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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. This study included 50 subjects (evenly distributed between sexes) and their range of ages starting from 2 to 67 years. According to the study's result, the ages and genders of subjects include susceptibility to COVID-19. Males were found to be more infected than females, and the ages of 36 to 67 were more common than other age ranges. Also, BMI calculations revealed that male patients with COVID-19 have 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 for positive COVID-19 patients (male and female) with mild symptoms of COVID-19 than for harmful COVID-19 infection, and CRP levels were higher in male than female patients. The results of D-dimer levels determined a non-significant difference in D-dimer levels in COVID-19 patients and non-COVID-19 patients than the average concentration (N: Less than 500mg/dl.). The results **of** hemoglobin blood levels demonstrated significant variations between COVID-19 and non-COVID-19 patients and a decreased Hb concentration compared to average 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 average (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. Recognizing and treating infection is essential to decrease the COVID-19 illness severity. Therefore, the workers of healthcare are in front of challenges in decreasing the severity of COVID-19 in the world. Studies clinically confirmed that changes in blood markers might be associated with the 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 is an early marker of infection and inflammation[3]. The average 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]. National and International Scientific Organizations have suggested the use of D-dimer markers when implementing new diagnostic strategies in COVID-19 patients. 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 as an essential predictive marker of heart diseases, and its most definitive function is monitoring the post-treatment clinical status of infections. Also, D-dimers were capable of differentiating patients with severe from moderate disease. The hemoglobin levels decreased significantly in infections with high concentrations of CRP when anemia and inflammation were 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 raises a two-three fold in a bad state when hemoglobin reduce[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 selected for this study, which included (32 males and 18 females) aged 19-68 years, were diagnosed by COVID-19 test (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, automating the procedures 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 that can 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 more vital 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. Separating the plasma via centrifugation at 24 h. from the clot after gathering whole blood for measurement is recommended. Do not maintain in a freezer the sample, which might influence the test assessment of the target.

Using C-tip for a 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 following at 3min. 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) Take 100 µl of samples and dispense them on the cartridge wells with a pipette.

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.

Hemoglobin (Hb) measured 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).

Methods

Fresh blood was added to common anticoagulants EDTA tube.

It was 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.

Detection of lactate dehydrogenase using (LDH-P) kit bio lab[13]

2.10. 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.

Methods

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

Statically 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 $\geq$ 0.05 was regarded as statistically significant.

Results

Distribution of subjects

Fifty blood subjects were collected from the Gastroenterology and Hepatology Hospital, Baghdad Teaching Hospital in Baghdad province. There were 29 (58 %) negative COVID-19 as the control group (18 males and 11 females) and 21(42 %) patients with positive COVID-19 (14 males and 7 females) (Table 2). 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 female patients (Table 3). 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 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.

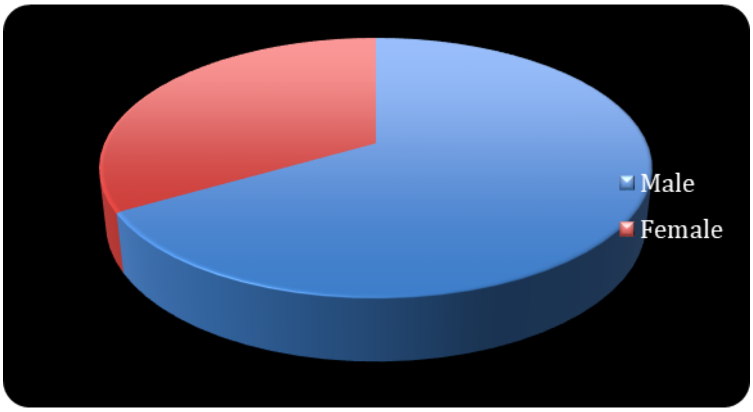

Figure 1. Rate of infection according to gender.

Distribution of subjects according to age

The distribution positive COVID-19 patients and negative COVID-19 patients into two age groups (2-35 and 36-67 years) revealed that patients were 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 4).

Covid-19 results	**Males No. (%)**		**Females No. (%)**		**Probability**
Age period years	**2 - 35**	**36 - 67**	**2 - 35**	**36 - 67**	
Positive	3 (6%)	11(22%)	3(6%)	4 (8%)	P > 0.05
Negative	4 (8%)	14(28%)	3 (6%)	8 (16%)	P > 0.05
Probability	P > 0.05		P > 0.05		

Table 4. Distribution of subjects according to age.

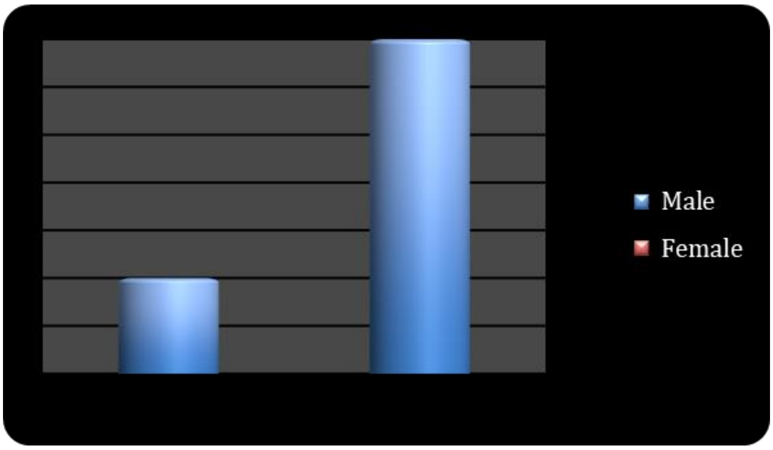

Figure 2. Distribution of negative COVID-19 infection according to age.

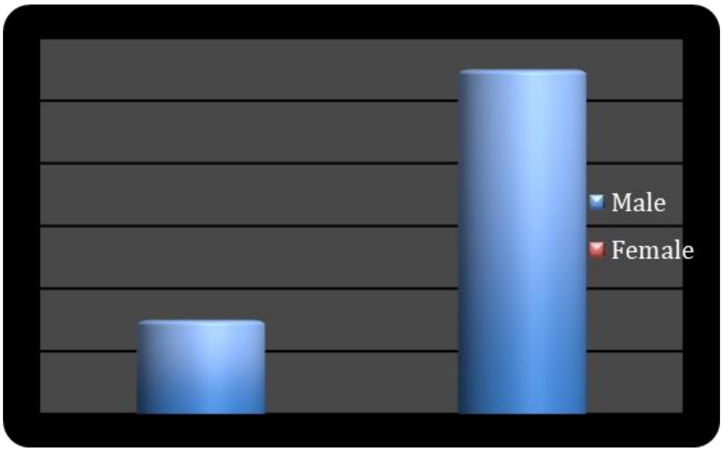

Figure 3. Distribution of positive COVID-19 infection according to age.

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 average weight (BMI between18.5–24.9). However, when calculating male patients with COVID-19, results revealed the highest percentage of 12% to be obese. Furthermore, 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 5) (Figure 4).

	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 5. Distribution of subjects' percentages according to weight categories obtained from BMI calculations.

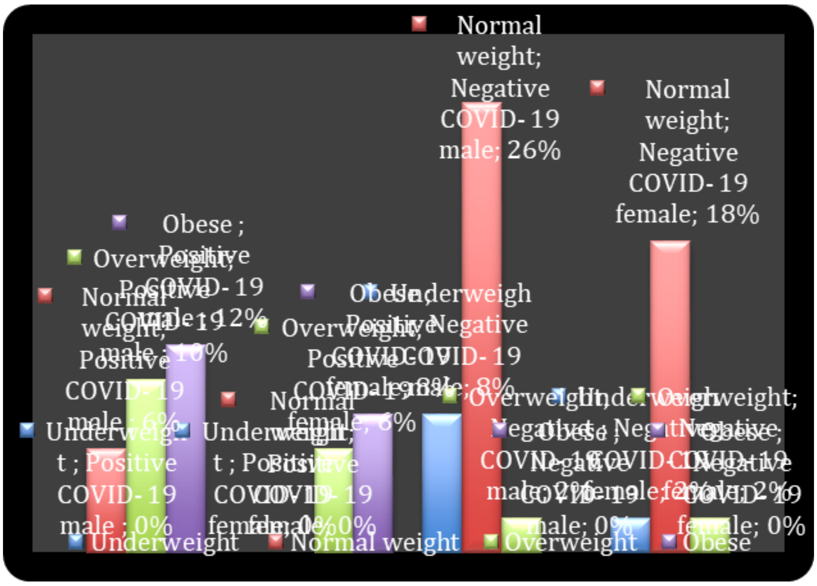

Figure 4. Distribution of subjects' percentages according to weight categories obtained from BMI calculations.

Hematological parameters and biochemical tests

C-reactive protein (CRP)

Studies have shown that the serum amount of CRP rises in positive patients with COVID-19 than the normal concentration (N: 0.4-10 mg/dl.).The mean amount of CRP was significantly higher in positive COVID-19 infection men (20.13 ± 14.57) mg/dl than in negative COVID-19 patients (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 (men and female) with mild symptoms of COVID-19 than harmful COVID-19 infection, and CRP levels were higher in men than in female patients (Table 6). [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 showed a significant association with aggravation of mild COVID-19 infections[1]. The authors proposed CRP as a suitable indicator for anticipating the aggravation possibility of mild COVID-19 infections, which can assist health workers 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 even though they do not have symptoms of 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 non significant difference				

Table 6. 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 non significant difference in D-dimer levels in COVID-19 infections and those with non-infection COVID-19 than the average concentration (N: Less than 500 mg/dl.). D-dimer might be an expression infection of severe virus and may perhaps expand into induce 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 non significant difference				

Table 7. D-dimer levels.

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 8). 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 evaluated CRP concentrations, decreased Hb levels linearly, and connected to inflammatory states extremely associated with elevated death.

Hb level mean ± SD	Males		Females	
	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 non significant difference				

Table 8. Hemoglobin levels.

lactate dehydrogenase (LDH) levels

Lactate dehydrogenase (LDH) levels increased in cheerful 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 100 mg/dl.), and significant variation was observed between positive and negative COVID-19 patients (Table 9). It was clear from the results that the level of LDH rises with the increase in the level of CRP in the blood. Furthermore, the most common abnormalities in the laboratory are the impact of high LDH levels on disease severity in patients with COVID-19—high lactate dehydrogenase values with lymphocytopenia.

LDH level mean ± SD	Males		Females	
	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 non significant difference				

Table 9. Lactate dehydrogenase levels.

Discussion

The theory is that men are more at risk than women, prompting COVID-19 causes many deaths in men and are more likely to die from diabetes, heart sickness, cancer and liver illness than women [14].

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 in these ages believe they are extra at risk of COVID-19 severity infections because they have weak health with the human body's immune system and the human immune system protective mechanisms opposing viral infections [15].

The current findings of BMI distribution among subjects agreed with [16] who reported that obesity is prevalent in the Iraqi community. 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 many 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 COVID-19-related hospitalizations and death for highly obese people. [17] were proposed that access to COVID-19 infection needs care and prioritization for COVID-19 vaccination.

CRP serum levels can predict the increase, severity, and disease progression in COVID-19 patients [18].

The current studies have reported that most confirmed infections with COVID-19 would current 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]. Elevated death rates of community-acquired pneumonia were also related to high levels of D-dimer [24] and D-dimer in the normal range, which showed low danger for disease [25]. Monitoring hemoglobin in infections with COVID-19 with inflammatory situations is essential, and monitoring of treatment [27]. Scientific literature has two critical pathophysiological mechanisms: 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].

Furthermore, 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 spread and is a mixture of five isoenzymes. High LDH serum levels in liver disease, renal disease, myocardial infarction, malignant diseases and progressive muscle dystrophy [30].

Conclusions

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

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