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Article

Predictive value of C-reactive protein, D-dimer, Hemoglobin and Lactate dehydrogenase levels in diagnosing COVID-19 patients

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused enormous issues worldwide and is the most infectious pandemic. 50 subjects (evenly distributed between sexes) were included in this study, as well as their range of ages starting from 2 to 67 years. According to the study's result, the age and gender of the subjects include susceptibility to COVID-19; males were found to be more infected than females, and the ages 36 to 67 were more common than in other age ranges. Also, BMI calculations revealed that male patients with COVID-19 had the highest percentage of obesity. The clinical parameter results have been found serum C-reactive protein (CRP) as an essential indicator that changes significantly in infection with COVID-19 and inflammation. The concentration of CRP is higher levels for positive COVID-19 patients (male and female) with mild symptoms of COVID-19 than those with negative COVID-19 infection, and CRP levels were found to be higher in male than female patients. The results of D-dimer levels determined a nonsignificant difference in D-dimer levels in COVID-19 patients and non-COVID-19 patients than the normal concentration (N: Less than 500mg/dl.). The results of hemoglobin blood levels demonstrated significant variations between COVID-19 patients and non-COVID-19 patients and a decrease in Hb concentration compared to normal concentration (N: 11-16 g/dl.); thus, a link between anemia and inflammation. The lactate dehydrogenase (LDH) levels increased in positive COVID-19 patients male were (178.79 ± 56.08) mg/dl, and positive COVID-19 patients female were (141.57 ± 46.90) mg/dl than normal (N: Less than100mg/dl.), and significant variation was observed between positive and negative COVID-19 patients.

Keywords: COVID-19; C-reactive protein; hemoglobin; lactate dehydrogenase.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an epidemic emerging global health threat. It is essential to recognize and provide the infection treatment to decrease the COVID-19 illness severity. Therefore, healthcare workers face challenges in decreasing the severity of COVID-19 globally. Studies clinically confirmed that

changed levels of several blood markers might be associated with the grade of severity of COVID-19 infection [1, 2]. Serum C-reactive protein (CRP), a type of these clinical markers, is a protein created by the liver that serves as an early marker of infection and inflammation[3]. The normal CRP concentration in blood is less than 10 mg/L; the disease starts when it increases quickly within 6 to 8 hours and gives the maximum mountain in 48 hours [4]. The use of D-dimer markers when implementing new diagnostic strategies in COVID-19 patients has been suggested by National and International Scientific Organizations. During activation of the coagulation system, D-dimer, a degradation product of cross-linked fibrin formed, is universally used to eliminate thromboembolic illness in pulmonary embolism (PE) and deep venous thrombosis (DVT) patients. D-Dimer is fit identified to be an essential predictive marker of heart diseases. Its most definitive function is to monitor the post-treatment clinical status of infections. Also, D-dimers were capable of differentiating patients with severe from moderate disease. The hemoglobin levels decrease significantly in infections with high concentrations of CRP when anemia and inflammation are prevalent than in individuals with normal CRP levels [5]. The enzyme lactate dehydrogenase (LDH) is spread in tissues, chiefly the heart, liver, muscle, and kidney. Elevated lactate dehydrogenase (LDH) has been associated with severity in patients with viral infections and COVID-19 patients. [6]. Lactate dehydrogenase is a dependable indicator of hemolysis that rises two to threefold in a bad state when hemoglobin is reduced [7]. This study aimed to examine the association between CRP, D-dimer, HB and lactate dehydrogenase (LDH) and expect the severity and progression of illness in patients with COVID-19.

MATERIAL AND METHOD

Sample collection

Fifty samples were selected for this study, which included (32 males and 18 females) aged 19-68 years diagnosed with COVID-19 tests (SARS-CoV-2 with PCR method) using nasopharyngeal swabs. A questionnaire sheet was completed for each sample, including personal data (age, gender, and body mass index (BMI). This work was done at Gastroenterology and Hepatology Hospital, Baghdad Teaching Hospital and private lab from November 2021 to January 2022.

Body Mass Index (BMI)

BMI of all subjects was calculated by two parameters: the subject's height (in meters) and the subject's weight (in kg) as the following equation:

*BMI = Weight (Kg) / square of height (m2***)**

Each person's BMI indicates his/her weight status according to the following classification [8]:

BMI	Weight Status
Below 18.5	Underweight
18.5 – less than 25	Normal weight
25-30	Overweight
More than 30	Obese

Table 1: Weight status in relation to BMI

Hematological parameters and biochemical tests
The following laboratory tests were also included to detect the target: C-reactive protein (CRP), D-Dimer, complete blood count hemoglobin (Hb) and Lactate dehydrogenase (LDH). For autoimmune diseases, monitoring, and COVID-19 infectious, measurement of targeted levels has been used as a clinical tool.

1. **C-reactive protein (CRP)** [9]
2. **D-Dimer [10,11]**

Instrument use
AFIAS-1 and AFIAS-6 (AFIAS-automated fluorescent immunoassay system) are automatic immunoassay systems for the measurement amount of targeted in whole blood of human, urine, and other samples using quantitative or semi-quantitative methods. The AFIAS reader is has a simple composition and easy to carry. Besides, AFIAS uses all-in-one cartridges that user loads samples only in cartridges, which automates the whole procedure from sample preparation to examination. The AFIAS-1 analyzer is optimized for mid and small-sized clinics and has a single channel testing up to six COVID-19 Ab samples per hour, while the AFIAS-6 comes with six channels with the capacity to process more than 36 samples per hour. An applicable C-tip (capillary tip) for quantitative tests, such as CRP and Hb of COVID-19 patients, can be determined using a small sample from a finger at (10uL or 50uL) of whole blood.
Principle
The antigen in the sample binds to the detector antibody in the buffer, forming antibody-antigen complexes. The extra antigen in the sample forms the extra antigen-antibody complex, then migrates onto the nitrocellulose matrix to be captured by the other immobilized antibody on the test strip. The extra antigen leads to a stronger fluorescence signal on the detector antibody. The test uses a sandwich immunodetection method by the tool for AFIAS examinations to demonstrate the amount of target in samples.

Methods
Blood sample collection and process
The human whole blood/plasma samples for AFIAS are the target. It is recommended to separate the plasma via centrifugation at 24 h. from the clot following the gathering of whole blood for measurement. Do not maintain in a freezer the sample, which might influence the test assessment of the target.

Using a C-tip for the collection of capillary blood sample
(1) Using a pre-injection swab, clean the area.
(2) With a sterile lancet puncture.
(3) First blood drop wipe away.
(4) A second drop softly massages the adjacent area towards a C-tip.
(5) Contact the tip of the C-tip to the drop of blood with a C-tip horizontally.
(6) Enter automatically the sample blood to the C-tip by capillary action
(7) Clean all overloaded blood in the region of the tip.
(8) AFIAS reader is prepared on the 'C-tip mode' for examination samples.
(9) Depress on the screen the ‘START’ icon.
(10) The test results were displayed at 3 min for CRP and 12 min. For D-Dimer on the screen.

Using pipette tip (General Method)
1) Select “General Mode” in the tool for AFIAS examinations
2) By a pipette, take 100 µl of samples and dispense it on the cartridge wells.

3) Into the cartridge holder, insert the cartridge.
4) Put a tip into the tip gap of the cartridge.
5) Depress on the screen the 'START' icon.
6) The results examinations were shown after 3 min on the screen.

3-Hemoglobin (Hb) measure by Drabkin cyanmethaemoglobin test [12]
Instrument (Spectrophotometer specific for Hb)
Principle
The product brownish-colored cyanmethaemoglobin is almost all forms of hemoglobin in blood measured at 546 nM when reacting with Pot—Ferricyanide at an alkaline pH.

Reagents kit composition ready to use
Drabkin's Reagent 1000 ml. Drabkin's reagent is stable at 20-35°C, and standard is stable at 2-8°C contains:
25 mMol/L Phosphate Buffer
0.6 mMol/L Potassium Ferricyanide
0.5 mMol/L Sodium Cyanide
Contains stabilizers and preservatives.

2- 10ml Cyanmethaemoglobin Standard
0.06 gm/dl equals 15.06 gm/dl of hemoglobin in the examine state. Contain (buffers, stabilizers and preservatives).

Method
Fresh blood was added to common anticoagulants EDTA tube.
Added into 2 test tubes using a pipette (Blank tube: 2.5 mL Drabkin's reagent No.1. and test tube: 2.5 mL Drabkin's reagent plus 0.01ml fresh blood of sample.
Fine mix.
Incubate at room temperature for five min.
Via spectrophotometer specific for Hb, measure levels of Hb at 546 nM (530-550 nM) or GREEN filter next to blank. The finishing color is constant at 30 min.

4 –Detection lactate dehydrogenase using (LDH-P) kit bio lab[13]
Principle
In the presence of NAD, lactate dehydrogenase catalyzes lactate oxidation to pyruvate, consequently reducing it to NADH. At 340 nm, the rate of NADH formation measured directly proportional to LDH activity in serum.

Method
Collection of sample
Separate the serum 1 hour after the blood was collected. Do not use samples in the presence of hemolysis. LDH is reportedly stable in serum for about 4 days at 15 - 25 ºC.

Preparation of reagents
In a disposable container, mix four (4) vol. of R1 (Enzyme Reagent) with one (1) vol. of R2(Substrate Reagent) to prepare the working reagent.
The working reagent is constant for fourteen days at 2-8°C.

Test procedure
Blank the photometer with distilled water.

Take 1ml working reagent plus 0.025 ml of serum sample were added to the test tube. Mix well, read the initial absorbance wavelength 340 nm after 1 min and repeat the absorbance reading after every 1st 2nd min.
Calculations
ΔE = Initial absorbance - Absorbance after 1st /2nd min.
Calculations determine ΔE/min. for every reading
Find the mean value of ΔE/min.
ΔA = (Avg ΔE/min) x 6592 = U/L of LDH

Statiscal analysis
Using IBM SPSS computer program version 25.0 for statistical analyses. By ANOVA table, determinant differences between the groups were statistically analyzed. Mean ± standard deviation (SD) is expressed for data. A P value of ≤ 0.05 was regarded as statistically significant.

RESULTS AND DISCUSSIONS

Distribution of subjects
Fifty blood subjects were collected from the Gastroenterology and Hepatology Hospital, Baghdad Teaching Hospital in Baghdad province. There were 29 (58 %) patients with negative COVID-19 as the control group (18 male and 11 female) and 21(42 %) patients with positive COVID-19 (14 males and 7 females) (Table 1). The positive and negative COVID-19 patients were characterized according to their gender, age, Body mass index (BMI), and following measures CRP, D-Dimer, Hb and LDH in specific laboratories.

Negative COVID-19	**Positive COVID-19**
N=29 (58%)	**N=21(42 %)**

Table 2: Study subjects distribution

Distribution of subjects according to gender
The gender of 21 patients with positive COVID-19 are included 14(28%) males and 7(14%) females. The results of collected specimens revealed that male patients' percentage is higher than that of female patients (Table 2). As well as the gender of 29 negative COVID-19 group males are 18(36%) while females are 11(15%), as shown in figure (1). The theory is that men are more at risk than women, prompting COVID-19 causes a high number of deaths in men and are more likely to die from diabetes, heart sickness, cancer and liver illness than women [14]. The consequences of the study showed that gender and COVID-19 had a physically powerful association. According to Pradhan and Olsson's Biology of Sex Variations, sex-related differences, counting variances in hormone composition, inheritance, and other physiological features between male and female bodies.

Negative COVID-19		**Positive COVID-19**		Total
Male=18 (36%)	Female=11(22%)	Male=14(28%)	Female=7(14%)	Male=32 (64%) Female18(36%)

Table 3: Distribution of subjects according to gender

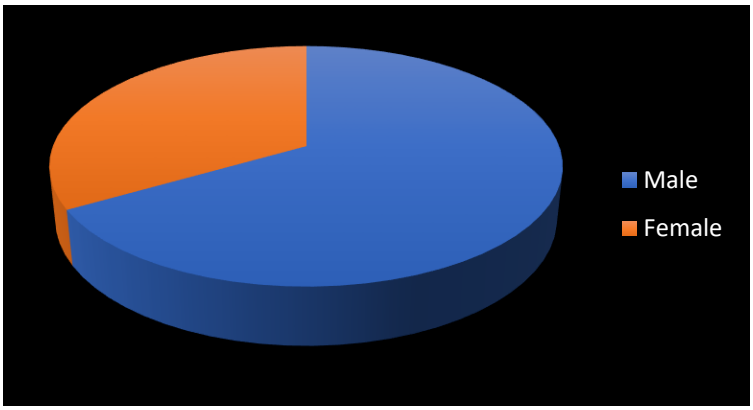

Figure 1: Rate of infection according to gender distribution of subjects according to age

The distribution of positive COVID-19 patients and negative COVID-19 patients into two age groups (2-35 and 36-67 years) revealed that patients are at the age group 36-67 years positive COVID-19 patients man represented (n=11(22%)) and negative COVID-19 patients man represented (n=14(28%)) than< 36 years represented(n=3 (6%);4 (8%)) respectively, while positive and negative COVID-19 patients female patients at the age group <36 years represented(n=3(6%)), the age group36-67years positive COVID-19 patients female represented (n=4 (8%)), while negative COVID-19 patients female patients at the age group 36-67 years represented (n=8 (16%)) (Table 3). The COVID-19 patient's infection showed older frequency in ages 36-67 years than those of < 36 years, as shown in figure (2,3). People at these ages believe they are extra at risk of COVID-19 severity infections, maybe because they have weak health with the human body's immune system and the human immune system protective mechanisms opposing viral infections [15].

1. **Covid-19 results**	2. **Males No. (%)**		3. **Females No. (%)**		4. **Probability**
5. **Age period years**	6. **2 - 35**	7. **36 - 67**	8. **2 - 35**	9. **36 - 67**	
10. **Positive**	11. 3 (6%)	12. 11(22%)	13. 3(6%)	14. 4 (8%)	15. P > 0.05
16. **Negative**	17. 4 (8%)	18. 14(28%)	19. 3 (6%)	20. 8 (16%)	21. P > 0.05
22. **Probability**	23. P > 0.05		24. P > 0.05		25.

Table 4: Distribution of subjects according to age

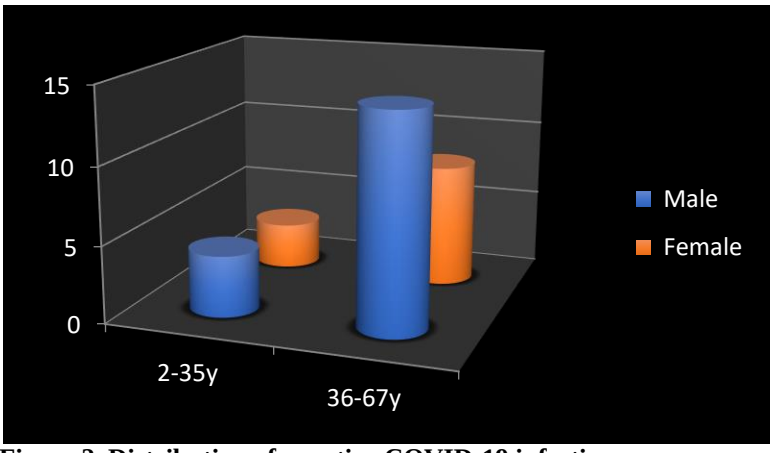

Figure 2. Distribution of negative COVID-19 infection according to age.

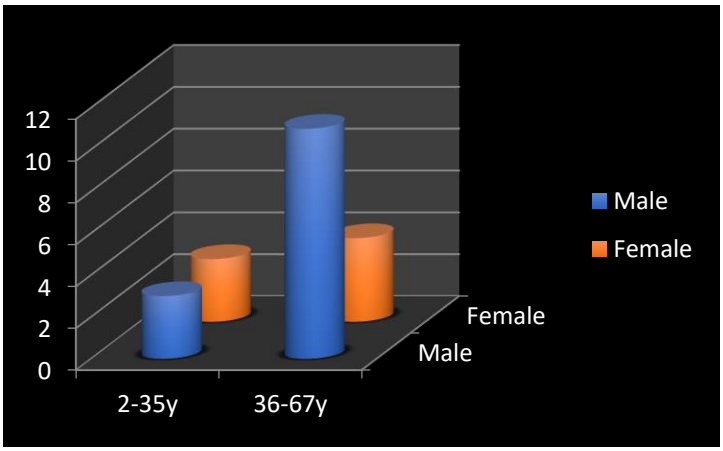

Figure 3. Distribution of positive COVID-19 infection according to age

Distribution according to Body Mass Index (BMI)

According to BMI calculations by [8], the current study revealed a majority of positive COVID-19 males who were found to be obese (BMI: ≥30.0) comprising up to (6(12%)) followed by over-weight (BMI range: 25.0–29.9) comprising (5(10%)) while the remaining (3(6%)) were found to be of normal weight (BMI between18.5–24.9). However, when calculating male patients with COVID-19, results revealed the highest percentage of 12% to be obese. Moreover, positive COVID-19 females were found to be obese (BMI: ≥30.0) comprising up to (4(8%)) followed by over-weight (BMI range: 25.0–29.9) comprising (3(6%)) (Table 4) (Figure 4).The current findings of BMI distribution among subjects agreed with [16], who reported that obesity is very common in the Iraqi community in which two out of every three individuals are obese or overweight with risk factors including being female or middle-aged, living in urban areas and having low physical activity. Obesity puts them at risk of severe illness COVID-19 and increases the risk for a lot of other serious chronic diseases. Obesity is a severe, widespread and costly chronic disease. Obesity increases the risk of COVID-19-related hospitalizations but not death, whereas it raises the risk of both COVID-19-related hospitalizations and death for extremely obese people. [17] were proposed that access to COVID-19 infection needs care and prioritization for COVID-19 vaccination.

	Positive COVID- 19 male N.(%)	Positive COVID-19 female N.(%)	Negative COVID-19 male N.(%)	Negative COVID- 19 female N.(%)
Underweight	0%	0%	8%	1(2%)
Normal weight	3(6%)	0%	13(26%)	9(18%)
Overweight	5(10%)	3(6%)	1(2%)	1(2%)
Obese	6(12%)	4(8%)	0%	0%

Table 4: Distribution of subjects' percentages according to weight categories obtained from BMI calculations

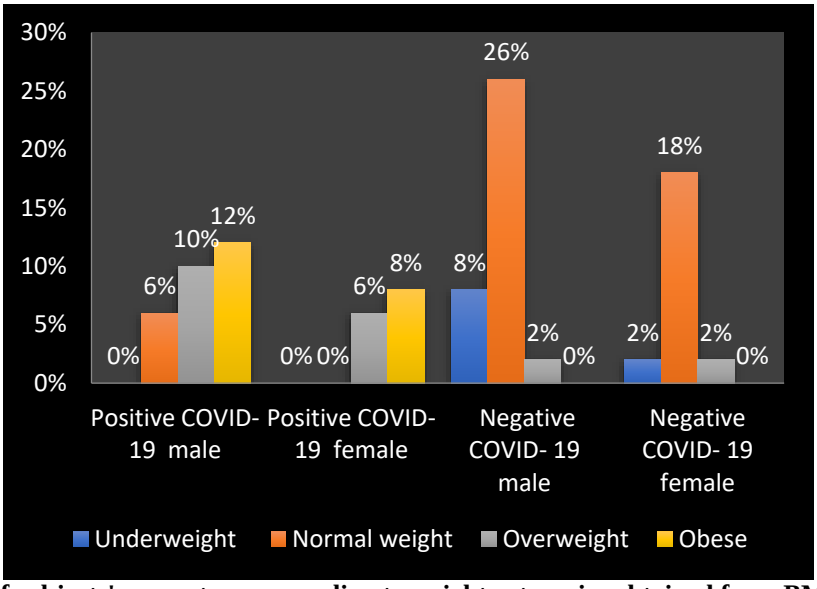

Figure 4: Distribution of subjects' percentages according to weight categories obtained from BMI calculations

Hematological parameters and biochemical tests

C-reactive protein (CRP)

CRP serum levels can predict the increase, severity, and disease progression in COVID-19 patients [18]. The results of studies showing serum amounts of CRP are higher in positive patients with COVID-19 than the normal concentration (N: 0.4-10 mg/dl.).The mean amount of CRP significantly rose in positive COVID-19 infection men (20.13 ± 14.57) mg/dl than in negative COVID-19 patients men (10.61 ± 2.71) mg/dl. Also, CRP was shown at higher levels in the positive covid-19 female at (13.77 ± 2.95) mg/dl than those in the negative covid-19 female at (9.96 ± 3.62) mg/dl. A study reported higher levels of CRP for positive COVID-19 patients (man and female) with mild symptoms of COVID-19 than those with negative COVID-19 infection, and CRP levels were higher in male than female patients (Table). [19] is found in mild inflammation and viral infections with high levels of CRP at (10–40 mg/dl), bacterial infection at (40–200 mg/dl)), burns, and severe bacterial infections at (>200 mg/dl). CRP concentrations are significantly associated with the aggravation of mild COVID-19 infections[1]. In addition, the authors proposed CRP as a suitable indicator for anticipating the aggravation possibility of mild COVID-19 infections, which can assist workers of health to recognize those mild COVID-19 infections at a before time stage for early cure. Also, other severe diseases associated with lung wounds indicate a high concentration of

CRP. Besides, high concentrations of CRP COVID-19 patients want close monitoring and cure. However, they did not show symptoms of expansion to the harsh infection.

CRP levels mean ± SD mg/dl	Males		Females	
	Positive	Negative	Positive	Negative
	20.13 ± 14.57^{A}	10.61 ± 2.71^{B}	13.77 ± 2.95^{B}	9.96 ± 3.62^{B}
The similar letters referred to nonsignificant difference				

Table 5: C-reactive protein levels

D-Dimer levels

The mean concentration of D-dimer in positive COVID-19 patients males was (142.71 ± 14.30) mg/dl, (148.61 ± 13.40) mg/dl for negative COVID-19 patients males, and (134.86 ± 10.32) mg/dl for positive covid-19 female than negative covid-19 female at(143.91 ± 10.39) mg/dl. The results study, as shown in Table (6), determined a nonsignificant difference in D-dimer levels in COVID-19 infections and those with non-infection COVID-19 than the normal concentration (N: Less than 500 mg/dl.). The current studies have reported that most confirmed infections with COVID-19 are currently a kind of mild infection [20.21]. The progression of COVID-19 disease has been demonstrated when irregular coagulation job, counting high D-dimer [22,23]. The elevated death rate of community-acquired pneumonia was also found to be related to high levels of D-dimer [24] in addition to D-dimer in the normal range, which showed low danger for disease [25]. D-dimer might be an expression infection of a severe virus and may expand into inducing coagulation dysfunction in addition to sepsis, which was general in serious illness sequence. Thus, the proof that high D-dimer concentrations in patients might contain the hazard of severe disease must attract extra attention in early time.

D-dimer levels mean ± SD mg/dl	Males		Females	
	Positive	Negative	Positive	Negative
	142.71 ± 14.30^{AB}	148.61 ± 13.40^{A}	134.86 ± 10.32^{B}	143.91 ± 10.39^{AB}
The similar letters referred to nonsignificant difference				

Table 6: D-dimer levels

3-Hemoglobin (Hb) levels

Male and female positive COVID-19 patients were decrease Hb concentration at(10.52 ± 1.94, 10.13 ± 3.21) g/dl. respectively compared to normal concentration (N: 11-16 g/dl.). Therefore, we may consider the present patients at the threshold of anemia. The Hb blood levels significantly varied between positive and negative COVID-19 patients (Table 7). The present study also demonstrated that a low hemoglobin concentration was noticed in positive infections for CRP; thus, a link between anemia and inflammation is suggested.[26] were found to evaluate CRP concentrations, decreased Hb levels linearly, and connected to inflammatory states extremely associated with elevated death. Thus, Monitoring hemoglobin in infections with COVID-19 with inflammatory situations is as important as monitoring of treatment [27]. Scientific literature has critical two pathophysiological mecha-

nisms: i) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was revealed to be associated with Hb at erythrocyte and bone marrow plane through CD26 and/or CD147 and other receptors located on erythrocyte and/or blood cell precursors, SARS-CoV2 attack to bone marrow erythroblasts as cytoplasmic/nuclear material in addition to the larger measurement of the precursors would make easy virus reproduction also interface with Hb; ii) hepcidin-mimetic action of a viral spike protein, inducing ferroportin blockage[28].

	Males		Females	
Hb level mean ± SD	**Positive**	**Negative**	**Positive**	**Negative**
	10.52 ± 1.94^{A}	12.08 ± 2.58^{B}	10.13 ± 3.21^{A}	13.51 ± 2.67^{B}
The similar letters referred to nonsignificant difference				

Table 7: Hemoglobin levels

4-lactate dehydrogenase (LDH) levels

Lactate dehydrogenase (LDH) levels increased in positive COVID-19 patients at (178.79 ± 56.08) mg/dl. Positive COVID-19 female patients were (141.57 ± 46.90) mg/dl than normal (N: Less than 100mg/dl.), and significant variation was observed between positive and negative COVID-19 patients (Table 8). It was clear from the results that the level of LDH rises with the increase in the level of CRP in the blood. Moreover, it demonstrated the impact of high LDH levels on disease severity in patients with COVID-19. High values of lactate dehydrogenase with lymphocytopenia are the most common abnormalities in the laboratory. LDH may be associated with respiratory job (PaO2/FiO2) and be a prophet of respiratory failure in patients with COVID-19. LDH should be regarded as a helpful examination for the before-time recognition of the severity of infection that requires earlier respiratory monitoring in addition to therapy to avoid progressing disease [29]. Also, LDH is distributed in tissues, mainly the liver, heart, kidney and muscle. It is found in the spread and is a mixture of five isoenzymes with high LDH serum levels in liver disease, renal disease, myocardial infarction, malignant diseases and progressive muscle dystrophy [30].

	Males		Females	
LDH level mean ± SD	**Positive**	**Negative**	**Positive**	**Negative**
	178.79 ± 56.08^{A}	126.89 ± 72.42^{B}	141.57 ± 46.90^{AB}	103.55 ± 37.31^{B}
The similar letters referred to nonsignificant difference				

Table 8: lactate dehydrogenase levels

CONCLUSIONS

When CRP, LDH, and decreased Hb levels, COVID-19 patients need close monitoring and should attract more attention to early treatment even though they did not expand symptoms to severe and progress of illness in patients.

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