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Some biochemical parameters as predictors of COVID-19: c-reactive protein, interleukin-6, lactate dehydrogenase, D-dimer, AST, ALT, ferritin, creatinine, and urea

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Abstract
The COVID-19 pandemic has infiltrated over 200 countries and negatively affected over three million people with confirmed cases. Biomarkers played a role in detecting this disease and determining its severity. This study aims to review various biomarkers to assess whether they can predict the clinical outcomes of COVID-19 and their correlation. As well as to determine the disease severity based on the patient's age and gender. A prospective study was applied to a sample of hospitalized patients who were laboratory- and clinically confirmed to be infected with COVID-19 of both sexes, aged 10-70 years, from March 15 to October 15, 2021. A blood sample of 5 ml was taken from each patient to perform the following biomarkers: C-reactive protein, interleukin-6, lactate dehydrogenase, D-dimer, AST, ALT, ferritin, creatinine, and urea. Results: The results of the study show that the means of studied biomarkers, including LDH (412.02), ferritin (411.96), CRP (22.53), PCT (0.02), urea (54.47), creatinine (1.63), AST (41.29), IL6 (25.49), and D-dimer (1044.94), rise significantly among patients compared to non-diseased persons. The study concluded that a rise in levels of any of the biomarkers, including PCT, CRP, LDH, D-DIMER, AST, ALT, Ferritin, Urea, IL-6, and Creatinine, were all significantly associated with COVID-19 cases, and older patients were found to be more susceptible to severe and critical cases of coronavirus disease.

Introduction:

A new strain of coronavirus evolved specifically in 2019; these strains are very different from SARS and Middle East respiratory syndrome (MERS), especially in terms of infection strength, severe symptoms, and high mortality rates [1]. This virus has spread day by day in more than 185 countries, starting with Wuhan, China, and then spreading to different regions all over the world [2]. COVID-19 causes a wide range of signs and symptoms, including fever, which often reaches 38 or 39 °C, and symptoms related to the upper respiratory tract, the most important of which are laryngitis, runny nose, and cough, and other symptoms related to the lower part of the respiratory system, the most common of which is pneumonia, shortness of breath (dyspnea), and other symptoms not associated with the respiratory system, the

most important of which is the patient's feeling of extreme fatigue [3]. However, the virus not only adversely affected the respiratory system but also included other body organs, such as the nervous and digestive systems, depending on the strength of the virus's effect and the resistance of the body [4]. Laboratory results of patients confirmed with COVID-19 infection showed a marked decrease in the number of white blood cells (WBCs) with a reduction in lymphocytes and a rise in LDH, D-dimer, serum ferritin, and C-reactive protein, and other studies have shown an increase in IL6, glucose, ALT, and AST levels [5, 6].

Studies and research published in many scientific journals worldwide have focused on the symptoms, epidemiology, and mortality rates of coronavirus disease, while those articles discuss limited laboratory standards [7]. This disease is still a viral respiratory and systemic disease of animal origin caused by a Coronaviridae virus, arising from Wuhan City, China, and increasingly spreading worldwide in an emergency [8]. Coronavirus did not cover a limited continent but involved all continents, according to recent statistics announced by the World Health Organization (WHO), with over 80,000 confirmed cases recorded in 34 countries and 2,700 deaths as of February 26, 2020 [9]. Despite the severity of coronary virus diseases, i.e., Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) that preceded COVID-19 virus disease, the length of the incubation period and the relatively low morbidity rate compared to the diseases mentioned above may contribute to the persistence and inflation of the outbreak in China and other surrounding countries [10]. The reverse-transcription polymerase chain reaction (rRT-PCR) test allows COVID-19 to be identified directly, while fully automated immune tests that detect anti-COVID-19 antibodies are vital for serological monitoring [11].

Aims of the study:

1. Using various biomarkers to assess whether they can predict the clinical outcomes of COVID-19 and their correlation with.

2. To determine the disease severity based on the patient's age and gender.

Materials and Methods

Study Population

In this article, the researchers highlighted various biomarkers because they played an effective role in decision-making about infection for other diseases. The role of these indicators in assessing the severity of the disease must be figured out to reduce the burden of costs and resources from the period between March 3, 2020, and April 29, 2020. All patients were tested carefully for biomarkers including [D-dimer, aspartate aminotransferase (AST), C reactive protein (CRP), aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), creatinine, pro-calcitonin (PCT), and alanine] and describe the outcome of the COVID-19 infection based on three independent points: the first is the severity of the outcomes of complications; the second is whether the patient is admitted to the intensive care unit; and the last is the state of oxygen saturation. We performed 55 total SARS-CoV-2 PCR tests by taking swabs, mostly from the nose and throat, and then performed biomarker tests for infection in 20 patients; these tests include ferritin, PCT, CRP, AST, and ALT, which were performed either in the local public health reference laboratory in Baquba City (PHB) or in

external laboratories. All asymptomatic cases in this study, during the sample collection and screening period, were excluded, while people with one or more typical COVID-19 symptoms such as fever, headache, body aches, cough, shortness of breath, sore throat, fatigue, loss of taste and/or smell, abdominal discomfort, and/or diarrhea were included in the study. When gathering demographic and epidemiological information from study participants, the patient's age, gender, and history of disease were considered. For the detection of COVID-19, according to the protocol recommended in the laboratory department of the hospital [12].

Analytic Methods:

A real-time PCR assay was applied. After confirming the infection, laboratory samples were collected from the patient's serum, and tests were performed for CRP, PCT, ALT, AST, LDH, urea, creatinine, IL-6, and ferritin. The results of all data were expressed as mean (M) ± standard deviation (SD), and the statistical significance level was performed with a P value of less than 0.05 as the minimum significance, with the unpaired Student's test applied using the SPSS program for Statistical Package for Social Sciences, version 16.0.

Statistical Analysis

The age range of the study subjects was between 10 and 79 years. The data were either expressed as mean ± standard deviation (SD) for the statistical tables or as the number of cases for the figures, and the level of statistical significance was performed using an unpaired Student's t-test to compare the mean between two separate independent groups with equal variance. Also, the chi-square test was used to compare observed results with expected results and determine if a difference between the two is due to chance or a relationship between the variables we are studying. A p-value < 0.001 was considered a statistically significant difference. All statistical analyses were analyzed using the SPSS software (16.0; SPSS, Inc., Chicago, IL, USA) [13]. The German Roche company made all the kits used for the laboratory tests.

Results

Table 1 shows that the means of LDH (412.02), AST (41.29), and ferritin (411.96) are significantly higher among patients compared to non-diseased persons (133.35, 17.43, 79.78), respectively.

Table 1: Distribution of diseased and non-diseased groups based on the mean ± standard deviation of their pulmonary function-related biomarkers

Pulmonary function related biomarkers	Studied groups		P-value
	Diseased with Covid-19	Non-diseased	
	Mean ±SD	Mean ±SD	
Lactate Dehydrogenase (LDH) u/L	412.02±149.93	133.35±15.98	<0. 001
Aspartate Transaminase (AST), u/L	41.29±4.16	17.43±4.32	<0. 001
Ferritin, ng/ml	411.96±151.41	79.78±50.97	<0. 001

Table 2 shows that the means of CRP (22.53), PCT (0.02), and IL-6 (25.49) are significantly higher among patients compared to non-diseased persons (0.02, 0.01, 1.07), respectively.

Table 2: Distribution of diseased and non-diseased groups based on the mean ± standard deviation of their inflammation and infection-related biomarkers

Inflammation and infection related biomarkers	**Study groups**		**P-value**
	Diseased with Covid-19	**Non-diseased**	
	Mean ±SD	**Mean ±SD**	
C-reactive protein (CRP), mg/dL	22.53±13.99	0.02±0.01	<0. 001
Procalcitonin (PCT), ng/mL	2.57±1.00	0.01±0.00	<0. 001
Interleukin-6 (IL-6), ng/mL	25.49±18.44	1.07±0.42	<0. 001

The means of urea (54.47) and creatinine (1.63) are rising significantly among patients compared to non-diseased persons (25.06, 0.77, and 17.51), respectively, as shown in Table 3.

Table 3: Distribution of diseased and non-diseased groups based on the mean ± standard deviation of their renal function-related biomarkers

Renal function related biomarkers	**Study groups**		**P-value**
	Diseased with Covid-19	**Non-diseased**	
	Mean ±SD	**Mean ±SD**	
Urea, mg/dL	54.47±10.31	25.06±5.50	<0. 001
Creatinine, mg/dL	1.63±0.18	0.77±0.19	<0. 001

Table 4 shows that the mean alanine ALT (41.29) and D-dimer (1044.94) are significantly higher among patients compared to non-diseased persons (17.51) and (121.90), respectively.

Table 4: Distribution of diseased and non-diseased groups based on the mean ± standard deviation of their other biomarkers

Other biomarkers	**Study groups**		**P-value**
	Diseased with Covid-19	**Non-diseased**	
	M±SD	**M±SD**	
Alanine aminotransferase (ALT), u/L	41.29±4.17	17.51±4.36	<0. 001
Coagulation related biomarker	1044.94±976.96	121.90±52.65	<0. 001

In Fig. 1, the study shows the lack of severe and critical cases at younger ages, while these cases increase significantly in older people by three severe cases and four acute cases for each of the age groups (50–69) years and (>70) years, respectively.

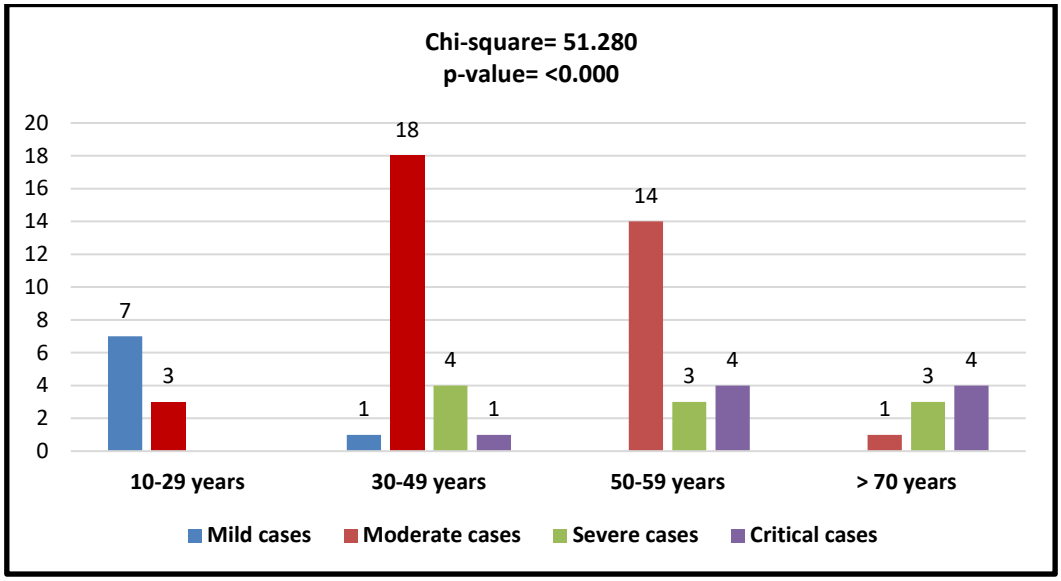

Fig. 1 Caption Age-wise severity of cases.

In Fig. 2, the study shows that male patients reported the highest number of severe and critical cases of COVID-19, with five severe cases and six acute cases, whereas females reported four severe cases and four other severe cases with no significant difference.

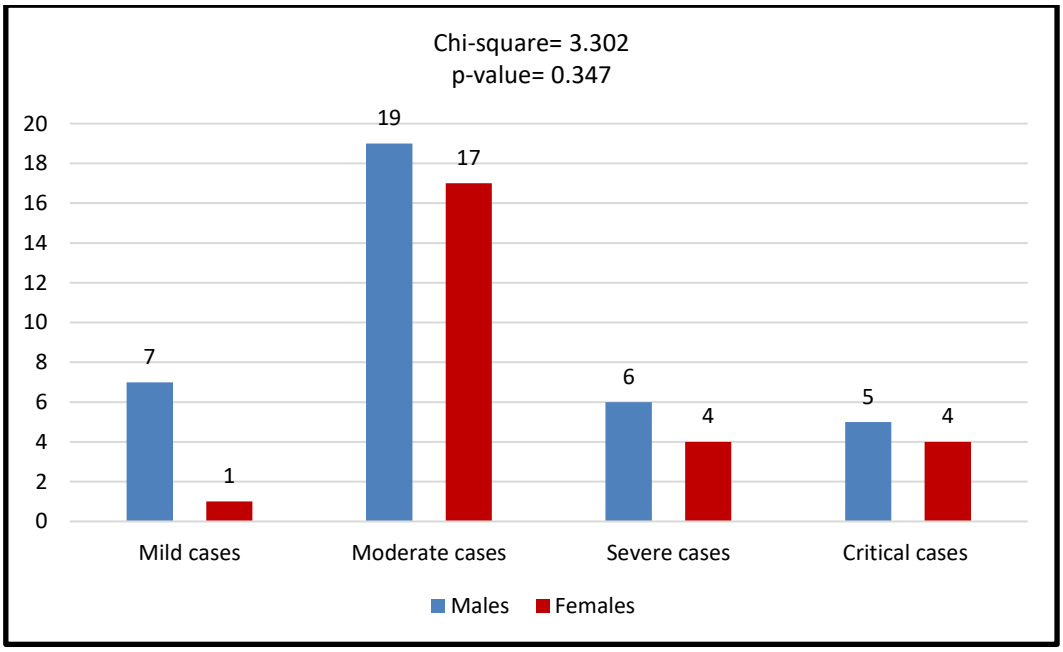

Fig. 2 Caption Gender wise severity of cases

Discussion

The study shows that the means of LDH, AST, and ferritin are rising significantly among patients with COVID-19. Elevated serum ferritin levels may reflect another bacterial or viral infection [14]. In this infection, ferritin increases and is associated with iron release in the reticuloendothelial system. Subsequently, the ability to transport ferritin in the liver and spleen decreases, which increases the synthesis and release of intracellular ferritin [15, 16]. Limited studies have shown that patients with bacterial infections have a higher level of ferritin than those with viral infections [17, 18]. In addition, high levels of ferritin in the serum help predict a poor outcome in hospitalized cases because of COVID-19 or influenza [19]. AST

levels in this study were found to be high among patients with COVID-19, whereas medical reports have shown that COVID-19 only increases AST values in transit, and the likely cause of liver dysfunction is most likely secondary liver tissue damage [20].

Our study shows that both CRP and PCT biomarkers increase significantly in COVID-19 cases, whether their infection is severe or very severe, especially in very severe cases, and their effect is associated with the results of ferritin variation in the serum, while many severe COVID-19 cases have viral infection and secondary bacterial infection. This study shows that the means of urea and creatinine that reflect renal functions are rising significantly among patients compared to non-diseased people. The highly significant urea and creatinine values align with a study conducted in China [21]. Investigations have reported that COVID-19 can reach and stabilize kidney tissue through the peripheral bloodstream, causing increased activity of ACE2 in kidney cells and thus destroying them [22]. A potential inflammatory kidney situation may affect SARS-CoV-2 cases with chronic kidney disease, making them more likely to develop pneumonia because of functional dysfunction of innate and adaptive immune cells [23], which may increase the risk of upper and lower viral respiratory infections [24].

Creatinine is a valuable indicator for predicting renal function. A prospective cohort study included 701 COVID-19 cases, and during hospitalization, it was found that the incidence of acute kidney issues and deaths increased among subjects that showed a marked rise in serum creatinine baseline values as compared to patients that did not show any increase, resulting in the virus's accumulation in the kidneys causing necrosis in their cells. In this study, we found that high creatinine standards almost double the chance of poor disease outcomes [21].

The study findings revealed a significant increase in IL-6 among COVID-19 cases. A retrospective study showed that high serum standards were a reliable, independent risk factor for COVID-19 cases, contributing to increased severity of disease morbidity and mortality and negative progress in computerized tomography (CT) scores, which showed a potential predictive capacity for lung injury [25]. IL-6 is released by chemokine T cells and macrophages to activate the immune response. Its level increases with inflammatory responses caused by many issues [26]. When someone develops COVID-19, the body may overproduce cytokines, such as IL-6, which can further activate clotting pathways, causing anticoagulant balance disorder with intravascular coagulation induction and multi-organ dysfunction [27]. This study showed that COVID-19 cases affected by a marked rise in IL-6 levels were more likely to develop kidney, liver, and lung health issues. Previous clinical investigations have shown that vulnerable risk factors for the severity of illness or mortality in COVID-19 cases are older males with cardiovascular problems, low lymphocytes, high D-dimer levels, and elevated lactate dehydrogenase standards [28, 29].

In this study, D-dimer values are rising significantly among patients compared to non-diseased people. The inflammatory responses and hypoxia in COVID-19 cases increased because of severe pneumonia, eventually leading to the activation of coagulating processes and fibrinolysis, followed by a hypercoagulable state leading to DIC and multi-organ dysfunction [30, 31]. Other investigations also suggest that high D-dimer levels of over 2.0 μg/ml in COVID-19 cases may effectively predict hospital mortality rates [32]. COVID-19 issues with D-dimer standards can also develop pulmonary embolism after hospitalization. An investigation conducted by Yu et al. noticed that elevation of D-dimer is linked to

inflammatory biomarkers, especially with CRP, and it will rise dramatically in COVID-19 cases compared to those with community-acquired pneumonia [33].

In the current study, the number of severe and critical coronavirus infection cases was concentrated among patients over 70 years of age. Two other Chinese studies reported that severe-to-critical coronavirus cases rose significantly in the older population [34, 35]. It is worth noting that COVID-19 virus disease symptoms rise in severity as they age, and their exposure to infection is likely to be similar between different age groups [36]. The increased severity of the disease symptoms in the elderly is usually explained by immunosenescence; the production of both naïve T and B cells decreases, with reduced immune activation during infection, and progress to an innate immune response does not occur in a coordinated manner [37], as well as age-related diseases such as diabetes, hypertension, and heart diseases [38].

Regarding gender, this study found that males are more affected by critical cases of COVID-19 than females. This finding is comparable to another Chinese study [35]. These differences have also been well illustrated in another literature review paper [39].It has been reported that acute inflammation of coronavirus disease in males facilitates the stages of development of their mild to severe infection, and this may be due to sex hormones such as estrogen and androgens within their varying functional levels in females and males, which can be the main reason for stimulating the differential immune response to COVID-19.

Conclusion

Our study shows that laboratory biomarkers adopted, including PCT, CRP, LDH, D-DIMER, AST, ALT, ferritin, urea, and IL-6, and creatinine, were significantly higher among COVID-19 cases. Older people are more affected by severe and critical COVID-19 cases than younger ones, and male patients are more affected by severe cases than females. We can use these findings as biomarkers in early management to improve disease prognosis, reduce mortality estimates, and aid in developing prevention strategies.

Conflict Of Interest

Authors declare no conflict of interest

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بعض المتغيرات الكيموحيوية كمتنبئات لمرض كوفيد-19: البروتين التفاعلي-سي، إنترلوكين-6، لاكتات ديهيدروجينيز، دي-دايمر، AST، ALT، الفيريتين، الكرياتينين، واليوريا

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الموبايل:

الخلاصة:

تسللت جائحة كوفيد-19 إلى أكثر من 200 دولة وأثر سلباً على أكثر من ثلاثة ملايين شخص مع حالات مؤكدة، إذ كان للمؤشرات الحيوية دور في الكشف عن هذا المرض وتحديد خطورته. تهدف هذه الدراسة إلى مراجعة المؤشرات الحيوية المختلفة لتقييم ما إذا كان بإمكانها التنبؤ بالنتائج السريرية لكوفيد-19 وارتباطها. وكذلك تحديد شدة المرض بناء على عمر المريض وجنسه. تم تطبيق دراسة استطلاعية على عينة من المرضى الموجودين في المستشفيات والذين تم التأكد مختبريا وسريريا من إصابتهم بفيروس كورونا (COVID-19) من كلا الجنسين، الذين تتراوح أعمارهم بين 10-70 سنة، في الفترة من 15 مارس إلى 15 أكتوبر 2021. عينة دم من (تم أخذ 5) مل من كل مريض لإجراء المؤشرات الحيوية الآتية (بروتين سي التفاعلي، إنترلوكين 6، نازع هيدروجين اللاكتات، D-dimer، AST، ALT، الفيريتين، الكرياتينين، واليوريا). أظهرت نتائج الدراسة أن متوسطات المؤشرات الحيوية المدروسة التي تضمنت LDH (412.02)، الفيريتين (411.96)، CRP (22.53)، PCT (0.02)، اليوريا (54.47)، الكرياتينين (1.63)، AST (41.29)، IL6 (25.49) و D-dimer (1044.94) ارتفعت بين المرضى مقارنة بالأشخاص غير المرضى. ولخصت الدراسة إلى أن ارتفاع مستويات أي من المؤشرات الحيوية ، بما في ذلك PCT و CRP و LDH و D-DIMER و AST و ALT والفيريتين واليوريا و IL-6 والكرياتينين ، ارتبطت جميعها بشكل ملحوظ بحالات COVID-19 ، ووجد أن المرضى الأكبر سنا أكثر عرضة للحالات الشديدة والحرجة لمرض فيروس كورونا.