animal reservoirs over the past two decades to cause serious and widespread illness and death [1]. There are hundreds of coronaviruses, most of which circulate among such animals as pigs, camels, bats and cats. Sometimes those viruses jump to humans—called a spillover event—and can cause disease [2]. When infecting humans, COVID-19 can cause diseases of varying severity, from upper respiratory tract infections similar to a common cold, to liver, enteric, neurological diseases and lower respiratory tract infections such as pneumonia, bronchitis and severe acute respiratory syndrome (SARS) [3].

Most people e (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging) and

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5% of patients suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction)[4] . At least a third of the people who are infected with the virus do not develop noticeable symptoms at any point in time. These asymptomatic carriers tend not to get tested, and they can spread the disease. Other infected people will develop symptoms later (called *pre-symptomatic*) or have very mild symptoms, and can also spread the virus [5]. However, checking inflammatory biomarkers is not the standard of care in the emergency department. Perhaps the clinical context enhances the benefit of these biomarkers for an inpatient team. It remains unclear whether the inflammatory marker indicators are biologic markers of disease or mediators of the hypothesized 'cytokine storm,' in which hyper inflammation and multi-organ disease arise through excessive cytokine release from uncontrolled immune activation [6]. The current study was aimed to investigate IL-6 levels and some biomarkers in patients with COVID-19 infection.

Subjects, materials and methods

This study was conducted on different hospitals in Baghdad city, Iraq. Samples were collected depending on data from patients to determine IL-6, Hematological, biochemical and some Inflammatory markers investigate in patients with COVID-19. The time of data collection was extended from November 2020 to April 2021. A total of Clinical samples were collected from 65 patients (41 males and 24 females), their ages ranges between 15-76 years. Subjects were studied on admission for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infection by quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) of nasal and pharyngeal swabs. Severity of COVID-19 was graded into three groups the according to severity of disease (17 mild ,24 moderate, and 24 sever). Each sample was separated into 2 parts; the first part is the serum for the serological tests, while the second is whole blood for ESR. The concentrations of the serum IL-6 levels in patients was determined by using ELISA Kit, according to the manufacturer's guidance (MyBiosource USA).

Statistical analysis

Analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data are presented as mean ± SD, median and standard divisions. Qualitative relations were evaluated using the Chi-square test. A p-value of ≤0.05 was considered statistically significant.

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Result

Demographic characteristics of the studied groups:

The present study describes results of the data analysis in a series of tables corresponding to the objectives of this study as following:

Sixty- five patient with COVID-19 were divided into three groups according to severity of disease (17 mild, 24 moderates, and 24 sever. The males was 41 at percentage 63.07 % and 24 females at percentage 37.8 %. Demographic characteristics of the subjects are present in table (1).

Table (1): The baseline characteristics of the studied groups.

Variables		Studied group		
		Patients according to CT scan		
		Mild	Moderate	Sever
Age (years)	Range	19-50	27-50	30-76
	Mean ± SD	44±10.677	49.52±17.778	50.30±15.884
Gender	Male No. (%)	41 (63.07)%		
	Female No. (%)	24(37.8%)		
Total No.		65		

Distributions of hematological parameters according to severity of diseases

Table (2) shown the hematological distribution according to diseases severity (mild, moderate and sever) Table (2) displays a summary of shows the summary statistics of relationship study between diseases severity and studied parameters. The result showed significant relationship between diseases severity and WBC, were observed there were significantly decreased in lymphocyte while increased in neutrophil. On other hand, normal reading among platelet count, HB and PCV % as in table 2.

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Table (2): Distributions of hematological parameters according to severity of diseases

Parameter Reference rang	Patients			P. Value
	Mild No:17 Mean± SD	Moderate No:29 Mean ±SD	Severe No:44 Mean ±SD	
PCV % **38-52**	38.24 ±5.00	39.03 ± 4.76	38.70 ± 4.79	P=0.863
Hb **12.0-16.0 g/l**	12.31±1.75	12.98±1.57	12.71 ± 1.60	P=0.409
WBC **4-11 x10^3/µL**	17.19±2.08	18.92±6.083	24.87 ± 8.75	P=0.063
LYM **18-45.3%**	7.4. ±1. 74	5.56 ±1. 51	5.4 ±1. 16	P=0.079
NEU **39.3-73.7%**	23.6±56.7	54.03±56.8	93.5±22.3	P=0.017
Platelets **155-450 x10^3/µL**	234.76±74.94	239.86±103.98	232.59±78.05	P=0.940

Concentration levels of ESR, CRP, ferritin & D-dimer related to severity groups

The ESR, CRP, D-dimer and serum ferritin parameters distribution according to diseases severity (mild, moderate and severe). According to CRP; there was significant difference between studied groups. The highly levels of CRP representing in severe group (141.39±137.67), then moderate and mild groups (66.249±29.52, 20.38±19.73 respectively) P=0.0003). While in, serum ferritin, the results showed a high levels of S. ferritin in severe patients (897.27±404.007) which is highly significant when other patients groups (moderate and mild) (P=0.004). Moreover, the results showed a high levels of D. dimer in moderate patients (1139.27±1938.60) which is highly significant

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when compare to other patients groups (severe and mild) (P=0.009). Finally increases in ESR level in sever groups as illustrated in table (3.).

Table (3) :mean concentration of CRP, D- dimer, ESR and serum ferritin in patients groups (severe moderate and mild).

Parameter	Patients			P. Value
	Mild Mean± SD	Moderate Mean± SD	Severe Mean± SD	
D-dimer **< 250 ng/mL**	399.00±98.73	1139.27±1938.60	9650.45±820.31	P=0.008
Ferritin **20 to 250 ng/mL**	421.65±166.59	795.03±204.35	897.27±404.00	P=0.0004
CRP **0.8 to 10mg/dL**	20 .38±19.73	66.249±29.52	141.39±137.67	P=0.0003
ESR **0-20 mm/h**	15. 76 ± 5.76	54. 98 ± 5.54	76. 98 ± 12.79	P=0.0005

HS: Highly Sig. at P=0.001

Mean levels of IL-6 among the studied groups

Regarding serum levels of IL-6 shows the Mean± SD was (50.35±11.72 ng /ml) in mild patients, in moderate group the Mean± SD (59.54 ±6.45ng /ml). In severe patients the Mean± SD was (63.39± 10.64 ng/ml). Moreover, analysis of serum levels of Il-6 showed a highly significant difference in the mean value in patients groups (P=0.0003) as in table 4.

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Table (4): Mean concentration of serum cytokines IL-6 among studied groups

Il-6		
Studied groups	**Mean ± SD NS**	**Reference range**
mild	50.35±11.72	39.23±9.47
Moderate	59.54 ±6.45	
Severe	63.39± 10.64	
P value	* P=0.003	

Discussion

The global pandemic caused by COVID-19 remains poorly understood by clinicians. Identifying biologic markers associated with prognosis can help clinicians recognize disease severity. Regarding the high infectivity and mortality rates of COVID-19, early diagnosis of the disease is essential. The definitive diagnosis of this disease is made by proving a viral presence in real-time PCR analyses. In this study the highest percentages of the studied groups were males. The p-values of the differences among the ages and genders of these groups were non-significant at P>0.05. This indicates that the baseline characteristics of the sample did not have any effect on the relationships between the studied parameters. It also shows that the following results are not statistically biased to the researcher's point of view. The most common hematological findings include leukocytosis, lymphocytepenia, neutrocytosis and, normal thrombocyte were associated with greater severity in COVID-19 cases.

At disease severity more expressive hematological changes are highlighted, particularly a significant reduction in the lymphocytes number. This finding was more evident in those who suffered death compared to those who survived. it is possible to admit that the dynamics of the absolute lymphocyte count, that is, its serial count may be predictive of the clinical outcome of patient. An analysis of the literature revealed that among all the hematological abnormalities, lymphocytopenia has been highlighted as the most frequent since admission to death. According to, Tolouian et al. [7], the possible explanations for significant reduction in lymphocytes count including : (a) direct infection in these cells, causing their lysis by SARS-CoV-2, since lymphocytes have ACE2 receptors on the surface; (b) possible lymphocyte apoptosis caused by the systemic inflammatory process with consequent large cytokines production; (c) atrophy of lymphoid organs, such as the spleen, impairing lymphocyte turnover and (d) lactic acidosis inhibiting lymphocyte proliferation, which is more

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evident in cancer patients, a risk group for COVID-19 complications. Another study represented the level of white blood cells was decreased [8 ,9]. Although WBC counts of COVID-19 patients were significantly higher in the severe cases as compared to the non-severe group monitoring the patients' WBC counts during hospitalization also disclosed a simple method of predicting COVID-19 prognosis [10]. Several study suggest that the number of platelets was reported to be significantly reduced in COVID-19 patients [11,12]. There were several reasons why the platelets count of COVID-19 patients declined in the early stages induced lung tissue damage, resulting in activation, aggregation, and entrapment of the platelet. This led to thrombosis at the lung injury site, which increased the consumption of platelet. On the other hand, mature megakaryocytes may release platelets in the lungs. Therefore, when the damaged lungs caused pulmonary fibrosis and pathological changes, production of platelet might be affected [13]. A study by Xu *et al.* revealed that thrombocyte counts are significantly low in pneumonia patients and this decrease was directly proportional to the patients' clinical status [14]. Another study represented *mild* thrombocytopenia and leukopenia was observed in some patients at first admission who were COVID-19 positive. Regarding to the hemoglobin there was no significant different among the studied groups. in Another studies shows lower hemoglobin level in more severe cases hemoglobin in patients with COVID- 19 are significantly lower compared with those without COVID – 19 [15,16]. Although blood tests refer to the examination of blood condition and disease by observing the quantity change and shape distribution in blood cells, including leukocyte (WBCs), erythrocyte RBC), hemoglobin (Hb) and platelets (PLTs). Routine blood test indicators are sensitive to many pathological changes, which may assist in diagnosis when the cause of the disease is unknown. In addition, evaluation of medication or discontinuation and disease recurrence or recovery [17]. According to, CRP, ESR, S. Ferritin and D – dimer in the study there was significant difference between studied groups severe, moderate and mild. In serum ferritin there was a significant difference between studied groups and show high levels in severe group. The serum D-dimer concentrations in patients with severe forms of the disease were significantly higher than those in patients with milder forms, same result was found by Paliogiannis, P. *et al*., 2020 [18]. The clinical predictive value of an elevated D-dimer corroborates findings observed in prior studies [19,20]. there were an elevated in D-dimer which associated with an increased risk of diseases severity needing ventilator support and in-hospital mortality. A report by Huang et al. was showed that patients with severe COVI-19 had D-dimer values five times higher than those of the other patients [21]. In another study, Tang et al. concluded that the D-dimer level was approximately 3-5 times higher in patients with severe COVID -19 than moderate and mild.

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Elevated biomarkers of, D-dimer, CRP, ESR and ferritin is associated with the SARS-CoV-2 patients severity.

In the current study the ferritin level was significantly elevated in COVID -19 patients group, the data confirm that increased ferritin level was directly associated with the disease severity. This result was in matching with Lin et al. who reported an increase of ferritin level in Chinese patients with severe COVID-19 than patients with non-severe COVID-19 disease [22]. Raised ferritin levels in circulation could indicate severe inflammatory reaction in COVID-19 patients, and elevated ferritin levels in circulation may play an important role by contributing to cytokine storm development resulting in pulmonary edema [23]. A significant increase in ferritin levels was demonstrated in patients with moderate and severe disease, compared to patients with mild disease. Severe patients had significantly higher levels of ferritin the result was found by [24].

Regarding to the CRP, ESR levels in the patient groups were significantly higher in severe COVID-19 patients compared with that in moderate and mild COVID-19, same results was found by [25]. Higher levels of CRP, ESR were proposed to be highly associated and can be useful to predict the prognosis with greatest risk of mortality in COVID19 infection [26]. The comparison of mean serum IL-6 levels for severe COVID-19 mild and moderate COVID-19 was performed in several studies. The elevation of IL-6 has been previously demonstrated in inflammatory state for multiple conditions. [27]. The pathophysiological hallmark of COVID-19 in the severe inflammation and chemokine storm, which explains the elevation of IL-6 [28,29]. The importance of identifying this elevated biomarker also lies in the potential use of antibody against IL-6 such as tociluzumab, which is currently undergoing a clinical trial. Tociluzumab has previously shown efficacy against autoimmune and inflammatory conditions [30,31]. Based on our results, IL-6 is an important marker of inflammation and can guide the clinicians in recognizing patients with severe COVID-19 early in the disease course.

Conclusion

Elevated levels of IL-6, D-dimer, CRP, ferritin and ESR all had an independent increased risk for severity which were statistically significant. Specifically, in patients with moderate and sever disease. Our findings suggest that regularly checking IL-6, D-dimer, CRP, ESR, and ferritin has clinical utility in this respect, especially when these markers are above the cut-off values

Furthermore, researchers should develop a scoring system including IL-6 to assist clinicians in early recognition of patients at risk for developing severe disease.

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