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Biochemical changes in Egyptian patients infected with COVID-19

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Abstract

A pandemic-scale outbreak of the newly discovered coronavirus disease 2019 (COVID-19), fast-spreading viral pneumonia, is currently occurring. Due to the disease's overall vulnerability, different age groups have different clinical characteristics and test findings. The purpose of this study was to describe the COVID-19 laboratory results in various age and sex groups. Reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-2 RNA was used in the study, which had 1100 individuals with typical cold symptoms. It was reported that 660 of these cases tested positive for the test, while 440 tested negatives, therefore all cases underwent laboratory testing. Our research revealed that males had higher COVID-19 positivity than females (215/660; 67.4%), with males scoring 445/660; 32.6%). Age does not statistically differ between COVID-19 positive and negative cases. Hematological parameters in blood cells revealed that Lymphocytes differ significantly between COVID-19-infected and uninfected patients as these cells decline in the presence of COVID-19 infection. There are no significant differences in hemoglobin (Hgb percent), red blood cells (RBCs), total white blood cells (WBCS), basophils, neutrophils, monocytes, and eosinophils, as well as blood platelets (PLTS). Erythrocyte sedimentation rate (ESR) is unimportant, whereas COVID-19 infection increases ferritin and C-reactive proteins.

Keywords: COVID-19; SARS-CoV-2; diagnosis; laboratory findings.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has rapidly evolved from an epidemic outbreak in Wuhan, China [1] into a pandemic infecting more than one million individuals all over the world, whereas billions of citizens are affected by measures of social distancing and the socioeconomic impact of the pandemic. SARS-CoV-2 is approximately 80% like SARS-CoV and invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor [2]. Although it is well documented that COVID-19 is primarily manifested as a respiratory tract infection, emerging data indicate that it should be regarded as a systemic disease involving multiple systems including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [1-2].

In the initial phases of the disease, symptoms like fever, cough, and dyspnea can occur [3-4]. Some patients rapidly develop acute respiratory distress syndrome (ARDS) and additional severe

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complications, which are ultimately followed by multiple organ failure 5, hence, timely diagnosis of patients is very essential. Although detection of viral nucleic acid using reverse-transcription polymerase chain reaction (RT-PCR) remains the gold standard of diagnosis and monitoring, it is very time-consuming and has a high prevalence of false-negative results [6-7]. Other laboratory tests, such as whole white blood cells (WBCs) count, neutrophil ratio, lymphocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) Ferritine and several other laboratory tests have been reported to change in COVID-19 patients [8-9].

Material and methods

Collection and processing of blood samples

All samples were collected from Sohag Fever Hospital, Egypt, and has been conducted from November 2020 through July 2021. In our study, we selected 1100 patients with symptoms of the common cold all individuals were interviewed, and a questionnaire was filled out to obtain information on age and sex. Blood samples were collected from each subject by venipuncture of the cubital veins. The site was cleaned thoroughly using 70% isopropyl alcohol in water and 1% iodine for one minute and allowed to dry. Taking precautions to avoid contamination of the site, about 5 milliliters of blood was collected using a sterile syringe and needle, and 4 ml dispensed into clean plastic. The blood samples were centrifuged at 4000 rpm for 10 minutes, and the serum obtained was stored at -70° C, and 1 ml in an EDTA tube for a complete blood count.

Respiratory Specimen Collection for RNA SARS-2 by Real-time PCR

Nasal swabs were taken by the hospital care physician under infection control measures, where the sample was taken from the nasopharynx using a sterile swab. Nasopharyngeal swabs have a flexible plastic arm where the swab is inserted through the nostril parallel to the mouth until it reaches a depth of the same distance from both the nasal opening and the external opening of the ear, leaving the swab for several seconds to absorb nasal secretions while rotating it and then slowly removing it.

The collected pharyngeal swabs were placed into a disposable virus sampling tube containing saline, the tail was discarded, and the cap tightened; Sputum sample should be liquefied with phosphate buffer containing 1 g/L proteinase K, then lid tight and sealed with a sealing film.

RNA SARS-2 by Real-time PCR, a model: real-time DNA technology, Russian made, SARS-Cov2 fluorescent PCR Kit, lot: 0921741, Maccura Biotechnology, Co., Ltd.

Biochemical analysis

Aspartate aminotransferase (AST/SGOT) colorimetric method

(Human Gesellschaft for Biochemia, Germany. LOT: 0169). Aspartate aminotransferase (AST) formerly called glutamate oxaloacetate (GOT) catalyzes the reversible transfer of an amino group from aspartate to alpha-ketoglutarate forming glutamate and oxaloacetate. The oxaloacetate produced is reduced to malate dehydrogenase (MDH) and NADH. The rate of decrease in the concentration of NADH, measured photometrically, is proportional to the catalytic concentration of AST present in the sample.

Procedure: 1000 µl of AST working reagent (buffer/enzyme reagent and substrate percent 1:4) incubated reagent for 10 min at 37°C then added 100 µl human serum. The reaction was mixed, read the absorbance at 340 nm by spectrophotometer after 1 minute, and at the same time start the stopwatch. Read the absorbance again exactly after 1, 2, and 3 minutes by Micro lab biochemistry analyzer semi-automation model: RX199.

Alanine aminotransferase (ALT/SGPT) colorimetric method

(Human Gesellschaft for Biochemia, Germany. LOT: 0142).

Alanine aminotransferase (ALT) or Glutamate pyruvate transaminase (GPT) catalyzes the reversible transfer of amino group from alanine to alpha-ketoglutarate forming glutamate and pyruvate. The pyruvate produced is reduced to lactate-by-lactate dehydrogenase (LDH) and NADH. The rate of decrease in the concentration of NADH, measured photometrically, is proportional to the catalytic concentration of ALT present in the sample.

Procedure: 1000 µl of AST working reagent (buffer/enzyme reagent and substrate percent 1:4) incubated reagent for 10 min at 37°C then added 100 µl human serum. The reaction was mixed, read the absorbance at 340 nm by spectrophotometer after 1 minute, and at the same time start the stopwatch. Read the absorbance again exactly after 1, 2, and 3 minutes by Micro lab biochemistry analyzer semi-automation model: RX199

Creatinine

(Human Gesellschaft for Biochemia kit, Germany. LOT: 19029).

Creatinine liquicolor creatinine reagent is based on a modified Jaffe reaction, photometric colorimetric test for endpoint measurement of creatinine, and method with deproteinization.

Creatinine forms in alkaline solution an orange-red colored complex with picric acid. The absorbance of this complex is proportional to the creatinine concentration in the sample.

Procedure: 1000 µl of creatinine reagent was added to 100 µl of serum in the test tube, and the tube was mixed after 30 Sec. The reaction was measured absorbance at 546 nm after 2 minutes by Micro lab biochemistry analyzer semi-automation model: RX199

Lactate dehydrogenase (LDH):

Spectrum Diagnostics liquizyme LDH kit (lot: 0235680) is intended for the invitro quantitative, diagnostic determination of LDH in human serum on both automated and manual systems, The lactate dehydrogenase (LDH) enzyme is widely distributed in heart, liver, muscle, and kidney. LDH catalyzes the conversion of lactate to pyruvate. The enzyme is a tetrameric protein and gives rise to five isoenzymes. Heart, kidney, brain, and erythrocytes have the highest proportion of LD-1 and LD-2. Liver and skeletal muscle have the highest percentage of LD-5. LDH is significantly increased during myocardial infarction. A maximum value is reached 48 hours after the onset of manifestation and persists up to 10 days. Elevated serum levels of LDH have also been observed in patients with megaloblastic anemia, disseminated carcinoma, leukemia, and trauma. Mild increases in LDH activity have been reported in cases of hemolytic anemia, muscular dystrophy, pulmonary infarction, hepatitis, nephrotic syndrome, and cirrhosis. [18, 19].

Procedure: 1000 µl working solution added to 20 µl serum samples at 37c then gently mix and read initial absorbance after 30 sec. by Micro lab biochemistry analyzer semi-automation model: RX199.

Hemoglobin (Hb%), Red blood cells (RBCs), Total leucocytic count (TLC), and Platelets (PLTs) tests

DIRUI Haematology analyzer Automation model: BCC-3000B

Reagent LOT: DIRUI 20210226

In an automated analyzer, analysis begins when a well-mixed whole blood sample is placed on a rack in the analyzer. The instrument utilizes flow cells, photometers, and apertures to analyze different elements in the blood. The cell counting component counts the numbers and types of different cells within the blood. A special photometer called a hemoglobin meter measures the amount of hemoglobin. This is done by adding a diluent that lyses the red blood cells which are then pumped into a spectro-photometric measuring cuvette. The change in color of the lysate equates to the hemoglobin content of the blood.

Blood cell counting occurs by flow cytometry when a very small amount of the specimen is aspirated, diluted, and passes through an aperture and

a laser flow cell. Sensors count and identify the number of cells passing through the aperture. The two main types of sensors used are laser light detectors and electrical impedance. The instrument determines the type of blood cell by analyzing data about the size and aspects of light as they pass through the cells. various red blood cell indices (parameters calculated from other CBC results) are often reported in addition to cell counts and hemoglobin.

C-reactive protein (CRP) Inflammatory Index Test

Ichroma™ CRP Kit (LOT: CRQBK06) is a sandwich immuno-detection method, such that by mixing the detection buffer with the blood specimen in the test vial, the fluorescence-labeled detector anti-CRP antibody in the buffer binds to the CRP antigen in the blood specimen. The sample mixture is loaded and migrates on the matrix of the test cartridge; the complexes of the detector antibody and CRP is captured to the anti-CRP sandwich pair antibody that has been immobilized on the test matrix. The fluorescence intensities are converted into a CRP concentration calculated by the pre-programmed calibration process. The result of the tests is displayed on the reader as ng/mL for CRP.

Procedure: 30 µl of whole blood was added to a tube containing the detection buffer and mixed about 10 times then added 75 µl of a sample mixture and load it into the sample well on the test cartridge and incubated at room temperature for 3 minutes. The reaction was read on an instrument for I Chroma, model I chroma PCT.

Serum Quantitative Ferritin:

Ichroma™ Ferritin Kit (LOT: FRPXA63) is a fluorescence Immunoassay (FIA) for the quantitative determination of Ferritin in human serum/plasma.

The test uses a sandwich immunodetection method; the detector recombinant protein in buffer binds to antibody in a sample, forming recombinant protein-antibody complexes, and migrates onto nitrocellulose matrix to be captured by the other immobilized antigen on the test strip. The more antibody in the sample forms the more recombinant protein-antibody complex and leads to stronger intensity of fluorescence signal on detector recombinant protein, which is processed by Instrument for ichroma™ tests to show ferritin concentration in the sample.

Procedure:

Transfer 30 µL of the sample (human serum/plasma/control) using a transfer pipette to a tube containing the detection buffer, close the lid of the detection buffer tube and mix the sample thoroughly by shaking it about 10 times Pipette out 75 µL of the sample mixture and load it into a sample well in the cartridge.

Insert the sample-loaded test cartridge into the slot of the i-Chamber or an incubator (25 °C) then leave the sample-loaded cartridge in the i-Chamber or an incubator for 10 minutes.

The instrument for ichroma™ tests will start scanning the sample-loaded cartridge immediately and read the test result on the display screen of the **i**nstrument for ichroma™ tests, a model I chroma PCT.

Erythrocyte sedimentation rate (ESR or sed rate) test

ESR is a test that indirectly measures the degree of inflammation present in the body. The test measures the rate of fall (sedimentation) of erythrocytes (red blood cells) in a sample of blood that has been placed into a tall, thin, vertical tube. Results are reported as the millimeters of clear fluid (plasma) that are present at the top portion of the tube after one hour and two hours.

Statistical Analysis:

Data were coded and entered using the statistical package SPSS version 21. Data were summarized using mean, standard deviation, median, minimum, and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages)for categorical variables. Comparison of quantitative variables was done using the nonparametric Kruskal-Wallis when comparing

more than 2 groups and using the nonparametric Mann–Whitney U test when comparing 2 groups. Chi-square or Fisher's exact test was used for comparison between groups; as appropriate. Odds ratios and their 95% confidence intervals were calculated. A p-value ≤ 0.05 was considered statistically significant.

Results:

Swabs were done for 1100 people to detect COVID-19, carrying symptoms of this virus such as fever, cough, and shortness of breath, our results showed that 660 (60%) cases were positive and 440 (40%) negative cases, and these results were confirmed by RT-PCR SARS2 RNA **(Table 1)**.

Our study showed that males were more COVID-19 positively compared to females and there is no significant difference (P. value = 0.542) between males and females in positive and negative cases of COVID-19. Whereas, in the case of positive COVID-19 are 445/660 (67.4%) males and 215/660 (32.6%) females, whiles in the case of negative COVID-19 found 237/440 (53.9%) males and 203/440 (46.1%) females (Table 2).

Table (1): COVID-19RNA detection rate in blood samples

No. patients / Total	Percent (%)	COVID-19 RNA
440 / 1100	40 %	Negative
660 /1100	60 %	Positive

Table (2): COVID-19 Estimating Gender-Related Patients

Gender-specific positive and negative COVID-19					
Variables			Sex		*P*-value
			Male	Female	
COVID-19 RNA	Positive	Count	445	215	0.542
		% Within Sex	67.4%	32.6%	
	Negative	Count	237	203	
		% Within Sex	53.9%	46.1%	
Total		Count	682	418	
		% Within Sex	100.0%	100.0%	

Table (3): Estimation of patients' COVID-19-related ages

Age relationship and SARS-2 infection				
COVID-19 RNA		Positive **660(100%)**	Negative **440(100%)**	***P*-value**
Age	< =20	22(3.3%)	27(6.1%)	0.304
	21- 40	242(36.7%)	217(49.3%)	
	41-60	242(36.7%)	152(34.6%)	
	> 60	154(23.3%)	44(10.0%)	
Mean ± Std		47.37 ± 18.258	41.60 ± 14.297	
Range		(18-84)		

In all ages and age groups, there is no significant difference (P. value > 0.05) between positive and negative COVID-19 cases. This is a result of the varied age groupings between positive and negative cases (Table 3).

Our analysis of blood cell hematological parameters revealed a significant difference (P value < 0.05) between patients who were infected with COVID-19 and those who were not, with a decrease in lymphocytes in the presence of COVID-19 infection. There are no significant (P. value > 0.05) differences in hemoglobin (Hb percent), red blood cells (RBCs), total white blood cells (WBCs), basophils, neutrophils, monocytes, and eosinophils, as well as blood platelets (PLTS) (Table 4).

Our biochemical analysis of the patient's liver and kidney function revealed a significant difference (P value < 0.05) in the levels of glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate (GOT) as these cells increased in the occurrence of COVID-19 infection. In contrast, there is no discernible change in creatinine levels between COVID-19-infected and uninfected individuals (P value > 0.05). (Table 5).

Our biochemical study on lactic dehydrogenase (LDH) and Ferritin showed patients who were infected with COVID-19 and not infected, that there is a significant difference in LDH and ferritin (P. value < 0.05), as these cells increased in the event of infection with COVID-19 a comparison between infected and non-infected with COVID-19 **(Table 6)**.

Our biochemical study on tests for evidence of inflammation showed patients who were infected with COVID-19 and not infected, that there is a highly significant in C- Reactive Protein, (P. value < 0.002) as these cells increased in the event of infection with COVID-19. While Erythrocyte Sedimentation Rate (ESR) there is no significant difference (P. value > 0.05) **in** a comparison between infected and non-infected with COVID-19 **(Table 7)**.

Table (4): Effect of COVID-19 on patients' hematological parameters

Effect of COVID-19 on hematological parameters					
Variables	**COVID-19 RNA**	**N**	**Mean**	**Std. Deviation**	***P*-value**
Total leukocytic count	Positive	660	7.59	3.079	0.312
	Negative	440	6.76	2.350	
Neutrophils	Positive	660	53.80	14.42	0.484
	Negative	440	52.30	13.54	
Lymphocytes	Positive	660	20.15	6.62	0.000
	Negative	440	32.71	3.71	
Monocytes	Positive	660	8.98	5.95	0.622
	Negative	440	9.63	5.45	
Eosinophil	Positive	660	0.93	1.041	0.330
	Negative	440	2.40	1.611	
Basophils	Positive	660	0.83	1.921	0.316
	Negative	440	0.41	0.334	
Red blood cells	Positive	660	4.91	0.548	0.490
	Negative	440	4.93	0.603	
Hemoglobin	Positive	660	13.43	1.745	0.250
	Negative	440	13.48	1.253	
Platelets Count	Positive	660	264.67	130.033	0.490
	Negative	440	275.07	113.070	

Table (5): Effect of COVID-19 on the patient's liver and renal function tests

Effect of COVID-19 on liver and kidney function tests					
Variables	**COVID-19 RNA**	**N**	**Mean**	**Std. Deviation**	***P*-value**
Creatinine	Positive	660	1.163	0.3489	0.249
	Negative	440	1.220	0.4057	
GPT	Positive	660	46.18	7.23	0.001
	Negative	440	30.90	6.23	
GOT	Positive	660	45.18	3.99	0.000
	Negative	440	26.45	11.30	

Table (6): Patients' lactic dehydrogenase and ferritin levels as a result of COVID-19.

Effect of COVID-19 on lactic dehydrogenase (LDH) and Ferritin					
Variables	**COVID-19 RNA**	**N**	**Mean**	**Std. Deviation**	***P*-value**
LDH	Positive	660	2.61	93.59	0.001
	Negative	440	1.42	67.88	
Ferritin	Positive	660	3.18	136.76	0.000
	Negative	440	76.91	59.23	

Table (7): Effect of COVID-19 on inflammatory tests in patients

Effect of COVID-19 on inflammatory test					
Variables	**COVID-19 RNA**	**N**	**Mean**	**Std. Deviation**	***P*-value**
ESR1hr	Positive	660	32.20	16.680	0.403
	Negative	440	16.40	11.710	
ESR2hr	Positive	660	62.20	23.864	0.911
	Negative	440	33.80	22.524	
C. Reactive Protein	Positive	660	40.43	42.205	0.002
	Negative	440	6.97	7.218	

Discussion

It has been established that COVID-19 patients admitted to ICUs have higher levels of proinflammatory cytokines and, more significantly, increased release of those T-helper-2 (Th2) cytokines that reduce inflammation. [3].

One thousand and one hundred participants in our study to detect COVID-19, carrying symptoms of this virus such as fever, cough, and shortness of breath, our results showed that 660 (60%) cases were positive and 440 (40%) negative cases, and these results were confirmed by RT-PCR SARS2 RNA.

COVID-19 has spread across multiple continents, the Global Health 50/50 research initiative presented an impressive overview of sex-disaggregated data from countries worldwide clearly demonstrating similar numbers of cases in women and men, but an increased case fatality in men [17]

Our study showed that males were more COVID-19 positively compared to females and there is no significant difference between males and females in positive and negative cases of COVID-19. Whereas, in the case of positive COVID-19 are 445/660 (67.4%) males and 215/660 (32.6%) females, whiles in the case of negative COVID-19 found 237/440 (53.9%) males and 203/440 (46.1%) females. Our study showed that there are no statistical differences between age in positive and negative cases of COVID-19, as in the positive cases there were different ages as in the positive cases.

Lymphopenia is a hematological criterion that is unmistakably linked to disease severity; COVID-19 patients who passed away had considerably lower lymphocyte counts than survivors. Lymphocyte replenishment may play a significant role in recovery [11]. White blood cells, neutrophils, eosinophils, platelets, and CD8 cell counts were other blood cells that were partially predictive in separating mild from severe COVID-19; however, their importance is still unclear. Granulocyte colony-stimulating factor (G-CSF) has been reported to be substantially correlated with illness severity in ICU patients [13].

Our hematological parameters study on blood cells showed patients who were infected with COVID-19 and not infected, there is a significant difference in Lymphocytes cells as these cells decrease in the event of infection with COVID-19. While in hemoglobin (Hb%), red blood cells (RBCs) and total white blood cells (WBCs), Basophils cells, Neutrophils cells, Monocytes cells, Eosinophil cells, and blood platelets (PLTS) there are no significant.

Patients with severe COVID-19 appear to have more frequent signs of liver dysfunction than those with milder disease. An increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels have been observed among many ICU patients [12]. Infection of liver cells with SARS-CoV-2 cannot be excluded as 2–10% of patients with COVID-19 have diarrhea and viral RNA has been detected in both stool and blood samples, which implies the possibility of hepatic virus presence [14]. It is also likely that any immune-mediated inflammation, in particular cytokine storm, but also pneumonia-associated hypoxia, may lead to liver damage in critically ill COVID-19 patients [12]. Our biochemical study on liver and kidney function showed patients who were infected with COVID-19 and not infected, that it is significant in Glutamate pyruvate transaminase (GPT), Glutamate oxaloacetate (GOT), as these cells increased in the event of infection with COVID-19. While creatinine there is no significant, comparison between infected and non-infected with COVID-19

AST and ferritin levels, a predictive H-score has been proposed to estimate the risk of developing secondary hemophagocytic lymph histiocytosis [15]. Other predictors of poor outcome include the serum levels of ferritin and lactate dehydrogenase (LDH) [16]. Other laboratory results including WBC count, neutrophil ratio, platelet, hemoglobin, procalcitonin, albumin, and serum creatinine were not significantly different between the study groups [6].

Our biochemical study on lactic dehydrogenase (LDH) and Ferritin showed patients who were infected with COVID-19 and not infected, that there

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is a significant difference in LDH and ferritin, as these cells increased in the event of infection with COVID-19 a comparison between infected and non-infected.

C-reactive protein (CRP) levels are increased in COVID-19 patients, and it has been shown that survivors had median CRP values of approximately 40 mg/L, while non-survivors had median values of 125 mg/L, indicating a strong correlation with disease severity and prognosis [16]. Our biochemical study on Tests for evidence of inflammation showed patients who were infected with COVID-19 and not infected, that there is a highly significant in C. Reactive Protein, As these cells increased in the event of infection with COVID-19, While Erythrocyte Sedimentation Rate (ESR) there is no significant, a comparison between infected and non-infected with COVID-19.

Conclusion

The results of our investigation, which included 1100 participants, showed that 660 (60 percent) of the patients were positive for COVID-19 and 440 (40 percent) of the cases were negative. These findings were supported by RT-PCR SARS2 RNA. Our analysis of hematological parameters in blood cells revealed that Lymphocytes differ significantly between COVID-19-infected and uninfected patients as these cells decline in the presence of COVID-19 infection. There are no appreciable changes in hemoglobin (Hb percent), red blood cells (RBCs), total white blood cells (WBCS), basophils, neutrophils, monocytes, eosinophils, and blood platelets (PLTS). Our investigation into the molecular alterations in COVID-19 patients found. According to our research on the chemical alterations in COVID-19 patients, liver enzyme levels rise along with ferritin and C-Reactive Protein levels.

Recommendation

We urge the Egyptian Ministry of Health to carry out the chemical tests for COVID-19 patients that were suggested in our research and to monitor the results of those tests to guarantee that the patients fully recovered and responded to COVID-19 recovery.

Authors' Contribution:

All authors agree with the content of the manuscript and were involved in all steps of its preparation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Disclosure statement

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