Original Research Article

Parameter changes of COVID-19 incidence in Baghdad/Iraq in 2020: Infected and cured individuals: A retrospective single center study

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ABSTRACT

Coronavirus disease 2019 (COVID-19) represented a highly respiratory syndrome to worldwide. Aim of current research was to determine the changes in hematology and inflammatory parameters into three categories: non-infected with COVID-19 as control groups, infected with COVID-19 and cured from the disease in Baghdad center. Current study was proved that the levels of hematology, inflammatory and liver enzymes were upregulated in infected with COVID-19 group and decreased to normal levels in cured groups. The Receiver Operating Characteristic curve (ROC) curve analysis presented that d-dimer marker and AST were the most accurate markers. The AUROC of d-dimer and AST were 0.747 and 0.760, respectively. And the OR 95 % CI of d-dimer and AST were (0.677-0.817) and (0.694-0.827), respectively. These findings give a highlight on d-dimer and AST as an important biomarkers in monitoring COVID-19 detection.

***Keywords*:** COVID-19, liver function, d-dimer, IL-6

INTRODUCTION

According to recent reports of WHO, Iraq statistics from January 2020 to April 2023, have more than 2 million confirmed cases of COVID-19 with 25,375 deaths, reported to WHO. And a total of 19,557,364 vaccine have been admin till January 2023 [1].

During the last three years since 2019, Iraqi institutions and academy including the Communicable Diseases Control Center

(Iraq CDC) have invested in crisis preparedness activities.

Considering the extreme scientific publications in regard of COVID-19, this paper aimed to describe the epidemiological picture of COVID-19 in Iraq, explore the specific challenges facing the Iraqi healthcare system, describe the country's response to the pandemic, identify shortcomings in the performance and provide recommendations for further measures to contain the pandemic. Also, to identify areas where most efforts need to be taken to strengthen the healthcare system to respond to future pandemics. We suggest that this prospective study could provide a comprehensive overview of the situation of the pandemic in Iraq within its political and economic context.

On 10 April 2022, WHO handed over 630 000 rapid antigen tests to the Ministry of Health to be used for a timely and accurate COVID-19 screening and detection of SARS-COV-2 infection. A WHO situation report about COVID-19 across Iraq form Feb 2020 till April 2022: 2.29 M cases recoveries and 2.32 M confirmed infected cases. [2]

The use of blood containing circulating biomarkers representing inflammation and the immune system was considered as a prognostic infection indicator in COVID-19 patients. [3]

The study mention that neutrophil lymphocyte ratio to be an independent risk factor for severe COVID-19 infection and it can be used as a biomarker in the identification of severe illness and aid in its early management. [4]

Both COVID-19 and SARS-CoV-2 infection induces an excessive inflammatory response in patients, causing an inflammatory cytokine in severe cases [5].

High level of IL-6, CRP and hypertension were independent risk factors for assessing the severity of COVID-19. The risk model established upon IL-6, CRP and hypertension had the highest predictability in this study. Besides, IL-6 played a pivotal role in the severity of COVID-19 and had a potential value for monitoring the process of severe cases. [6]

Ali and his group revealed that there were significant differences in D-dimer, CRP and troponin level between survived and deceased patient groups after first week of hospitalization. In the second week of the admission, both groups had significant differences in the level of all studied parameters; troponin I, D-dimer, CRP, and WBCs. WBC levels positively correlated to CRP in male survivors (r=0.75, p<0.0001), and to troponin in deceased male patients (r=0.74, p=0.007). The second week of patient admission was critical in the group of families who lost more than one person, when troponin was correlated positively with D-dimer, CRP, and WBCs. [7]

The aim of this proposed study was to survey examining the changes in the inflammatory markers in the blood of control, patients infected with COVID-19 and cured from the infection. Then determine the correlations with age and genders.

MATERIALS AND METHODS

Sample collection

We conducted a prospective study on 239 individuals (healthy, patients (infected with COVID-19) and cured) recruited from medical private laboratory (Baghdad, Iraq). All patients diagnosed as positive COVID-19 by conventional PCR and Computerize Tomography scan (CT scan). Collection of all participants were between of March 2020 to November 2020. Our patients were classified based on severity of symptoms according to the World Health Organization (WHO) interim guidance for COVID-19. [8]

For our work, we have resembled our participants on three principal groups: healthy group (n=37), patients infected with COVID-19 group (n=146) and cured group (n=54).

Laboratory examinations

About (5 ml) of blood samples were collected using an ethylene diamine tetraacetic acid (K_2-EDTA) containing vacationer tube for analysis of hematological parameters and other chemical tests.

The demographic and clinical information were collected from medical private laboratory records. We have analyzed: blood parameters: platelets, White Blood Cells (WBCs) and Hemoglobin (HB); immune-inflammatory parameters: IL-6, CRP, d-dimer, IgG and IgM; liver enzyme parameters: Alanine Transaminase (ALT) and Aspartate Transaminase (AST); ferritin and LDH. By using 3 parameter hematology analyzer (Spin Analyzer (Automatic) Spinreact-120, Spain) for hemoglobin and complete blood count. White blood cell concentration and lymphocyte percentage. The immunoassay was performed using immune analyzer (Spin Analyzer (Automatic) Spinreact, Spain) to measure the level of ferritin, CRP and d-dimer levels, of ALT, AST, LDH, IgG, IgM and IL-6 levels respectively.

Statistical analysis

Normally distributed data were presented as mean±SD, a comparative analysis of this data was performed between healthy, infected and cured groups using unpaired 2-sided student's t-test. Categorical variables were described as percentages and the significance was tested by the chi-square test. The correlations between age, sex and type of samples with other variables were analyzed using spearman correlations. All these statistical calculations were performed using SPSS version 24 software statistical analysis. A Probability equal to 0.05 was suggested statistically significant.

A non-parametric test was used to evaluate the prognostic value of different immune-inflammatory biomarkers, by taking the sample types of COVID-19 as dependent variable. The Receiver Operator Characteristic (ROC) curves were built to assess predictive values and the optimal discriminating cut-off values. The Odds Ratio (OR) with their confidence intervals 95 % (95 % CI) were also calculated.

RESULTS

Demographic and clinical characteristics

A total of 239 participants were included in this study. Among them 104(44 %) were under 44 year age and 103(43 %) were higher than 44 year age, male 110(46 %) and 124(51 %) female. Participants were grouped to: control 38(15 %), infected with COVID-19 was 146(61 %) and cured from infection 55 (23 %), as presented in Table 1.

Prognostic values of immune-inflammatory markers

Two prognostic values of immune-inflammatory markers were analysed: first examined the CBC parameters: WBC, HB and platelets. Second we examined the levels of: ferritin, IL-6, ALT, AST, LHD, IgG, IgM, D-dimer and CRP, as presented in Table 2. From 239 participants: levels of Ferritin was higher than normal range in 197 participants (82.9 %), levels of IL-6 higher in 225(94.1 %), levels of ALT and AST were higher in 193 (80.8%) and 166 (69.5) respectively. And levels of IgG and IgM were higher than zero and found in 51 (21.3 %) and 197 (82.4 %) respectively. The markers d-dimer and CRP levels were higher in 193 (80.8 %) and 172 (72 %) participants respectively. While, levels of

CBC parameters were determined to be: WBC lower in 157 (65.7 %) and platelets were lower in 202 (84.5 %) and HB levels were measured to be lower in male less than <13 in 71 (29.7 %) while in female less than <11 in 77 (32.3 %).

Next, comparing levels of Ferritin in plasma samples between age, gender and the type of sample groups as presented in Table 3. The normal range of ferritin level was less than 60 according to the leaflet used. There was a significant correlation between increasing ferritin levels and all the age groups less and higher than the mean 44 years, and group samples infected with COVID-19, ($p<0.02$ and $p<0.00$) respectively.

The correlation in levels of IL-6 in plasma according to age, gender and the type of sample was determined as presented in Table 4. The normal range of IL-6 was less than 2 according to the leaflet used. There was a significant correlation between increasing IL-6 levels and infected with COVID-19 groups ($p<0.00$). Also the correlation in levels of ALT according to age, gender and the type of sample was determined as presented in Table 5. The normal range of ALT was less than 10 according to the leaflet used. There was a significant correlation between increasing ALT levels and group samples infected with COVID-19 ($p<0.00$). The normal range of AST was less than 32, and there was a significant correlation between the increasing levels of AST and the infected group with COVID-19 ($p<0.00$), as presented in Table 6.

The correlation in levels of IgG according to age, gender and the type of sample was determined as presented in Table 7. The normal range of IgG was equal to be zero according to the leaflet used. There was a significant correlation between increasing IgG levels and group samples infected with COVID-19 ($p<0.00$).

Also the correlation in levels of IgM according to age, gender and the type of sample was determined as presented in Table 8. The normal range of IgM was equal to be zero according to the leaflet used. There was a significant correlation between increasing IgG levels and all ages of participants and with group samples infected with COVID-19 ($p<0.00$).

When measuring the correlation in levels of d-dimer according to age, gender and the type of sample was determined as presented in Table 9. The normal range of d-dimer was less than 0.1 according to the leaflet used. There was a significant correlation between increasing d-dimer levels and all ages of participants and with group samples infected with COVID-19 ($p<0.00$) respectively. And in Table 10, the CRP levels was determined to be a significantly increased in patients infected with COVID-19 ($p<0.00$).

Table 1. Demographic and clinical characteristics of control, infected and cured volunteers with COVID-19

Variables	(n=239) %	Mean ±SD
Age(years):		
<44	(104) 44.8%	1.67 ± 0.68
>44	(103) 43.1%	
Gender :		
Male	(110) 46%	1.56 ± 0.53
Female	(124) 51.9%	
Type:		
Control	(38) 15.9%	1.54 ± 0.75
Infected	(146) 61.1%	
Cured	(55) 23%	

Data was presented as mean ±SD (range), n (%): total number of participants

Table 2. Laboratory findings of participant's volunteers in current retrospective study

Variables	(n=239) %	Mean ±SD
Ferritin		
>60	(41) 17.2%	1.91± 1.35
<110	(197) 82.9%	
IL-6		
<2	(14) 5.9%	1.94 ± 0.235
>2	(225) 94.1%	
ALT		
<10	(46) 19.2%	1.80 ± 0.39
>32	(193) 80.8%	
AST		
<32	(73) 30.5%	1.69 ± 0.46
>38	(166) 69.5%	
IgG		
=0	(188) 78.7%	1.21 ± 0.41
>0	(51) 21.3%	
IgM		
=0	(42) 17.6%	1.82 ± 0.38
>0	(197) 82.4%	
D-dimer		
<0.1	(46) 19.2%	1.80 ± 0.39
>0.5	(193) 80.8%	
CRP		
<1	(67) 28%	1.71 ± 0.45
>1	(172) 72 %	
LDH		
<260	(62) 25.9%	1.74 ± 0.43
>430	(177) 79.1%	
PLts		
<150	(202) 84.5%	1.15 ± 0.36
>400	(34) 14.2%	
WBC		
<4	(157) 65.7%	1.34 ± 0.48
>10	(81) 33.9%	
HB		
Male <13	(71)29.7%	
>15	(38) 15.9 %	2.47 ± 1.14
Female<11	(77) 32.3%	
>13	(52) 21.8%	

Table 3. Comparison between ferritin levels and variables (age, gender and groups samples)

Variables	**Ferritin**		**p-value**
	<60	**>110**	
Age:			
<44	22	85	0.02
>44	12	91	
Gender:			
Male	15	94	0.36
Female	26	98	
Groups:			
Control	29	9	0.00
Infected	3	143	
Cured	9	45	

Table 4. Comparison between IL-6 levels and variables (age, gender and groups samples)

Variables	**IL-6**		**p-value**
	<2	**>2**	
Age:			
<44	8	99	0.60
>44	5	98	
Gender:			
Male	4	106	0.198
Female	9	115	
Groups:			
Control	6	32	0.00
Infected	1	145	
Cured	7	48	

Table 5. Comparison between ALT levels and variables (age, gender and groups samples)

Variables	**ALT**		**p-value**
	<10	**>32**	
Age:			
<44	23	84	0.08
>44	14	89	
Gender:			
Male	17	93	0.386
Female	28	96	
Groups:			
Control	29	9	0.00
Infected	7	139	
Cured	10	45	

Table 6. Comparison between AST levels and variables (age, gender and groups samples)

Variables	AST		p-value
	<32	**>38**	
Age			
<44	33	74	0.157
>44	27	76	
Gender:			
Male	30	80	0.481
Female	42	82	
Groups:			
Control	35	3	0.00
Infected	15	131	
Cured	23	32	

Table 7. Comparison between IgG levels and variables (age, gender and groups samples)

Variables	IgG		p-value
	=0	**>0**	
Age			
<44	84	23	0.996
>44	81	22	
Gender:			
Male	92	18	0.161
Female	93	31	
Groups:			
Control	38	0	0.00
Infected	146	0	
Cured	4	51	

Table 8. Comparison between IgM levels and variables (age, gender and groups samples)

Variables	IgM		p-value
	=0	**>0**	
Age			
<44	19	88	0.001
>44	11	92	
Gender:			
Male	16	94	0.253
Female	26	98	
Groups:			
Control	38	0	0.00
Infected	3	143	
Cured	1	54	

Table 9. Comparison between d-dimer levels and variables (age, gender and groups samples)

Variables	**D-dimer**		**p-value**
	<0.1	**>0.5**	
Age			
<44	19	88	0.00
>44	13	90	
Gender:			
Male	15	95	0.083
Female	29	95	
Groups:			
Control	34	4	0.00
Infected	0	146	
Cured	12	43	

Table 10. Comparison between CRP levels and variables (age, gender and groups samples)

Variables	**CRP**		**p-value**
	<1	**>6**	
Age			
<44	33	74	0.175
>44	23	80	
Gender:			
Male	30	80	0.088
Female	36	88	
Groups:			
Control	36	2	0.000
Infected	21	125	
Cured	10	45	

The levels of LDH also measured and presented in Table 11, a significant increase was determined in all age group levels was higher than normal 260 ($p<0.004$), and in infected groups ($p<0.00$).

When testing the blood parameters, the correlation in levels of HB according to age, gender and the type of sample was determined as presented in Table 12. The normal range of HB in females rage from 11-13, and for males from 13-15 according to the leaflet used. There was a significant correlation between increasing HB levels and gender of participants and with group samples infected with COVID-19. While in examining the levels of WBCs, there were no significant differences in all the variables, as presented in Table 13. Then the levels of platelet and lymphocyte did not present any significantly correlation with all the variables as presented in Tables 14 and 15, respectively.

From ROC curve analysis, it showed that none of the parameters measured have high area under ROC curve (AUROC) = 0.9, and both AST and d-dimer with corresponding AUOC of 0.76 and 0.747 respectively, this reflect an acceptable discrimination and prognostic performance of these inflammatory parameters to assess infection with COVID-19.

The multivariate logistic regression analysis revealed that AST and d-dimer are independent predictors of COVID-19 infection. The combined detection of these two markers allowed to reach an AUROC curve of 0.76 as presented in Table 16 and Figure 1.

The AUC for ROC curves was used here to check the overall adequacy of the logistic regression models in this study. Originates from signal theory, provides a means to measure the model's ability to detect true responses in the presence of noise. While there is no set standard for gauging the adequacy of model discrimination, the criteria developed by Hosmer and Lemeshow, sets the guidelines for the AUC analysis employed. [9]. The AUC discrimination measures were as follow: if AUC =0.5 represent no model of discrimination, while AUC between 0.5 and 0.7 represent poor discrimination, AUC between 0.7 and 0.8 it acceptable discrimination. However, AUC between 0.8 and 0.9 represent excellent discrimination, AUC higher than 0.9 represent superior discrimination.

Table 11. Comparison between LDH levels and variables (age, gender and groups samples)

Variables	**LDH**		**p-value**
	<260	**>430**	
Age			
<44	34	73	0.004
>44	16	87	
Sex			
Male	28	82	0.935
Female	33	91	
Type			
Control	30	8	0.00
Infected	22	124	
Cured	10	45	

Table 12. Comparison between HB levels and variables (age, gender and groups samples)

Variables	**HB**				**p-value**
	<13	**>15**	**<11**	**>13**	
Age					
<44	30	16	37	23	0.962
>44	33	18	30	22	
Sex					
Male	67	36	3	3	0.000
Female	3	1	71	49	
Type					
Control	11	4	19	4	0.05
Infected	44	30	40	31	
Cured	16	4	18	17	

Table 13. Comparison between WBC levels and variables (age, gender and groups samples)

Variables	**WBC**		**p-value**
	<4	**>10**	
Age			
<44	75	31	0.527
>44	64	39	
Sex			
Male	76	33	0.536
Female	77	47	
Type			
Control	31	7	0.209
Infected	93	52	
Cured	33	22	

Table 14. Comparison between platelets levels and variables (age, gender and groups samples)

Variables	PLts		p-value
	<150	**>400**	
Age			
<44	92	14	0.514
>44	83	18	
Sex			
Male	96	13	0.851
Female	102	20	
Type			
Control	36	2	0.064
Infected	125	20	
Cured	41	12	

Table 15. Comparison between lymphocyte levels and variables

Variables	Lymphocyte		p-value
	<20	**>40**	
Age			
<44	90	16	0.319
>44	92	11	
Sex			
Male	93	16	0.730
Female	106	18	
Type			
Control	32	6	0.946
Infected	125	20	
Cured	47	8	

Table 16. Area under the ROC curve of the immune inflammatory and liver enzymes markers according to the severity

Variables	AUROC	Model of discrimination	Sensitivity	Specificity	p value	OR 95% CI
ALT	0.686	Poor discrimination	0.952	0.581	0.000	0.612 - 0.759
AST	0.760	Acceptable discrimination	0.897	0.376	0.000	0.694- 0.827
Ferritin	0.689	Poor discrimination	0.000	0.011	0.000	0.615 - 0.763
IL	0.566	No model discrimination	0.993	0.860	0.083	0.490 - 0.643
D-dimer	0.747	Acceptable discrimination	1.5000	1.000	0.000	0.677- 0.817
CRP	0.675	Poor discrimination	1.5000	0.856	0.000	0.603 - 0.748
LDH	0.640	Poor discrimination	0.849	0.570	0.000	0.565 - 0.714
IgG	0.226	No model discrimination	0.000	0.548	0.000	0.158 - 0.293
IgM	0.699	Poor discrimination	0.979	0.581	0.000	0.626 - 0.772

AUROC: Area under the receiver operating characteristic curve; CI: confidence interval; OR: odds ratio.

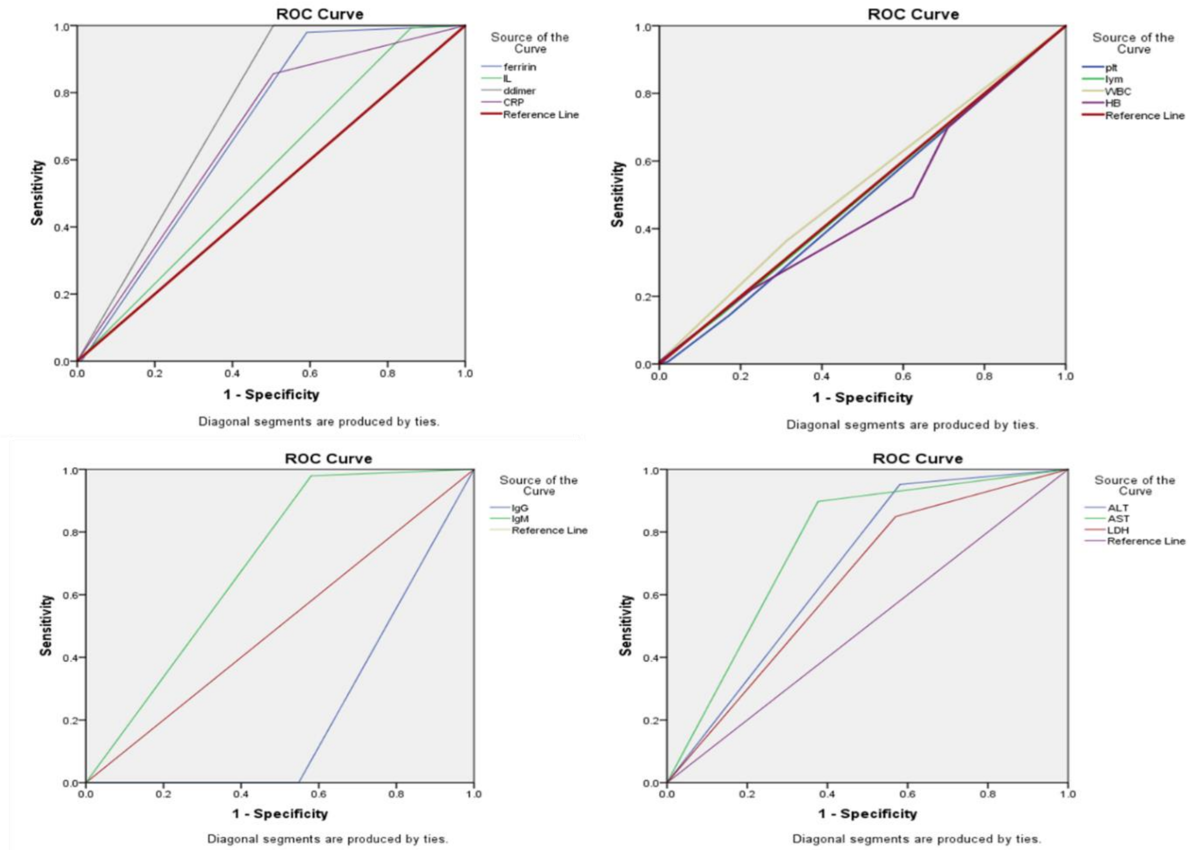

Figure 1. Receiver Operating Characteristic (ROC) curve analysis of the immune inflammatory markers. Univariate and multivariate regression analysis were detected to assess the prognostic value of different immune inflammatory biomarkers and liver enzymes, by taking the type of sample and COVID-19 infection group as dependent variable.

DISCUSSION

In order to detect COVID-19 virus in patients and avoid the complications it is important for quick identification and supply of the right treatments, this managed by evaluating the ideal biomarker. Here in the Middle East especially Iraq, the time of epidemic and urgent need for vaccination, detection kit and also even the routine kits of hematology and inflammatory markers were all needs to be supplied in time.

Several studies designed in time of infection and after the epidemic all focused on determining the ideal marker the monitor this infection. Less information in

Iraqi studies determined levels of biomarkers in infected and after therapies and curing stage but all deals with patients in stage of infection.

Accumulation evidence data and Iraqi studies concerning correlation between COVID-19 infection and inflammatory biomarkers and hematology analyses. With increasing levels of neutrophils count and neutrophil, CRP levels to lymphocyte ratio and increased with COVID-19 infection severity, also increasing in IgM levels determined in the study of (2021). The study determined the ROC analysis demonstrate the sensitivity 85 %and the specificity was 75 % and concluded that neutrophil to lymphocyte ratio in COVID-19 patients represented a good biomarker and a potential prognostic factor.[10]

While a study carried in Najaf a provenance in Iraq, presented that patients with COVID-19 have higher levels of WBCs, neutrophils, d-dimer, ferritin, CRP, ALT, AST and c-reactive protein respectively in the serum of patients compared to healthy volunteers. [11]

Also in Najaf, another study estimated high levels of d-dimer, ferritin, IL-6 and CRP in COVID-19 infected patients compared to healthy group. [12]

Using molecular diagnostic qPCR to determine the levels of leucine –rich α-2-glycoprotein-1 (LRG-1) in patients infected with COVID-19 in Baghdad city. They found decreasing levels of LRG-1 and increasing in d-dimer levels in serum of infected patients with COVID-19 compared to healthy. [13]

Serum levels of creatinine, AST and IL-24 were highly expressed in recovered patients from COVID-19 disease compared to healthy volunteers. [14]

Due to the previous studies considering vaccination to COVID-19, a recent study (2023) found that a non-vaccinated reinfection people with COVID-19 show higher levels of IL-10, IL-2, IL-6, IL-1β, IL-8 and TNF-β expression in the serum respectively, compared to vaccinated mild reinfection peoples. And concluded that vaccination play important supportive role in strengthen the immune system and prevent disease progression. [15]

In the study of Xu and colleagues, they classify COVID-19 infected patients into 3 categories (mild, severe and fatal) according to the estimated levels of biomarkers including: cytokines, chemokines and growth factors, during the period days, 1, 5, 10, and 14 after diagnosis.

Levels of IFN, IL-1, IL-2 and IL-6 found to be upregulated and roughly similar to levels on days 1 and 5 in all three categories, but highly upregulated in fatal patients on day 14 after diagnosis, but remain at constant levels in survivors volunteers. And increasing levels of LDH, AST and ALT suggested as an early biomarkers to sever disease and mortality. [16]

ACE2 is the SARS TMPRSS2 for spike (S) protein receptor for initiation of infection; hence, it is a target for pharmacological intervention. Furthermore, designing novel monoclonal antibodies binding specifically to COVID-19 RBD is essential. A viral S proteins (TMPRSS2) was proposed for clinical use by blocking the viral intake by cell [17].

Another study found a significant difference between the age groups in terms of ESR and concluded that LDH and CPK, CRP and ESR could be considered as laboratory tests in the hospitalized COVID-19 patients with mucormycosis. [18]

There are several strengthen points in current study, the data selected according to routine visiting of volunteers during the period of their infection and after curing according to physician advise and treatment. Data not full according to selected categories (non-infected, infected and cured) were excluded. Several parameters were tested: hematological, enzymatic and inflammatory markers to select the ideal biomarker. Age and gender were about be normalized also to exclude any bias in data collection.

Also there were several limitations as any study have: first: most Iraqi studies have insufficient data about treatment, follow-up and mortality, second: most Iraqi studies have insufficient data about the ROC curve, specificity and cut-off that limit the possibility of prognosis and predictively since sensitivity analysis is important to avoid any bias in the selection or omission, third: selection bias of single center may affect the reproducibility and results and limiting describing the whole geographic area and also not all centers have the same checkup list of markers in diagnosis, finally larger population is important to give a large illustration of the results.

CONCLUSION

It could be concluded from current study that AST and d-dimer could be the ideal biomarkers to be selected in monitoring COVID-19 infection and curing and as inflammatory response. These markers represented accurate and low cost and their levels in blood stream also strength their selection.

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