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Advantage study of ferritin to D-dimer ratio to differentiate asymptomatic from Coronavirus disease-2019 patients

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ABSTRACT

Background: Several laboratory markers have been studied for use in diagnosis and assessing severity of COVID-19 at the time of clinical presentation. Aim: We seek to find the FDR relationship as a value for diagnosing the onset of Covid-19 disease for the purpose of starting to treat the patient early, at the cheapest cost and fastest diagnostic method. *Methodology*: We employed a model-based approach that led us to focus on D-dimer (DDM) and the ironstorage protein ferritin. Our model predicts the ratio of circulating ferritin level (ng/mL) and D-dimer (ng/mL), called the Ferritin/D-dimer ratio (FDR), it may help in early identification of patients with COVID-19. *Results*: A significant association was reported between advance age and severity of COVID-19 especial more than 55 years. These results demonstrate that older patients were at higher risk of developing COVID-19. The number of male patients exposed to infection is approximately 70% higher than the number of female patients. Comorbidities showed a significant correlation between severe, mild and moderate cases as compared with diabetes, hypertension and cardiac disease. There is a high prevalence of abnormal liver biochemical on presentation in patients with COVID-19. In light of the risk for additional injury due to the complications and management of moderate to severe disease, it is important to monitor hepatic enzymes during the course of disease. *Conclusion*: Through this study, it was observed that there is a significant correlation between the severity of the Coronavirus (COVID-19) and the ratio of these two biomarkers (F/DDM). Therefore, it has been proposed to use the ratio as one of the biomarkers for COVID-19 patients in order to better monitor the disease. Such preventive measures may significantly reduce the case fatality rate.

KEYWORDS

D-dimer, ferritin, procalcitonin, troponin, ferritin/D-dimer ratio

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1. INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic is considered a global public health problem. It begins in Wuhan city, South China at 31-12-2019 and spread rapidly across the globe. COVID-19 is a zoonotic disease like other two previous coronavirus diseases [Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV)] which causes regional epidemics.

The term corona came from its external part shape (fringe) [1].

Different types of coronaviridae are the causative agents of many human and animal diseases [2]. CODID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. This virus belongs to ribonucleic acid (RNA) viruses. The RNA genome has a unique replication which results in a nested set of viral mRNA molecules [3]. This replication is affected by different host factors leading to a lot of changes in the structure and function of the cells [4].

Previous studies looked into a variety of laboratory markers to better understand the disease's pathogenesis and see how they play a part in the COVID-19 process: The acute-phase protein, C-reactive protein (CRP), acts as a precursor to infection or inflammation. When it comes to bacterial illnesses, the number is usually much higher. The protein is made in the liver and is found in blood in amounts of less than 10 mg/L in most people [5]. Previous studies looked into a variety of laboratory markers to better understand the disease's pathogenesis and see how they play a part in the COVID-19 process: The complete blood count (CBC) is used as tool for diagnosing various diseases. However, there are certain limitations of the CBC in the diagnosis of occult abnormalities. Therefore, differential white blood cell counts and assessment of the blood film are essential initial tools in the diagnosis of different clinical conditions [6]. complete blood count (CBC) is a blood test that assesses the cells that circulate in the bloodstream. White blood cells (WBCs), red blood cells (RBCs), and platelets are three types of cells suspended in a fluid called plasma (PLTs). They're made and matured mostly in the bone marrow, and they're released into the bloodstream when needed under normal circumstances [7].

Patients can have a moderate aberration in their blood count during asymptomatic forms or the incubation period, indicating the potential value of eosinopenia as predictors of early COVID-19 detection. In terms of clinical forms, lymphopenia is the most common symptom; indeed, the coronavirus attacks lymphocytes both directly and indirectly through immunological and inflammatory mechanisms. The lymphocyte count analysis is thus a trustworthy predictor of severity, which can be extremely valuable in monitoring and therapy adaption; also, the lymphocyte count is corrected following clinical improvement [8].

In conclusion, the blood count, as a regular biological assay, continues to act as an essential tool in the detection and monitoring of COVID-19. Blood cell abnormalities are thought to be prognostic indicators, and careful study and interpretation of lymphocyte and platelet counts allows a clinician to not only assess the prognosis, but also to alter treatment care [9]. Any of the renal functional indices outside of the normal range was considered as renal dysfunction. Serum creatinine levels were greater in severe patients than in moderate patients, according to Xiang *et al*. Furthermore, urea nitrogen and CRP had a weekly positive connection [10].

According to previous research, 43.9% of COVID-19 patients exhibited proteinuria upon admission, whereas 14.4% had an increased blood creatinine level [11]. However, because the trials conducted thus far have been limited to observations during hospitalization, the rehabilitation of kidney disease in COVID-19 patients who live following hospitalization is unknown [12].

Control of iron availability in cells depends largely on ferritins, which are ubiquitous proteins with storage and detoxification capacity. Ferritin stores iron inside cells and protects cell components from the generation of iron-induced free radicals [13].

In the current study, we seek to find the FDR relationship as a value for diagnosing the onset of Covid-19 disease for the purpose of starting to treat the patient early, at the cheapest cost and fastest diagnostic method.

2. METHODOLOGY

In the current study, we used various laboratory biomarkers in the diagnosis of COVID-19 and evaluation of its severity at the time of presentation. The approach depends on using D-dimer (DDM) and ferritin (the iron-storage protein). The ratio of serum ferritin level (ng/mL) over D-dimer (ng/mL) is high in asymptomatic individuals with COVID-19.

2.1. Patients

The current prospective investigation was carried out at the Department of Hematology and Biochemistry at the Al-Ramadi Teaching Hospital, Ramadi City, Anbar Province, Iraq, during a nine months duration (April to December 2020). The study included 100 patients, their ages ranged from 20 to 70 years. The enrolled participants were classified into the following groups.

2.2. Patients group

The patients (60) were confirmed to have SARS-CoV-2 through nasopharyngeal swab by polymerase chain reaction (PCR) technique. The patients were tested for IgM to grouping according to the

severity of COVID-19. IgM levels were shown in Table 1. The name, age, sex, symptom's, drug history should be recorded.

Data were taken from every participant through a direct interview by specific questionnaire. The enrolled participants were classified into three age groups (20-35 years, 36-50 years, and > 50 years), as shown in Table 1.

Table 1. The mean ± standard deviation of age in both groups.

Groups	Age subgroup (Year)	No (%)	Age (Year) mean ± SD (range)	*p*-value
Mild case (Asymptomatic) (N= 25)	20- 35	4 (16 %)	28.68 ± 6.30 (Range 22-33)	0.003
	36- 50	9 (36 %)	36.5 ± 7.05 (Range 35-47)	
	More than 50	12 (48 %)	56.06 ± 11.25 ((Range 35-47)	
	Total	25 (100%)	39±6.92 (Range 20-70)	
Moderate case N=18	20-35	2 (11.1 %)	33.66 ± 6.82 (Range 20-35)	0.0031
	36- 50	9 (50 %)	40.75± 7.55 (Range 37-50)	
	More than 50	7 (38.9%)	55.68 ±12.58 (Range 50-70)	
	Total	18 (100 %)	44±8.33 (Range 20–70)	
Severe case N= 17	20-35	1 (5.9 %)	29.38 ± 4.48 (Range 30-45)	0.003
	36- 50	3 (17.6 %)	44.16 ± 9.03 (Range 36-50)	
	More than 50	13 (76.5 %)	63.11 ± 11.30 ((Range 56-70)	
	Total	17 (100 %)	65± 13.1 (Range 20–70)	
Healthy subject (control) N= 40	20-35	21 (52.5 %)	25.38 ± 3.18 (Range 20-31)	0.03
	36- 50	10 (25.0%)	48.16 ± 9.03 (Range 36-45)	
	More than 50	9 (22.5 %)	59 ± 11.30 ((Range 56-64)	
	Total	40 (100 %)	26.41± 4.11 (Range 53–69)	

2.3. Control group

This group included 40 subjects with a negative nasopharyngeal swab for SARS-CoV-2 virus by PCR test and they had no previous history of COVID-19. They were also divided into three similar age groups as patient group (Table 1).

2.4. Excluded criteria

Patients with asthma, chronic renal failure (CRF), hypertension (HT), heart failure (HF), or thyroid dysfunction should be excluded.

2.5. Determination of biochemical study in serum

Collecting whole blood in EDTA tubes to determine haematology parameter by Erma analyzer (Japan), and Biochemical markers in serum samples have been carried out once in all subjects of the two major groups (control and patients). Hormones TSH, ferritin were performed by AIA 600 TOSOH (Japan), Procalcitonin and Covid IgM by MiniVides (France), and Liver function test (LFT) by Spin Xp (Espin).

2.6. Statistical analysis

Data were entered and analyzed using the IBM SPSS (Statistical Package for the Social Sciences) version 25. Normality, homogeneity, and normal distribution were all checked on the data. The continuous variables were expressed as means ± standard deviation (SD). A student independent *t*-test was used for the comparisons of the continuous variables and use ANOVA to test a *p-value* between groups. Hardy-Weinberg equilibrium calculator was used to test genotyping and allele frequencies. The likelihood of the Odd ratio and Fisher exacts were assessed using WinPepi version 11.65. a *p*-value of less than 0.05 was considered as a statistically significant difference.

3. RESULTS

3.1. Baseline characteristics of the enrolled patients

The result of this study covers 100 Iraqi patients (60 patients was coronavirus (COVID-19) and 40 normal subject samples) divided into four groups according to IgM, which listed in Table 1. Study sample at mild case (Asymptomatic) with beginning of infection (IgM=1-2) N=25. Study sample with receiving moderate case (2<IgM<4), N=18. Study sample with severe to critical cases (IgM>4.0), N=17. Healthy subject as control group IgM (<1.0) N=40.

The age of the participants (patients and controls) ranged from 20-70 year). Both groups are matched together regarding the age (*p*-value<0.01).

Demographic and clinical characteristics of patients illustrated in Table 1, showed sixty patients were admitted to an isolated room and 17 (33.5%) patients needed intensive care unit (ICU) admission, then more than 50% from critical cases had died. The mean age of the patients was 65 years (20-70).

Present research revealed that the ROC curve of age was used, and the best age cut-off point was 55 years as shown in Table 2.

Table 2: The cutoff value, sensitivity and specificity of age in COVID-19 patients.

Sample size			Disease prevalence	Area under the ROC curve (AUC)	SD	*t*-test	*p*-value
Age	Positive	Negative	52.5 %	0.961	0.0313	14.754	<0.0001
	21(52.50%)	19 (7.50%)					
	Associated criterion		Specificity		Sensitivity		
	>55		89.47		100		

Table 3: The clinical and demographic characteristics of patients groups with COVID-19.

Characteristics	Total (60 patients)	Asymptomatic	Moderate cases	Severe cases (Critical cases)	*p*-value
Gender					
Male	44 (70%)	17 (28.3%)	12 (20%)	13 (21.7%)	<0.01
Female	16 (30%)	7 (11.7%)	7 (11.7%)	4 (6.6%)	
Comorbidities					
Smoking	6 (10%)	4(66%)	-	2 (33%)	NS
Hypertension	12(20%)	5 (41.66%)	-	7 (58.33)	0.0027
Diabetes	17 (28.3%)	4 (23.5%)	3 (17.6%)	10 (58.82%)	0.003
Cardiac disease	15 (25%)	8 (53.3%)	3 (20%)	4 (26.66%)	0.036
Asthma	8 (13%)	4 (50%)	1(12.5 %)	3 (37.5%)	<0.001
Signs and symptoms					
Fever	28 (55.5%)	11(40%)	4(14%)	13 (46%)	-
Headache	9 (18%)	7(78%)	-	2 (22%)	-
Dry cough	39 (78%)	19 (49%)	5 (13%)	15 (38%)	-
Chest pain	11 (22%)	-	2 (19%)	9 (81%)	-
Abdominal pain	5 (10%)	1(20%)	-	4(80%)	-
Vomiting	9 (18 %)	7 (78%)	1(11%)	1 (11%)	-
Diarrhea	11 (21%)	-	9 (82%)	2 (18%)	-

Demographic and clinical characteristics of patients illustrated in Table 3, observed that the number of confirmed COVID-19 patients were admitted to single bedroom. According to the current results, the number of male patients exposed to infection is approximately 70% higher than the number of female patients, who recorded 30%. Only 45 percent of infected male patients were critical and severe cases, while 22% were moderate cases and the rest were mild totaling 31%. On the other hand comorbidities had shown a significant correlation between severe, moderate and mild cases as compared with cardiac disease (p<0.05) but highly significant appeared in asthma case (p<0.001) and diabetes (p<0.01), while non-significant may be showed in smoking.

Hypertension has a significant in severity cases in contrast to another group. Present study shown signs such as dry cough and fever which are acound as COVID-19 symptoms with highly percentage 55%, 78%, respectively.

The chemical unites, mean, standard deviation and *p*-value (determined by ANOVA – in using one-way ANOVA – the relationship between an independent variable and one quantitative

dependent variable) for all groups of COVID-19 patients are shown in Table 4. The cut-off, sensitivity and specificity of Biochemical parameters in COVID-19 patients are shown in Table 5.

Table 4. The mean, standard deviation, and *p*-value for biochemical parameters.

Variable	N.V.	Control	COVID-19 [Mean/(± SD)]			
	Unit	Normal case without inflammation	Asymptomatic	Moderate	Severe	Total
		Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)
		Duncan's letter	*Duncan's letter*	*Duncan's letter*	*Duncan's letter*	*p*-value
Age	Year	46.18 (±6.47)	46.88 (±6.56)	48.53 (±8.96)	56.06 (±6.59)	48.47(±7.79)
		*a**	*a**	*a**	*b*	*p* =0.062
IgM	<1.0	0.55 (±0.29)	1.48 (±0.24)	3.05 (±0.65)	9.28 (±3.66)	2.73 (±3.46)
	ng/mL	*a***	*b***	*c***	*d***	*p* <0.001
FBS	60-110	82.58 (±10.86)	90.50 (±5.32)	101.74 (±4.41)	110.06 (±4.59)	92.79 (±13.04)
	mg/dL	*a*	*b*	*c*	*d*	*p* <0.001
CRP	10-Aug	1.99 (±0.23)	11.40 (±2.26)	23.78 (±5.99)	72.62 (±14.05)	20.40 (±25.82)
	mg/L	*a*	*b*	*c*	*d*	*p* <0.001
DDM	<500	81.88 (±7.00)	454.3 (±75.7)	706.6 (±99.1)	1127.7 (±202.8)	467.8 (±394.6)
	ng/mL	*a*	*b*	*c*	*d*	*p* <0.001
URE	15-45	21.60 (±5.43)	34.81 (±6.09)	50.83 (±3.52)	91.94 (±19.41)	42.28 (±26.59)
	mg/dL	*a*	*b*	*c*	*d*	*p* <0.001
CRE	0.7-1.4	0.74 (±0.14)	0.91 (±0.13)	1.41 (±0.10)	1.72 (±0.13)	1.07 (±0.40)
	mg/dL	*a*	*b*	*c*	*d*	*p* <0.01
GPT	≤40	19.37 (±6.10)	34.17 (±3.99)	52.15 (±9.87)	94.72 (±18.85)	41.96 (±28.50)
	IU/L	*a*	*b*	*c*	*d*	*p* <0.05
GOT	≤40	20.53 (±6.51)	30.24 (±3.35)	63.13 (±18.89)	154.12 (±42.53)	53.66 (±51.99)
	IU/L	*a*	*a*	*b*	*c*	*p* =0.07
ALP	98-279	77.3 (±8.9)	141.0 (±30.7)	222.4 (±20.6)	355.9 (±61.8)	167.5 (±105.3)
	IU/L	*a*	*b*	*c*	*d*	*p* <0.05
LDH	230-460	266.3 (±20.4)	325.9 (±18.4)	405.8 (±51.5)	624.6 (±80.5)	368.0 (±134.0)
	U/L	*a*	*b*	*c*	*d*	*p* <0.001
WBC	4.0-10.0	6.53 (±0.84)	6.35 (±0.71)	4.92 (±1.20)	3.17 (±0.69)	5.61 (±1.53)
	10^9g/L	*c*	*c*	*b*	*a*	*p* <0.05
NUT	3.0-15.0	7.71 (±0.24)	43.07 (±10.58)	60.45 (±7.61)	65.38 (±7.22)	36.02 (±25.37)
	%	*a*	*b*	*c*	*d*	*p* <0.001
LYM	20-40	29.82 (±3.34)	33.14 (±4.84)	30.29 (±1.91)	14.85 (±4.21)	28.16 (±7.20)
	%	*b*	*c*	*b*	*a*	*p* <0.01
HGB	11.0-16.0	13.7 (±6.29)	13.92 (±0.40)	13.09 (±0.71)	11.08 (±1.15)	12.85 (±1.40)
	g/L	*b*	*b*	*b*	*a*	*p* =0.436
PLT	150-400	228.6 (±77.2)	166.5 (±40.2)	263.4 (±44.3)	382.9 (±56.7)	258.5 (±100.1)
	10^9/L	*b*	*a*	*c*	*c*	*p* =0.093
TRP	<0.04	0.039 (±0.002)	0.22 (±0.12)	6.41 (±3.36)	21.05 (±10.27)	8.08 (±10.32)
	ng/mL	*a*	*b*	*c*	*d*	*p* <0.001
FER	24-236	78.8 (±13.8)	179.9 (±48.2)	307.3 (±34.6)	609.2 (±165.6)	236.6 (±202.2)
	ng/mL	*a*	*b*	*c*	*d*	*p* <0.001
PCT	<0.1	0.05 (±0.03)	0.17 (±0.05)	0.38 (±0.09)	0.93 (±0.25)	0.29 (±0.33)
	ng/mL	*a*	*b*	*c*	*d*	*p* <0.001
FDR	-	0.96 (±0.15)	0.39 (±0.07)	0.44 (±0.03)	0.53 (±0.07)	0.65 (±0.28)
	-	*c*	*a*	*a*	*b*	*p* <0.001

According to Duncan's test:
* Similar letters mean there are no significant differences at 5%.
** Different letters mean there are significant differences at 5%.

Table 5. The cutoff value, sensitivity and specificity of biochemical parameters in COVID-19 patients.

Variables	Cut-off	Area under the ROC curve (AUC)	SD	*t*-test	Sensitivity	Specificity	*p*-value
CRP	>6	0.956	0.03	13.33	95.45	94.74	<0.0001
DDM	>411	0.631	0.041	16.11	83.2	64.2	<0.001
URE	3.75	0.958	0.029	15.620	95.8	87.5	<0.001
CRE	53	0.880	0.054	6.961	95.8	68.7	<0.001
GPT	>28	0.957	0.0307	14.8	87.9	100.0	<0.001
GOT	>14.2	0.764	0.079	3.332	81.8	71.4	<0.001
ALP	>92	0.807	0.066	4.65	69.7	100.0	<0.001
LDH	>198	0.974	0.026	18.100	97.0	100.0	<0.001
WBC	<5.9	-0.791	0.081	3.60	65.0	100.0	0.0003
NUT	>4.3	0.794	0.096	3.34	100.0	68.7	0.002
LYM	<0.943	0.906	0.063	6.41	90.0	100.0	<0.001
HGB	<12	0.567	0.092	0.65	50.0	81.2	0.494
PLT	>318	0.872	0.0582	6.388	70.0	100.0	<0.001
TRP	>31	0.988	0.013	36.5	100	94.7	<0.0001
FER	>332.9	0.96	0.024	19.13	88.4	100.0	<0.0001
PCT	>0.041	0.926	0.054	7.77	100.0	89.5	<0.0001
FDR	>0.746	0.817	0.031	12.1	87.1	73.4	<0.001

4. DISCUSSION

Following the discoveries in 2003 and 2012, of SARS-CoV-1 and Middle East respiratory disease (MERS)-CoV, respectively, SARS-CoV-2 is the third of the coronaviruses which results in a pandemic in the last twenty years. During the years 2002–2003, 774 people died as a result of SARS-CoV-1 infection, which was detected in 8,096 persons. MERS-CoV was the cause of a small-scale pandemic in the Middle East in 2012. The death rate in this event was 38% [14,15].

Using a sample of 60 patients, the current study revealed the clinico-biological characteristics of COVID-19 disease in the AL-Anbar government zone. The demographic parameters found in present study back up the findings of other authors, who found that old age is a factor that predisposes individuals to COVID-19 and accelerates disease development to severe disease [15].

The current study was also corroborated by a study conducted by Zhu and his team [16], which found that COVID-19 occurrence was strongly linked to age over 50, while mortality was linked to age over 65. Advanced age, on the other hand, has been recognized as a key independent predictor of mortality in SARS and MERS cases [17]. In present study, the most common age-related comorbidities were infection-related mortality (especially viral infections) and age. This could be linked to the elderly's diminished cellular immunological activity and long-term inflammation and agreement with study by Lu and colleagues (2020) who was reported that average of age may be play a critical role in comorbidities of severity cases. Findings also showed that patients with severe sickness were older and had more comorbid diseases than those with mild to moderate illness [18]. Similar results were found by Wang and his groups (2020) who reported that poor outcomes may be linked to age and comorbidities [19].

Most authors have identified male gender as a factor determining the severity of COVID-19; similar findings have been discovered by Peckham *et al.* (2020) [20]. In contrast, an Iranian study found that gender may not be a factor in aggravation [15].

COVID-19 infection is clearly linked to severe morbidity, especially in patients with chronic conditions, with at least 20% of these patients requiring supportive treatment in medical ICUs, which are scarce in most poor countries. Furthermore, despite the deployment of appropriate supporting measures, the inpatient mortality rate is still higher than 1.4 percent, while over 60-year-olds accounted for 6.4 percent of the total [21]. Diabetes people are more prone to have issues with COVID-19. People with diabetes are more likely to develop severe symptoms and problems when infected with any virus [22]. Fleming with colleagues (2021) reported the risk from COVID-19 is likely to be lower if diabetes is well-managed [23]. Also revealed that persons with diabetes who also have heart disease or other problems may have a higher risk of becoming

critically ill from COVID-19, in addition to other viral infections, because possessing more than one ailment makes the body's ability to fight the infection more difficult. In persons with diabetes, viral infections can cause inflammation, or internal swelling. This can also be caused by blood sugar levels that are higher than normal, and the resulting inflammation can lead to more serious consequences. In the United States, over 34 million people have diabetes, with 26.9 million having been diagnosed [23].

According to Hussain research team (2020), hypertension and extreme obesity are prevalent comorbidities in diabetic patients [24]. It's unclear if diabetes alone has a role in the elevated risk of COVID-19-related morbidity and mortality. Poor glycemic management has been linked to poorer outcomes in patients with diabetes, according to studies. COVID-19's capacity to effect diabetic patients has been investigated extensively, and the following five mechanisms have been identified: poor viral clearance; reduced T-cell function; increased susceptibility to hyper inflammation and cytokine storm; and the existence of cardiovascular disease [25].

This study found no association between smoking and the severity of the COVID-19, which is consistent with the findings of Xu colleagues studies (2020) [26].

4.1. Relation of biochemical parameter with COVID-19

According to the results of Al-Malkey research team (2020) elevated CRP concentrations are related with higher liver enzymes [27]. Because of immunological responses, liver injury can occur not just from hepatotropic viruses (hepatitis viruses), but also from systemic, respiratory infections (EBV, Influenza, and SARS-CoV).

The serum CRP, an acute-phase protein of liver origin, will be increased in the inflammatory phase as a result of the secretion of interleukin-6 from the T-cells and macrophages. Therefore, it rise in COVID-19 infection and considered as good marker for follow up disease condition [28].

4.2. Relationship of renal function tests and patients with COVID-19

The serum levels of urea and creatinine were measured for all patients and controls. The mean ± SD of the serum creatinine and urea are shown in Table 4. There were an increased serum creatinine and urea levels in patients with severe form in comparisons with patients with other severities and control group (p-value<0.05).

The finding results agree with what other researchers reported that although COVID-19 is a virus that mostly affects the lungs, it can also damage the heart, blood, central nervous system, kidneys and gastrointestinal tract [29]. COVID-19 infects nerve cells in the central nervous system (CNS), causing loss of taste and smell in most patients, confusion, destroy to the respiratory system, disorientation, weariness, as well as other signs linked with brain dysfunction [30]. COVID-19 in the kidney can lead to acute renal damage and other kidney problems [31]. Acute kidney injury is characterized by attributable to the retention of nitrogenous wastes, an increase in blood urea and creatinine concentrations, a decrease in GFR, and a disruption in extracellular fluid volume and electrolyte equilibrium [32]. Moreover, present data results showed the ROC curve of RFT was administrated, and the best cut-off point of as shown in Table 5. COVID-19's specific action on the kidney is unknown, however researchers believe it affects the kidney both directly and indirectly. Because COVID-19 is identified in the urine, the virus's kidney damage pattern is limited to areas with angiotensin converting enzyme-2 receptor, and the presence of COVID-19 virus in the urine corresponds to the commencement of acute renal injury, it was assumed that the virus instantly damages kidneys [33].

The virus is said to infiltrate kidney cells through attaching to membrane-bound angiotensin converting enzyme-2 receptors in the proximal tubule cells' apical membrane and glomerular podocyte cells and it damages kidney epithelial cells while also disrupting the renin-angiotensin system's balance [34]. The convertion of angiotensinogen to angiotensin-I occurs via renin, then converted to angiotensin-II via angiotensin converting enzyme activity. Furthermore, the angiotensin converting enzyme-2 receptors convert angiotensin II to angiotensin 1, which dilates blood vessels. When the SARS-CoV-2 virus binds to angiotensin converting enzyme-2 receptors, angiotensin-II levels will be raised and causing vasoconstriction, inflammation, glomerular dysfunction, and fibrosis [34].

Similarly, COVID-19 invades host cells through the CD 147-spike protein route, according to Wang *et al*. (2020) and in the proximal tubule, this glycoprotein is highly expressed [35]. COVID-19 also damages kidneys by triggering an inflammatory and cytokine storm, activating the pathways of coagulation, damaging the kidney vascular endothelium, causing hypoxemia, sepsis, and hemodynamic instability. Endothelial dysfunction and reduced generation of vasodilators, including nitric oxide, are caused by the viral infection of the endothelium through immune cell recruitment. Reduced vasodi-

lators increase the reactivity to vasoconstrictors, which leads to acute kidney disease when combined with ischemia-induced oxidative stress [33].

4.3. Relationship of blood sugar with COVID-19

The results of serum glucose levels in Table 4 showed that there was a statically significantly higher level of glucose in patient with COVID-19 (mild case with beginning of infection, Moderate case, severe cases) compared with healthy subject (control group) and increased levels with severity cases.

Traumatic brain damage, systemic inflammatory response syndrome, and severe sepsis are all illnesses that can cause hyperglycemia. A rise in certain cytokines levels as well as high blood glucose levels, is the primary responses to hyperglycemia. The establishion has occurred between the level of serum glucse and mobidity [36].

Other researchers noted that the breakdown of glucagon hormones, glycogen, insulin resistance, and adrenocorticotrophic synthesis occur via metabolic stress and leading to elevate blood glucose, which account as proinflammatory phase in severe COVID-19 [37].

Glucose levels were greater in those with severe diabetes in present study, and the glucose levels in these two groups were significantly different. These findings are comparable to those described in investigations assessing risk factors for Middle East respiratory syndrome, community-acquired pneumonia, and SARS mortality and morbidity, which have found that hyperglycemia and/or diabetes are involved [35].

Also present data results are in agreement with the finding of Wang and colleagues [35] indicated the relationship between SARS-CoV-2 and the level of fasting blood sugar (FBS) at admission time. A significant difference has reported in the rise of level of serum glucose at the admission time the severe COVID-19 group and lesser COVID-19 group. The present study is consistent to Wang and colleagues [35].

The mean blood glucose level in outpatients was lower than in ICU patients. A mild increase in blood glucose may be linked to patient stress, according to a recent study [35]. Hyperinsulinemia and hyperglycemia; Acute insulin resistance; has been related to a greater glucose level in ICU patients, according to some researchers [38].

4.4. Relationship of hematological tests with COVID-19 patients

Table 4 shows low white blood cells count in severe COVID-19 cases with regards to other patients and controls. There were highly statistically significant differences between COVID-19 severity and low white blood cells count (p-value<0.05). Similar finding was recorded regarding the relationship between the white blood cells count in patients with mild and moderate severities and controls.

Present study patients' biological profiles are comparable to those described in previous studies, with severe patients having lymphopenia upon admission and lymphopenia worsening during their stay. During COVID-19, lymphopenia usually follows leukopenia, despite the normal level of white blood cell (WBC) count. The first blood count revealed significant lymphopenia (less than 1.0 x 10^9C/L) in 69.6% of COVID-19 cases and leukopenia (less than 3.5 x 10^9C/L) in 33.9 percent of patients, whereas the neutrophil and monocyte counts were mainly normal [39].

Present study findings are consistent with those of other studies, such as Liu *et al.* [39], who found lymphopenia (less than 1.0 x 10^9C/L) in 98 percent of COVID-19 patients over the illness course, the transient leukopenia is in 64 percent of patients within the seven-days of illness.

Within seven-days of commencement, the first subject of COVID-19 disease confirmed in the United States of America with a small diminished in white cell count [40]. An early study of 41 COVID-19 patients admitted to Jin Yin-tan Hospital found that their blood counts on entry suggested leukopenia (25 percent) and lymphopenia (25 percent) (accounted for 63 percent). Because lymphocytes are virus-fighting effector cells, most viruses cause lymphocytosis in humans [41].

COVID-19 patients' peripheral blood lymphocyte counts decreased to various degrees, according to certain researchers, it is unclear why COVID-19 patients resulting lymphocytopenia. According to limited pathologic and autopsy findings, COVID-19 patient showed lymph nodes, spleen necrosis, lymph nodes, and other lymphoid organs, as well as decreased in lymphocytic infiltration and bone marrow hematopoiesis in the alveolar septum.[9] In addition, the amount of $CD4^+$T and $CD8^+$T lymphocytes in the patient's peripheral blood was dramatically reduced, yet they were overactivated. In $CD4^+$T cells, the ratio of highly positive CCR6+Th17 cells rose, while $CD8^+$T cells had high levels of cytotoxic T cells [9]. This demonstrated that COVID-19 patients' T cell overactivation was characterized by an elevation in pro-inflammatory regulatory T cells and increased $CD8^+$T cell cytotoxicity, which led to the patients' over-immune response to COVID-19 infection causing significant immunological harm [42].

The results of serum CRP levels in Table 4 showed that there was a statically significantly

higher level of CRP in patient with COVID-19 (mild case (asymptomatic) with beginning of infection, Moderate case, severe cases) compared with healthy subject (control group) and increased levels with severity cases.

The research by El Aidaoui *et al*. (2020) [43] was shownin their meta-analysis: the amount of lymphocytes, especially CD4 lymphocytes, can functionas a biological indicator of severity and mortality; concerning COVID-19, they also stated the theory that survival could hinge on the capability to replenish lymphocytes that are destroyed by the virus.

Previous research by Tjendra and colleagues (2020) has shown that ICU cases in COVID-19 patients were more likely to have neutrophilia, which is a marker of disease progression [44].

According to statistics from Jin Yin-tan Hospital, the neutrophil count was 10.6 (5.0–11.8) $x10^9$C/L in ICU cases, substantially it is higher 4.4 (2.0–6.1) 10^9C/L compared to non-ICU cases (p=0.00069) [39].

In a study from Beijing Ditan Hospital (2020), the neutrophil count of mild type of COVID-19 was 2.4 (1.9–3.4) 10^9C/L, whereas the neutrophil count of severe or critical CVID-19 was 2.8 (2.3–4.4) 10^9C/L (p=0.025). Another study ICU patients have a higher chance of developing neutrophilia during stay at hospitals, with a median peak ANC of 11.6 10^9C/L compared to the non-ICU group 3.5 10^9C/L, according to a study in Singapore that confirmed 69 cases of COVID-19 [39].

Furthermore, present study revealed that the ROC curve of a hematological parameter was used and the best cut-off point of as shown in Table 5.

The mean±SD of platelet levels for the study groups was shown in Table 4. Platelet account was significantly (p<0.05) higher in both moderate and severe (but not in mild) cases in comparison with that of control group.

The lung has been identified for having potential hematopoietic activity and a key location of terminal platelet generation, within the half of the total platelet production, according to several researchers. Based on earlier research demonstrating that the lungs serve as a reservoir for hematopoietic progenitor cells and resident megakaryocytes, thrombocytopenia may be induced by lung injury [45].

COVID-19 lung injury could also lead to aberrant vascular endothelial cell and coagulation system functions, as well as platelet activation and aggregation, all of which could increase platelet consumption [45].

D-dimer level, as has been hypothesized, can be used as an essential biomarker to predict the mortality and morbidity rates in hospitalized patients with COVID-19 [46].

In patients with higher levels of D-dimer, there was a high CRP. The elevation of D-dimer is frequently seen in subjects with acute stage of COVID-19. This may be due to acute insult to the lung or thromboembolic phenomena that results frequently from COVID-19. Therefore, it is of utmost importance to screen and monitor the levels of D-dimer on regular basis to determine the COVID-19 severity and guide the anticoagulation treatment [47].

4.5. Ferritin, D-dimer, and FDR

By adopting the Duncain test (Table 4), it is noted that for all parameters with statistically significant differences, the values of means increased from the control group up to the sever group, especially DDM & FER, while in the case of FDR the relationship was descending, with a clear difference between the control group (letter c) and the asymptom group (letter a according to ANOVA-Duncain's test).

Meaning that there is a possibility of separating between both groups, and this supports the idea of research into the possibility of adopting changes in the FDR value in the natural state (at the control group mean: 0.96) and its sudden decline to the minimum values (at the asymptoms group mean: 0.53) (Table 4) and by adopting the cut-off value which shown in Table 5.

In summary, the novel FDR may help in early identification of patients with COVID-19, and furthermore studies should be conducted to evaluate its ability to determine COVID-19 severity and prognosis.

The FDR may have fantastic clinical applicability. The levels of ferritin and D-dimer can be effortlessly obtained through routine blood tests on admission, with the results providing real-time PCR information about whether patients are at increased risk of contracting COVID-19.

5. CONCLUSION

This study demonstrated the possibility of proper use of FDR, which requires that ferritin and DDM be obtained simultaneously instantly possible after clinical presentation.

In the future, we recommend a more comprehensive study using more samples to confirm our above conclusion.

To benefit from this relationship FDR, we suggest that the study include separating COVID - 19 cases from cases of bacterial pneumonia.

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ETHICS STATEMENT
By adopting the recommendations of the Ethical Approval Committee of Anbar University, the consent of the patients included in our study is obtained, and the nature of the research and its objectives are explained to them, which includes helping people understand a healthy eating style, periodic follow-up to measure some parameters in the blood, and following up on treatment protocols to recover from the disease.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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