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Utility of inflammatory makers, alanine aminotransferase, aspartate aminotransferase, and procalcitonin tests in COVID-19

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Abstract

Background and objective: Many tests are conducted for monitoring the progression and the severity of coronavirus disease (COVID-19) infection. However, the extent to which these tests are helpful in clinical practice and therapeutics of COVID-19 is still ambiguous. This study aimed to evaluate the feasibility of performing inflammatory marker tests, liver function tests, and procalcitonin test in the diagnosis and monitoring of COVID-19 infection.
Methods: The current study compares the results of alanine aminotransferase, aspartate aminotransferase, ferritin, and procalcitonin tests in two different populations of 123 COVID -19 suspects and a control group of 110 healthy individuals in Erbil city of Kurdistan region of Iraq to search for possible significant differences in both groups.
Results: The COVID-19 group had significantly higher ferritin and procalcitonin mean values than the control group (P = 0.001). The differences between alanine aminotransferase and aspartate aminotransferase were significant in some age and gender classes of both groups. However, the overall differences were not statistically significant (P = 0.339 and 0.286, respectively).
Conclusion: The outcome of the current study suggests that among the group of tests conducted for the study population, the most useful tests are ferritin and procalcitonin to monitor the COVID-19 patients' health status.
Keywords: COVID-19; SARS-CoV-2; Ferritin; Procalcitonin; Alanine aminotransferase; Aspartate aminotransferase.

Introduction

The coronavirus disease (COVID-19) pandemic is still a major epidemiological threat to public health worldwide. The pandemic continues in harvesting the lives of the most vulnerable groups of those infected. As of the end of October 2020, more than 42 million cases and 1.150 million deaths are recorded worldwide, and the number is still likely to go higher.[1] The most trusted test for diagnosing COVID-19 is the relatively expensive and time-consuming molecular Polymerase Chain Reaction (PCR) test, which detects the active infection with SARS-CoV-2 virus.[2] However, other less reliable tests are also available at lower costs but are less accurate in detecting the infection. These are referred to as rapid diagnostic tests (RDS).[2] Moreover, there is an antibody testing option for people who suspect their infection and recover from the virus even though their infection was asymptomatic.[2]

Besides, nowadays, physicians and people turn to testing other common markers of infection as an interpretation of possible COVID-19 infection. According to the results of many studies, there is an association of the COVID-19 severity with inflammatory markers.[3]

As an inflammatory response to the rapid replication of the virus and destruction of the cells, the monocytes and macrophages can induce chemokines and cytokines release.[4]

So, proceeding with inflammatory marker tests may help physicians monitor the

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health status of COVID-19 possible patients. These markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum ferritin tests. Also, some information points out to abnormalities in liver function tests, including the alanine aminotransferase (ALT), aspartate aminotransferase (AST) as a result of infection to COVID-19.[5]

Moreover, there are indications of an increase in procalcitonin (PCT) levels in COVID-19 patients that the range rises with the severity of the disease accordingly.[6]

In the current study, we searched for the feasibility of testing such markers as helpful tools for diagnosing or monitoring the COVID-19 infection. The study includes tests for inflammation markers, liver function markers, and procalcitonin levels in a group of patients with COVID-19 symptoms and compares the results to a group of healthy individuals as a control group. The World Health Organization (WHO) describes the most common symptoms of infection with SARS-CoV-2 virus as fever, dry cough, and fatigue.[2]

This study aimed to see whether performing such tests on a wide scale is worthy or not in clinical practice for monitoring COVID-19 progression and which tests are better in predicting the severity of COVID-19 infection.

Methods

Study design

A cross-sectional study based on a standardized questionnaire about the most common signs and symptoms of COVID-19 infection was prepared and directed to all patients who visited (Pharma private medical laboratory) in Erbil city in the Kurdistan region of Iraq to select the candidates with COVID-19 infection symptoms. Candidates who had comorbidities associated with an elevation of the tested variables were excluded from the final results of the study. The data were collected from August to September 2020. The patients with certain symptoms of COVID-19 have been chosen on the onset of their symptoms among different age and gender groups. The most common questions of the survey were the presence or absence of fever, dry cough, and tiredness. All of the 123 candidates in the COVID-19 suspect group had the mentioned signs and symptoms, and some were suffering from severe symptoms. Also, for comparison purposes, a control group of 110 participants was selected in healthy conditions without any obvious diseases such as diabetes and hypertension from different ages and gender. All the encounters of the study provided their informed consent to all procedures and tests performed for this study and also agreed on publishing their data anonymously in the current study.

All tests performed in an authorized medical laboratory by Erbil's general health directorate obeying the regulations and ethical considerations of the Ministry of Health in the Kurdistan Region's Government.

Sampling and biochemical assessments

All the blood samples were collected from both the patients and healthy control individuals. The blood was processed, and clear serum samples were obtained. Then the samples underwent testing to determine the ranges of ALT, AST, ferritin, and procalcitonin on an automatic biochemical analyzer (Cobas E311 and E411). The reference values were provided by the kit manufacturer (Roche) for ALT and AST are (0-33 and 0-32 U/mL), respectively. The ferritin's reference interval for adults up to 100 years old is (13-150 ng/mL). The PCT's reference intervals for healthy individuals is (Low risk <0.5 ng/mL, High risk > 2.0 ng/mL).

Statistical analysis

The statistical package for the social sciences (IBM SPSS statistics 26) was employed for the data analysis. Descriptive and frequency analysis was used for viewing and summarizing the data. Mean comparison of the data between the two groups was made by the independent

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Samples t-test. The results are presented using APA style. The statistically significant *P* value was calculated at smaller than 0.05.

Results

The test results of a total number of 123 patients with a mean age±SD of 36.62±13.444 years who had the symptoms of SARS-CoV-2 infection, including 74 males aged (36.54±11.871 years) and 49 females aged (36.73±15.655 years) were included in the final results of this study. The results were compared to a control group of healthy individuals who experienced no COVID-19 symptoms. The control group of 110 participants aged (36.55±10.420 years) comprised 70 males aged (37.86±11.309) and 40 females aged (34.25±8.289 years). The *P value* from the mean comparison of ages in both genders from both groups resulted in a non -significant difference between the males (*P* = 0.496), females (*P* = 0.369), and the total (*P* = 0.965), as shown in Table 1.

The results were broken down according to age groups for both classes. Comparisons of results between the two groups of encounters for the tested parameters (ALT, AST, ferritin, and procalcitonin) are shown in Table 2.

For the youngest group (≤20), there was a statistically significant difference in the mean value of the control group and infected group in ALT, AST, and The results were broken down according ferritin *(P* = 0.02, <0.001, and 0.002, respectively). There were no significant differences in PCT between the healthy individuals and the COVID-19 group *P* = 0.062). The second age group (21-30 (years) exhibited various results from the first group in ALT, AST, PCT, and ferritin. There is no significant difference between the control and COVID-19 suspected patients (*P* = 0.316, 0.983, 0.080, and 0.109, respectively). However, the third age group (31-40 years) showed a significant difference (*P* = 0.026, 0.001, and 0.042) for each ALT, ferritin, and PCT, respectively, and a non-significant difference (*P* = 0.096) in AST results between the two groups. The fourth (41-50) and fifth (51-60) age groups exhibited non-significant differences between the two groups for all parameters except for PCT in the fifth age group (*P* = 0.034). For the oldest age group (>70 years), since there were only 3 individuals in the patient group and no participants in the control group, the *P-value* could not be calculated. In the final comparison, regardless of the age of participants, the results showed a strong statistically significant (*P* = 0.001) between each group in both ferritin and PCT and a non-significant (*P* = 0.339 and 0.286) for both ALT and AST, respectively.

In Table 3, the results are broken down according to the gender for both the COVID-19 suspect group and the control group. The comparison between the ALT, AST, ferritin, and PCT results proved a significant difference (*P* = 0.014, 0.025, <0.001, and <0.001, respectively) in male participants from both groups in which the difference was the strongest for ferritin and PCT(*P* <0.001). For females in the study, there was a statistical significance difference (*P* <0.001, 0.003, and <0.001) in ALT, AST, and PCT, respectively, and a non-significant (*P* = 0.841) in ferritin.

Table 1 Gender frequency distribution, mean age, standard deviations, and *P value* of the sample populations

	COVID-19 suspect group		Control group		*P value*
	N	Mean age ±SD	N	Mean age ±SD	
Male	74	36.54±11.871	70	37.86±11.309	0.496
Female	49	36.73±15.655	40	34.25±8.289	0.369
Total	123	36.62±13.444	110	36.55±10.420	0.965

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Table 2 A comparison of the test results between the COVID-19 suspects and the control group according to the age classes

Test results	Statistics	Age groups							Total
		≤20	21-30	31-40	41-50	51-60	61-70	>70	
ALT1 U/mL	Mean±SD	18.6±13.2	36±47	34.2±21	28.4±17.6	33.6±32.8	29.5±25.5	20.7±2.3	31.7±30.7
	N	11	35	37	22	11	4	3	123
ALT2 U/mL	Mean±SD	30.3±3.6	27.8±8	27±4	33.1±5.9	34.3±2.9	38.7±4.6		29.3±6.2
	N	4	27	50	17	8	4	0	110
P-value		0.020	0.316	0.026	0.251	0.952	0.502		0.339
AST1 U/mL	Mean±SD	19.3±6.4	26.6±27.1	24.2±9.3	26.8±14.8	26.5±5.6	33.2±31.8	29.7±3.5	25.5±17.5
	N	11	35	37	22	11	4	3	123
AST2 U/mL	Mean±SD	34.8±1.3	26.7±7.2	21.4±6.1	21.4±4.2	26.4±2.5	26.3±2.6		23.7±6.5
	N	4	27	50	17	8	4	0	110
P-value		< 0.001	0.983	0.096	0.114	0.930	0.677		0.286
Ferritin1 ng/mL	Mean±SD	84.5±96.7	196±172	254.6±249	274.9±287.4	224.9±164	640±581	361.7±52	238.8±246.6
	N	11	35	37	22	11	4	3	123
Ferritin2 ng/mL	Mean±SD	204.3±4.6	144±68	131±80	203.8±129.6	245.5±45.5	220±2.2		159.7±89.9
	N	4	27	50	17	8	4	0	110
P-value		0.002	0.109	0.001	0.310	0.700	0.199		0.001
PCT1 ng/mL	Mean±SD	0.013±0.015	0.057±0.0862	0.0518±0.060	0.0390±0.040	0.073±0.049	0.088±0.056	0.057± 0.015	0.051±0.063
	N	11	35	37	22	11	4	3	123
PCT2 ng/mL	Mean±SD	0.0275±0.00957	0.031±0.0175	0.0304±0.014	0.0344±0.010	0.0360±0.009	0.042±0.009		0.032±0.014
	N	4	27	50	17	8	4	0	110
P-value		0.062	0.080	0.042	0.616	0.034	0.159		0.001

1: COVID-19 Suspect group
2: Control group

Table 3 A comparison of test results between the COVID-19 suspects and the control group according to the gender classes

Test results	Statistics	Test results			
		ALT U/mL	AST U/mL	Ferritin ng/mL	PCT ng/mL
M1	Mean±SD	40.1±37	29±21.2	309.8±251.2	0.065±0.0737
	N			74	
M2	Mean±SD	29±6.3	23.1±6.3	172.1±94.8	0.0327±0.0158
	N			70	
P-value		0.014	0.025	<0.001	<0.001
F1	Mean±SD	19.1±7.3	20.2±6.8	131.6±197.6	0.0300±0.0343
	N			49	
F2	Mean±SD	29.6±6.2	24.7±6.9	137.9±76.9	0.0305±0.0111
	N			40	
P-value		<0.001	0.003	0.841	<0.001
Total 1	Mean±SD	31.7±30.8	25.5±17.5	238.8±246.6	0.0510±0.0633
	N			123	
Total 2	Mean±SD	29.3+6.2	23.7±6.5	159.7±89.9	0.0319±0.0142
	N			110	
P-value		0.399	0.286	0.001	0.001

1: COVID-19 Suspect group
2: Control group

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Discussion

The outgoing COVID-19 pandemic is still on the rise, and the daily new cases are at all times higher levels worldwide.[1] However, the mortality rates because of the virus seem to be decreased in hospitalized patients. The reason for this decrease is not completely confirmed whether it is because the newer treatment strategies are improved, or the virus has become less mortal.[7]

The release of reports about therapeutic drugs used in treating COVID-19, such as remdesivir, that reduced the recovery time significantly, are promising.[8]

Even now, the virus is a major source of unrest and fear for the public. Besides physiological disorders caused by the virus, fear and confusion led to rising in many psychological and mental disorders as well.[9]

This unprecedented situation enhances the public to fill their curiosity desire of testing for COVID-19 even if they had no clear symptoms or exposure to the virus. As a result, the demand for testing for SARS-CoV-2's PCR test is very high that sometimes it takes about a week to release the results, especially when the demand is at its highest and the pandemic is peaked.

So, the public and physicians turn to use other than the molecular test for monitoring the progression and maybe sometimes for diagnosis purposes. These tests include well-known inflammatory markers and some organ function tests. In the current study, the liver enzymes ALT and AST, ferritin, and PCT tests are performed for two groups of participants. One group with symptoms of SARS-CoV-2 infection and a control group of healthy individuals with no COVID-19 symptoms. The reasoning behind conducting this study is to compare the results of the tested variables for both groups and search for possible significant differences to prove which markers are the most useful in the interpretation of the infection with the virus or the severity and progression of the disease or whether these tests are worthy enough to be performed for COVID-19 patients? The out coming results by comparing the mean values from both groups for all variables show that ferritin and PCT are the most significant difference between the two groups. The difference has a *P value* (0.001) for the total number comparison between the suspected and control groups. Also, the outcome for the gender classes shows similar results. In males, the difference is even greater (P <0.001) in both ferritin and PCT, while in the female groups, there is only a significance in PCT and no significance in ferritin. While comparing the age groups for ferritin and PCT resulted in no statistical significance between the age classes of the suspect and control group except for two classes. Knowing that ferritin is the major immune dysregulation mediator that contributes to the cytokine storm and many studies suggest the higher severity of COVID-19 is accompanied by cytokine storm, the postulation is that progression and severity of COVID-19 is a cytokine storm syndrome dependent.[10]

Many studies support the results of our study in which the overall mean values of ferritin are higher in the suspected COVID-19 group than in the control group.[10,11] Similarly, the PCT levels are also elevated due to the severity of the infection as well.[11,12] Also, it is advisable to perform serial measurements of PCT to better understand the progression of SARS -CoV-2 infection.[12] The overall total numbers of participants mean comparison for the liver function tests resulted in a non-significant difference between the two groups. However, many significant differences could be observed among various age classes in both groups. The ALT in the youngest and individuals aged 31-40 years is significantly different between the suspected COVID-19 and the control group. However, the AST test results are only significant in the youngest encounters of both groups. Unlike the age classes, the gender comparison for both groups showed a relatively strong

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significant differences between males and females between the two COVID-19 suspects and control populations in both the ALT and AST. According to the data available on the mechanism by which the liver damage may occur in response to SARS-CoV-2 infection is through the inflammation that the immune system or the toxicity could mediate through inducing drugs.[13]

A retrospective study in China showed that COVID-19 patients with abnormal liver functions need to stay more in hospital compared to those with normal liver function.[14] So, abnormal liver function worsened the severity of COVID-19 infection. However, we could not detect any significant difference in the sample populations in the current study. The current study results contain significant differences between the two groups (suspected COVID-19 and control groups). However, these results have some limitations due to the fact that the patients who had COVID-19 infection symptoms were not confirmed by the molecular PCR testing at the time of sampling. Also, as we have tried our best to secure a higher accuracy in terms of choosing the population in the COVID-19 suspect group. However, they might contain individuals who had other diseases that cause alterations of the targeted markers that they did not mention in the survey we used for choosing the candidates. Moreover, the patients in the COVID-19 group were not categorized according to the severity of their symptoms. So, we could not determine the direct relationship between the markers in our study with the severity of COVID-19 infection.

Conclusion

To conclude the results of this study, there are many advantages of testing common inflammatory markers and organ function tests for monitoring the progression and severity of COVID-19 infections. However, the feasibility of such tests for diagnostic purposes in COVID-19 is questionable and should not be considered as alternatives for the molecular PCR test. Although, the best tests in the current study that showed a significant difference in the control and COVID-19 suspect groups from the study population were ferritin and PCT rather than the ALT and AST tests, in which there was no significant difference between the two groups.

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Competing interests

The authors declare that they have no competing interests.

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