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Original Article

Assessment of some Physiological Biomarkers in COVID-19 Patients in Thi-Qar, Iraq

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Abstract

It is believed that many biomarkers and factors could be linked to the prognosis of coronavirus disease 2019 (COVID-19). Therefore, this study aimed to evaluate the association of lactate dehydrogenase (LDH), D-Dimer, vitamin D, and ferritin statuses with the prognosis of COVID-19; moreover, it was attempted to investigate its prevalence according to age, employment status, body mass index (BMI), and place of residency in a population sample of hospitalized patients in Thi-Qar, Iraq. This study evaluated 200 COVID-19 patients and 100 controls. The BMI of all individuals was calculated, and such demographic characteristics as age, gender, place of residency, and occupational status were collected from all participants. Blood samples were taken and used to estimate D-Dimer, LDH, vitamin D, ferritin, oxygen, and pulse rate. The mean age of the patients approached the fifth decade, and 72% of the cases were more than 40 years of age. In addition, 60% of the patients were living in the countryside, and 52% of the participants were employed, compared to only 8% of the cases who were students. The BMI of the patients was obtained at 31.44±10.2 kg/m^2; accordingly, 47% and 40% of the cases were obese and overweight, respectively, compared to only 12% of the patients who had normal weight ($P<0.05$). There were significantly lower vitamin D levels in the patients; however, the concentrations of LDH, serum ferritin, and D-Dimer were significantly higher in the patients, compared to the control group ($P<0.05$). Not only age and body weight but also employment status and place of residency maybe also the important risk factors for COVID-19 distribution. LDH, D-dimer, vitamin D, and ferritin statuses could be used as good biomarkers for this disease and its severity.

Keywords: Blood parameter, COVID-19, Iraq, Livelihood condition

1. Introduction

In the current two years, the so-called coronavirus disease 2019 (COVID-19) caused by the novel coronavirus, severe acute respiratory syndrome-related coronavirus (SARS-CoV-2), has spread globally (1). In December 2019, its first infection was reported in Wuhan, and then it spread worldwide. During the incubation period, which is 1-14 days or over 14 days in some cases, this virus spreads by close contact and/or respiratory droplets (2). The rate of spread or progression of the disease varies according to many factors, including age, gender, body weight, and ABO blood group (3). The severity of the symptoms of this disease varies from asymptomatic infection to multiple organ failure and death (2, 4). Several studies from different countries reported that symptoms are mild or not present in more than 80% of patients, while about 14% of the cases had severe symptoms and required hospitalization (5). However, the most important symptom among hospitalized patients is the presence and severity of respiratory failure due to hypoxemia, which is the most important reason for whether patients need intensive care unit (ICU) support or treatment (6). Currently, many different other biomarkers are being investigated to establish their role in determining the prognosis in COVID-19 patients.

One of these biochemical parameters is lactate dehydrogenase (LDH). In the past, its elevation was linked with the worst patient cases infected by other viruses (7); therefore, significant differences in LDH have been suggested among COVID-19 patients even and without severe symptoms (8). The other important biochemical parameter is D-Dimer. Since several researchers have shown coagulation in severe cases of COVID-19 patients (9), the elevation of D-Dimer concentration has been suggested in patients with COVID-19 because it is one of the ways to determine thrombotic disorders (10). Several observations have suggested that vitamin D, which acts as an immune regulator and plays an anti-inflammatory role, especially in viral infections, can modulate the risk and reduce the severity of COVID-19 (11).

Conversely, the adverse effect of the underlying disease and related inflammatory background on 25OHD metabolism according to the reverse causation hypothesis is questionable (12). Therefore, vitamin D could be one of the most important biochemicals used in determining the prognosis in COVID-19 patients (13). Ferritin blood disorders appear to have little diagnostic significance in both SARS as no abnormalities have been reported in its level (14) and Middle East Respiratory Syndrome in which no abnormalities have not been measured or at least not reported yet (15). In contrast, it has been suggested that serum ferritin is one of the important diagnostic parameters in COVID-19 (16).

In Iraq, there are very few studies regarding the diagnostic biomarkers and risk factors of COVID-19 discussed above; accordingly, this study aimed to evaluate the association of oxygen (O_2), LDH, D-Dimer, vitamin D, and ferritin statuses with prognosis in COVID-19 patients in Iraq; moreover, it was attempted to investigate the prevalence of this disease regarding different age groups, occupational status, body mass index (BMI), and the place of residency in hospitalized patients in Thi-Qar, Iraq.

2. Materials and Methods

2.1. Sampling

In total, 200 patients with COVID-19 and 100 healthy controls were evaluated in this study. These patients were randomly selected from the hospitalized patients in different hospitals in Thi-Qar, Iraq. The healthy individuals were also randomly selected from students and employees in Thi-Qar University, Thi-Qar, Iraq. The age range of the patients was from 18 to 70 years in both genders.

The subjects were provided with a questionnaire if they were willing to join the research procedure. The questionnaire covered such information as gender, age, occupational status, and place of residency.

2.2. Physiological Biomarker Analysis

BMI was calculated for all individuals by weight in kilograms measured by body balance divided by height in square meters. Afterward, the BMI of individuals was classified according to the World Health Organization classification (17) in table 1. 5 ml blood samples were collected from all individuals by a disposable syringe in a sterilized test tube. Serum was separated after centrifuging the samples for 5 min at 5000 rpm and used to determine the following:

1. D-Dimer, LDH, vitamin D, and ferritin by Cobas ® kit from Roche Diagnostics GmbH, USA. This method is a fully automated, random-access, software-controlled system for immunoassay and photometric analysis intended for quantitative and qualitative *in vitro* determinations using a wide variety of tests. Test ordering end execution on Cobas and data entry in STARLIM host computer system were performed manually. The tests were carried out according to the instructions indicated in the commercial kit.

2. O_2 and pulse rate were measured through a finger by a pulse oximeter (CMS50D) device from Contec™, China. Photoelectric oxyhemoglobin screening technology was adopted according to the amplitude pulse scanning and recording technology so that two

beams of different wavelengths of lights were focused on the tip of the human nail through a finger clip-type sensor. Subsequently, the measured signal was obtained by a photosensitive element, and the information obtained was displayed on the screen through processing in electronic circuits and microprocessors.

Table 1. Body mass index classification according to the WHO guidelines

Categories	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese	>30

2.3. Statistical Analysis

The data were analyzed in SPSS software (version 25) through the Chi-square test (X^2) and summarized using frequency and percentage (cases %) (18). Moreover, the obtained data were presented as mean±standard error (M±SE), and for multiple comparisons, the Fisher's test was used to analyze these data using Statview statistical software (version 5.0). Values were considered to be statistically significant when the obtained P was <0.05 (19).

3. Results

In total, 200 patients (100 females and 100 males) were included in this study. The age, employment status, place of residency, and BMI of the participants are illustrated in table 2. Regarding age, 145 (72.5%), 50 (25%), and 5 (12.5%) cases were ≥40, 20-39, and <20 years old, respectively. Considering the employment status, the majority of the patients were employed (n=105; 52.7%) and unemployed (n=80; 40%), while the students constitute the minority (n=15; 7.5%). Furthermore, the majority of the cases were living in the countryside (n=120; 60%), compared to others residing in a city (n=80; 40%). The results of BMI revealed that 59 (47.5%) and 80 (40%) patients were obese and overweight, respectively, while 25 (12.5%) cases had normal weight. It is worth mentioning that all these differences were significant ($P<0.05$).

The physiological parameters were studied, and the results are presented in table 3. There was no significant difference between the patients and controls in terms of pulse rate (89±16.25 and 87.17±6.93, respectively) ($P\geq0.05$). Statistically significant differences were observed in the patients and controls regarding O_2 rate (88.32±2.72 and 96.37±1.7, respectively) ($P<0.05$). Furthermore, the patients had lower vitamin D levels, compared to the controls (10.81±0.44 and 56.04±5.03, respectively) ($P<0.05$). The LDH, serum ferritin, and D-Dimer concentrations were significantly higher in patients (520.9±23.6, 465.1±13.2, 629.3±11.6,), compared to the control group (138.9±4.6, 203.3±27.2, and 179.2±11.08, respectively) ($P<0.05$).

Table 2. Distribution of COVID-19 patients according to age, employment status, place of residency, and body mass index

Parameters			N	%	X^2	*P*-value
Age	**Mean±SD**		**49.97±14.91**			
	Age interval	< 20	5	2.5	11.2	0.011
		20-39	50	25		
		≥40	145	72.5		
Employment status	Employed		105	52.5	19.8	0.002
	Unemployed		80	40		
	Students		15	7.5		
Place of residency	Countryside		120	60	21.3	0.0001
	City		80	40		
Body mass index	**Mean±SD**		**31.44±10.2**			
	Body mass index interval	Normal	25	12.5	9.58	0.048
		over	80	40		
		obese	95	47.5		

Table 3. Value of the studied physiological parameters in COVID-19 patients and controls

Parameters	Control	Patients	*T*-value	*P*-value
O_2%	96.37±1.7	88.32±2.72	15.855	<0.0001
Pulse rate (bpm)	87.17±6.93	89±16.25	0.653	0.517
LDH (u/l)	138.9±4.6	520.9±23.6	10.164	<0.0001
D-Dimer (ng/ml)	203.3±27.2	629.3±11.6	20.034	<0.0001
Vitamin D (ng/ml)	56.04±5.03	10.81±0.44	17.887	<0.0001
Ferritin (ng/ml)	179.2±11.08	465.1±13.2	10.194	<0.0001

4. Discussion

Many COVID-19 risk factors, such as age, gender, body weight, and blood groups in different regions in the words were studied in previously conducted research. This study demonstrated that employment status and place of residency may also be important risk factors along with age and body weight in Iraqi hospitalized patients.

In this study, the mean age of the patients approached 50 years (49.97±14.91 years), and 72.5% of the patients were classified as ≥40 years. These results are nearly consistent with the results of all previous studies that have calculated age-specific risk factors for developing COVID-19. They report that older adults are more likely to get infected with COVID-19 with more severity than younger adults (20). The reasons for the increased risk of COVID-19 and death in the elderly may be the increased risk of developing certain co-morbidities (cardiovascular diseases, diabetes, obesity, respiratory diseases, and immune disorders) (21). It has been reported that ambient pro-inflammatory mediators are effective in aging and immune inflammation (22) leading to a cytokine storm, which plays an important role in disease severity in most diseases of the elderly (including COVID-19) (21, 23).

On the other hand, there are no previous investigations studying the employment status and place of residency. In this study, a low number of patients with COVID-19 was in the student group (7%). It may be because all the participants of this group were <20 and within 20-40 age groups which accounted for fewer numbers of the patients in this study. The higher number of patients with COVID-19 was in the employed group (52%). It may be because the participants of this group were interacting with many people which make them at high risk of COVID-19. Moreover, a higher number of COVID-19 patients was living in the countryside, compared to those residing in the city. It may be because the countryside is very crowded which make the participants of this group under a high risk of COVID-19, especially if there is no application of health guidelines as it was prevalent in the areas studied.

Obesity may be one of the risk factors for the COVID-19 evolution, which increases the risk of ICU admission (24). Obese patients are known to have changes in respiratory mechanisms (25) and an increased risk of developing co-morbidities, such as diabetes mellitus, arterial hypertension, or cardiovascular disease (26). All of these conditions predispose obese patients to the organ failure associated with pneumonia as Stapleton and Suratt (27) previously reported during the H1N1 influenza pandemic 2009 in Canada, Mexico, and the United States of America. Accordingly, it has been recently hypothesized that obesity is a uniform risk factor for severe COVID-19. Sattar, McInnes (28) showed that the mean BMI of patients was 31.44±10.2 kg/m^2, which was in line with the results of our study; moreover, 47% and 40% of the patients were obese and overweight, respectively, compared to only 12% of patients who had normal weight.

Many studies have suggested many biochemical parameters, including what have been studied in this study (O_2, LDH, D-Dimer, vitamin D, and ferritin) to diagnose and follow up COVID-19 patients. It is well-established that hypoxemic respiratory failure is usually the most important symptom among COVID-19 patients and for deciding whether the patient should be under treatment in ICU for respiratory support (21, 23). It should be noted that only less than half of the patients showed shortness of breath despite respiratory failure caused by hypoxemia, which may easily lead to reducing the disease clinical severity. It is therefore recommended to measure peripheral O_2 saturation in all COVID-19 patients on routine admission regularly during the hospital stay (29).

Since LDH is an intracellular enzyme, it is present in almost all organ cells in body systems as five separate enzymes, namely LDH-1 in cardiac muscle, LDH-2 in the reticuloendothelial system, LDH-3 in lung cells, LDH-4 in the pancreas and kidney, and LDH-5 in the skeletal muscle and liver. Since the 1960s, LDH has traditionally been used as one of the important markers of heart damage; however, it is also known that its abnormal values can be caused by low oxygenation and injury of many other organs. The severe infection and tissue injury activate metallic proteases and promote macrophage-mediated angiogenesis which leads to increased lactate in acidic extracellular pH. This may cause the damage of tissues by cytokines and then LDH release (30). As mentioned earlier, LDH (isomer 3) is found in lung tissue; therefore, COVID-19 patients can release a high concentration of LDH into the blood from lung tissue injury that can be increased with disease severity since multiple studies have found that LDH is predictive of worse outcomes in patients in the hospital (7). However, since LDH is found not only in the lung tissue but also many other organ tissues as mentioned, the increase of LDH present in the COVID-19 patient (31) found in this study and other studies could be caused by the multiple organ injury and failure which occurs in the COVID-19 patients (8).

In addition, the concentration of LDH increase in thrombotic microangiopathy is associated with myocardial injury and renal failure (32). An increase in the D-Dimer level and the number of thrombocytes have also been indicated in severe cases of COVID-19 patients leading to a hypercoagulable state which could be contributing to the disease severity and mortality (33). In other words, the elevation of D-Dimer is associated with the disease severity (34) and mortality (35) in respiratory disease. A case-control study demonstrated that COVID-19 patients had elevated D-Dimer levels, which was consistent with the results of our study (36), while other studies indicated that the influenza patients (37) or pneumonia had increased D-Dimer levels, compared to those in the COVID-19 patients. On the other hand, in the severe cases of COVID-19, the clots of blood could occur in several organs which could lead to organ failure; accordingly, the measurement of D-Dimer level is a necessary biomarker to evaluate COVID-19 or other respiratory viral infections and monitor the severe cases of COVID-19 (38).

In this study, there was a lower significant level of vitamin D in COVID-19 patients. This result could explain it in two ways. First, the effect of vitamin D on the infection since evidence has suggested that vitamin D has immune-modulatory functions and plays an anti-inflammatory role, particularly in viral infection. It has also been shown to be inversely associated with acute respiratory distress syndrome and elevated C-reactive protein levels (39). Second, the effect of disease on vitamin D deficiency under the reversible causation hypothesis, as the type of disease and its inflammatory background may adversely affect the metabolism of 25OHD, especially its bound protein, leading to a significant bias in its assessment (40). Therefore, the low concentration of vitamin D found in this study could be another risk factor for COVID-19 (13).

In addition to the use of serum ferritin measurement as a biomarker to assess the metabolism of iron and as the differential diagnosis context of anemia (41), it has also been used as an indicator of the acute stage of many inflammatory diseases, infectious, or non-infectious, as a laboratory marker to diagnose the syndrome of macrophage activation (42) and monitor the response to medications (43). In this study, the ferritin level was twice much in the patient group than in the control group as suggested in many other studies (44, 45), which indicated that serum ferritin could be pertinent for the assessment of COVID-19 severity and patients' outcomes because it was increased more in acute patients than on average and was the last diagnostic test marker normalized in the course of the disease after at least five days. The pathophysiological background of SARS-CoV-2 that leads to ferritin deficiency is not totally understood but could be caused by the cytokine storm or the activation of macrophages as mentioned above (46).

In conclusion, not only age and body weight but also employment status and place of residency may be important risk factors for COVID-19 distribution. Furthermore, LDH, D-Dimer, vitamin D, and ferritin statuses may be good biomarkers for this disease to determine its severity. They are of significant importance since some of these results are unique; however, future research is needed to be conducted on large and more comprehensive population groups for the purpose of proving them and reaching the physiological and molecular activities of these biomarkers stated here.

Authors' Contribution

M. G. M. and Y. A. K. collected the data and samples. E. A. K. J. conducted laboratory analyses of the serum samples. J. J. conducted the statistical analyses of the data and wrote the manuscript.

Ethics

This study was performed according to the ethical forms commended by the Human Ethics Committee Guidelines of Department of Medical Basic Sciences, College of Nursing, University of Thi-Qar, Thi-Qar, Iraq (no. 22/2020), and informed consent forms were signed by all participants.

Conflict of Interest

The authors declare that they have no conflict of interest.

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