Short Communication

Assessment of Some Immunological and Physiological Indicators for Infected and Uninfected Coronavirus Disease Patients

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Abstract

Background: The most serious respiratory consequences of coronavirus disease (COVID-19) include the common cold, coagulopathy, multiorgan failure, and death. It can also harm essential organs, including the kidney, liver, gastrointestinal tract, lungs, and brain system. **Objective:** The study's objectives were to investigate the impact of COVID-19 infection on liver damage by analyzing a range of indicators such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, C-reactive protein (CRP), and D-dimer protein. **Materials and Methods:** To achieve the study's goal, blood samples were collected from a group of patients (both males and females), and a series of serological tests were performed, including immunological testing and measurements of CRP, D-dimer, and liver function. **Results:** In this study of 80 patients (age range between 17 and 70 years), the female-to-male ratio in both groups was 20:20. The difference in CRP level between study groups was statistically significant ($P \leq 0.001$). The D-dimer level (ng/mL) in patients with infected COVID was significantly higher ($P \leq 0.001$) than in the control group, while there was no statistically significant variation in blood liver enzymes between infected and noninfected COVID groups. According to statistical analysis, there is no discernible gender difference between groups of noninfected people and infected patients. **Conclusion:** The study findings indicate that there are no significant differences between infected males and females when compared to the comparison group; however, there are distinct variances in CRP and D-dimer levels in the infected group. The results of liver function tests and enzyme measurements revealed no significant changes between the infected and healthy groups.

Keywords: Alanine aminotransferase (ALT), alkaline phosphatase (ALP), angiotensin-converting enzyme 2 receptor (ACE2R), aspartate aminotransferase (AST), COVID-19

Introduction

The most severe respiratory effects caused by coronavirus disease (COVID-19) include the common cold, coagulopathy, multiorgan failure, and death. Additionally, it can harm vital organs, including the kidney, liver, gastrointestinal tract, lung, and neurological system.[1,2]

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin levels are abnormal concentration, along with slightly elevated bilirubin, gamma-glutamyl transferase, and alkaline phosphatase (ALP) levels though COVID-19 causes varying degrees of liver damage.[3] Despite the fact that the precise source of liver damage is uncertain, it can be brought on by a direct viral infection of the hepatocytes, immune-related harm, or pharmaceutical hepatotoxicity.[4] In order to impair liver function, it has also been suggested that the virus may adhere to cholangiocytes via the angiotensin-converting enzyme 2 receptor.[5]

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When exposed to infections and wounds, the body uses inflammation as one of its defense mechanisms to protect the tissues. This aids in the diagnosis of inflammatory primary and secondary health issues.[6,7] CRP binds the phosphocholine that is produced on the surface of dead or dying cells as well as some microorganisms. This promotes macrophage phagocytosis, which gets rid of pathogens and necrotic and apoptotic cells and stimulates the complement system.[8]

This so-called acute phase response is brought on by an increase in Interleukin-6, which adipocytes and macrophages produce in response to a variety of acute and chronic inflammatory conditions, including viral, bacterial, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue damage and necrosis.[9]

The AST enzyme, formerly known as serum glutamate oxalate transaminase, is present in all tissues, with the exception of bone. AST can be present in practically every organ of the body, including the skeletal muscles, red blood cells, liver, heart, kidneys, and brain. Since elevated AST is more frequent than elevated ALT and can be an indication of a variety of disorders, including cardiac, pancreatic, anemia, renal, and musculoskeletal diseases, elevated AST is frequently accompanied by further tests to support a diagnosis. Although elevated AST alone is generally specific for liver damage, as was earlier mentioned,[10] elevated AST alone in combination with elevated activity of the likely specific for the renal difficulties.[11]

The ALT enzyme is found in significant quantities in serum and organ tissues, particularly the liver, as well as the kidney, skeletal muscle, and myocardium. ALT levels are lower in the lung, spleen, and pancreas. The blood level of ALT rises and is used as a measure of liver function when there is significant cellular necrosis.[12] ALT levels may be elevated in cases of hepatitis, liver or bile duct damage, myopathy, or congestive heart failure. Diet, physical restraint, and drug administration may have an impact on rodent plasma ALT.[13]

When humans breathe in air that is polluted by the droplets of the virus, COVID-19 can spread. The risk increases the closer people get to one another, even though they may be breathing from a far from the place, particularly indoors. An illness may be transferred by contaminated fluids that spray or leak into the eyes, mouth, nose, or less frequently, on infected surfaces. Despite the fact that they may not have any symptoms, people can spread the illness for up to 20 days.[14] The liver, the main organ only present in vertebrates, is responsible for a wide range of vital biological processes, such as detoxification of the body, protein production, and biochemical needed for development and digestion.[15]

Through the measurement of many indicators, including ALT, AST, ALP, C-reactive protein (CRP), and D-dimer protein, the current study sought to ascertain the impact of liver impairment caused by COVID-19 infection.

Material and Methods

Between October 2021 and February 2022, this study was conducted in the Fallujah Teaching Hospital and Department of Biotechnology at Al-Fallujah University College of Science in Fallujah, Iraq. Of the cases known, 80 (40 men and 40 women) were chosen at random from the lab clinic to participate in the study. A professional provided each patient with a physical examination and collected data for this study relevant to their illnesses at the time the entry was made.

Blood samples collection

At the time of the receiving patients, 5 mL of venous blood was taken using sterile, disposable syringes. In order to allow for the formation of a clot, three milliliters of blood were placed in a simple tube with gel clot. After being let to leave it for an hour at room temperature, the tube was centrifuged for 10 min at a speed of 3,000 revolutions per minute in order to collect the serum (rpm). The serum is extracted with a Pasteur pipette, placed in a sterile Eppendorf container, and stored at -20°C until needed. Collect whole blood into widely available anticoagulant tubes.

To separate the cells, the plasma is spun for 10 min at 1000–2000×*g* in a cooled centrifuge. To eliminate platelets, the plasma sample is spun at 2000×*g* for 15 min. The excess liquid is referred to as plasma or supernatant. The liquid component (plasma) needs to be transferred into a clean polypropylene tube using a Pasteur pipette when centrifugation is finished. The samples should be kept between 2 and 8°C while being handled. If the plasma will not be examined immediately away, it needs to be separated into 0.5 mL aliquots, transported, and maintained at -20°C or lower.

IgM and IgG assay

The tests were completed using VIDAS® SARS-COV-2 IgG and VIDAS® in accordance with the manufacturer's instructions. Automated qualitative tests for SARS-COV. IgM that quickly differentiates antibodies.

D-dimer test

The tests were completed using VIDAS® SARS-COV-2 IgG and VIDAS® in accordance with the manufacturer's instructions. Automated qualitative tests for SARS-COV. IgM that quickly differentiates antibodies.

Sample collection and processing

- ✓ The sample is whole blood or plasma from a patient.
- ✓ Please conduct the test on the sample within 24 h of collection. Within 3 h of collecting whole blood, the plasma should be separated free of the clot.
- ✓ The plasma should be collected in the tube which has been added coagulants.
- ✓ At -20°C, the samples should be frozen. If the test will be delayed further than 24 h.
- ✓ The samples kept frozen at -20°C for three months showed no difference in performance. If heated samples are used.

Test procedure

Multimode

1) Using a pipette, transference 10 µl of the sample (human whole blood, plasma, or control) to a tube containing the detection buffer.
2) Close the detection buffer tube's lid after thoroughly shaking the sample 10–15 times for mix it.
3) Pipette a sample mixture out in 75 mL and put it into the cartridge's sample well.
4) At room temperature for 12 min, leave the sample-loaded cartridge. When the incubation period is over, scan the sample-loaded cartridge as soon as possible. Otherwise, it will result in unreliable test results.
5) Insert the sample-overloaded cartridge into the ichroma™ test device's cartridge holder to scan it. Before squeezing the cartridge, all the methods inside the cartridge holder; be sure it is concerned with correctly. To serve this function, a special arrow is marked on the cartridge.
6) To start the scanning procedure, press the "Select" or "START" button on the Instrument for ichroma™ testing.
7) The sample-loaded cartridge will instantly begin to be scanned by the Instrument for ichroma™ testing.

CRP

CRP can be measured quantitatively determination in human whole blood in serum or plasma using the fluorescence immunoassay ichroma™ CRP. It aids in the management and observation of autoimmune diseases and infectious diseases such as rheumatoid arthritis and infections.

GOT/AST test

The activity of glutamic oxaloacetic transaminase, often known as AST, is measured in serum or plasma, solely for in vitro diagnostic purposes.

Procedure

1. As soon as you switch to a new box of slides, read in the new QC-card.
2. FUJI DRI-CHEM ANALYZER slides set.
3. Place a tube of sample within the specified sample rack.
4. If appropriate, include a sequence number and a sample ID.
5. To start the test, press the "START" key. Consult the "INSTRUCTION MANUAL" for the FUJI DRI-CHEM ANALYZER for further information on the operation process.

GPT/ALT test

The activity of glutamic pyruvic transaminase (alanine: aminotransferase) in plasma or serum is quantified. Use exclusively for in vitro diagnostics.

Procedure

1. When you switch to a new box of slides, read the new QC-card.
2. FUJI DRI-CHEM ANALYZER slides set.
3. Place a tube of sample in the specified sample rack.
4. If appropriate, include a sequence number and a sample ID.
5. To start the test, press the "START" key. Consult the "INSTRUCTION MANUAL" for the FUJI DRI-CHEM ANALYZER for further information on the operation process.

ALP test

Determination of ALP in plasma or serum quantitatively. Only for use in in vitro diagnostics.

Procedure

1. When you switch to a new box of slides, read the new QC-card.
2. FUJI DRI-CHEM ANALYZER slides set.
3. Place a tube of sample in the specified sample rack.
4. If appropriate, include a sequence number and a sample ID.
5. To start the test, press the "START" key. Consult the "INSTRUCTION MANUAL" for the FUJI DRI-CHEM ANALYZER for further information on the operation process.

Statistical analysis

The statistical analysis for this prospective study was performed using Microsoft Excel 2016 and the Statistical Package for Social Sciences (SPSS) 22.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Categorical statistics are based on counts and percentages. To explain numerical data and compare groups, mean, standard deviation, and least significant difference tests were used.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of

Table 1: The characteristics of the study. Comparison between levels of C-reactive protein (>6 mg/L) (CRP) for infected COVID and noninfected COVID of the patients

Status	Noninfected COVID (n = 40)	Infected COVID (n = 40)	Total (80)
Gender: female: male	20:20	20:20	40:40
Age (year) range	15–66	17–69	15–63
C-reactive protein (>6 mg/L) (CRP)	3 (40)	34 (40)	37 (80)

Helsinki. It was carried out with the patient's verbal and analytical approval before a sample was taken. The study protocol, the subject information, and the consent form were reviewed and approved by a local ethics committee according to document number 7662 on March 7, 2021, to get this approval.

Results

Table 1 provides a list of the patients' characteristics. In terms of gender, 50% of Group 1's members were females as opposed to 50% of Group 2's members. Patients in Group 1 ranged in age, although not considerably ($P > 0.05$). When comparing infected COVID to uninfected COVID, the difference in CRP reached a significant level ($P \leq 0.001$).

According to a qualitative CRP test, 3 out of 40 patients with noninfected COVID and 34 out of 40 with infected COVID showed positive results [Table 2]. The difference does signify a significant difference ($P \leq 0.05$). Inflammation's function in the etiopathology of COVID was taken into consideration in a number of research. Therefore, it is expected that this investigation will detect considerable high-level CRP (i.e., 6 mg/L).

As shown in Table 2, the D-dimer level (ng/mL) in patients with Infected COVID was considerably ($P \leq 0.001$) greater than the comparable value in individuals with noninfected COVID in both males and females.

There was no link between the gender factor and changes in the blood level of GOT (U-L) in this study. Males had the reverse effect, with a higher mean level of serum GOT (U-L) in the noninfected COVID comparable level. In females, the mean serum 50.436 43.933 of the noninfected COVID group was lower than the comparable value in the Infected COVID group. The changes in serum GOT (U-L) between infected and uninfected COVID patients were not significant enough to change the serum of GOT (U-L) [Table 3].

The results in Table 4 reveal that there was no relation between the gender factor and changes in the blood level of GPT (U-L) in this study. Males had a higher mean level of serum GPT (U-L) in the noninfected COVID comparable level. In females, the mean serum 67.153 ± 51.522 of the noninfected COVID group was lower than the comparable value in the infected COVID group. The changes in serum GPT (U-L) between infected and uninfected COVID patients were not significant enough to change the serum GPT (U-L).

Table 2: Compared between the level of D-dimer (ng/mL) for infected COVID and noninfected COVID of the patients

Sex	Noninfected COVID mean ± SD	Infected COVID mean ± SD
Female	393.175 ± 264.187	2390.356 ± 408.124
Male	206.171 ± 101.799	1787.115 ± 301.762
Total	297.276 ± 217.268	2088.735 ± 358.85

Table 3: Assessment of GOT (U-L) according to the gender of infected and noninfected patients

Gender	Noninfected COVID mean ± SD	Infected COVID mean ± SD
Female (no.)	50.436 ± 43.933	83.014 ± 58.830
Male (no.)	60.170 ± 51.501	39.533 ± 23.776
Total	55.428 ± 47.589	61.273 ± 49.182

Table 4: Assessment of GPT (U-L) according to gender of infected and noninfected patients

Gender	Noninfected COVID mean ± SD	Infected COVID mean ± SD
Female (no.)	67.153 ± 51.522	65.320 ± 57.364
Male (no.)	53.609 ± 46.719	40.440 ± 22.152
Total	57.561 ± 52.679	53.380 ± 44.337

Table 5: Calculation of ALP (U-L) according to gender of infected and noninfected patients

Status (gender)	Noninfected COVID mean ± SD	Infected COVID mean ± SD
Female	219.74 ± 117.381	123.400 ± 93.674
Male	201.792 ± 128.073	131.168 ± 85.142
Total	210.326 ± 121.666	178.284 ± 116.056

According to the mean and SD of ALP (U-L), there is no statistically significant difference in gender between the noninfected patient category and the infected patient category [Table 5].

Discussion

Individuals with severe COVID-19 are typically treated in the critical care unit, but those with nonsevere or mild cases are commonly treated in the hospital's standard separation unit. A significant challenge is that only a

small percentage of moderate or nonsevere COVID-19 instances advance to a severe illness course.[16,17]

Serum CRP has been identified as a critical marker that changes in severe COVID-19 patients, among other clinical measurements. CRP is a protein generated by the liver that acts as an early sign of infection and inflammation.[18] CRP's normal blood concentration is less than 10 mg/L, but when the illness begins, it climbs fast within 6 - 8 hours and peaks in 48 hours.[19]

CRP levels in COVID-19 individuals were found to be considerably higher, ranging from 20 to 50 mg/L.[20,21] CRP levels in patients with severe COVID-19 have been shown to be 86% higher.[22] Individuals with severe disease courses had significantly higher CRP levels than those with mild or nonsevere disease courses.[23] CRP levels were found to be greater in the severe group than in the moderate group at first. In another study, severe patients had much higher mean CRP levels (46 mg/L) than nonsevere patients (23 mg/L). CRP levels were approximately ten times higher in COVID-19 patients than in recovered individuals (median 100 vs. 9.6 mg/L).[24]

According to a recent study, 7.7% of COVID-19 patients with nonsevere disease histories proceeded to severe illness after hospitalization, and the aggravated patients had significantly higher CRP concentrations than the nonaggravated cases median 43.8 vs. 12.1 mg/L.[25] The progression of nonsevere COVID-19 patients and CRP levels were discovered to be strongly related. Additionally, the authors suggested CRP as a useful biomarker for forecasting the possibility of aggravation in patients with nonsevere COVID-19, with an ideal threshold value of 26.9 mg/L. The likelihood of getting serious illness in COVID-19 patients rises by 5% for every unit of CRP level, according to the scientists[26]

Furthermore, patients with (SpO_2 90%) had considerably greater CRP levels (median 76.5 mg/L) than those with high oxygen saturation (SpO_2 > 90%), who had 12.7 mg/L median CRP levels, showing that more severe patients with lung injury have higher levels of concentration CRP. Higher CRP levels are thus associated with a more severe illness course, a worse prognosis, and lung injury. Because of the significant relationship between CRP levels and the intensity of symptoms in COVID-19 patients, this marker, in conjunction with other clinical data, may be useful in evaluating a patient's status.[14] CRP levels in COVID-19 patients, who may progress from mild to severe instances, need to be more thoroughly explored in large-scale multicenter studies.

Increased levels of D-dimer, a by-product of fibrinolysis' breakdown of fibrin, indicate secondary fibrinolysis and a hypercoagulable state in the human body. It is very beneficial for thrombotic disease detection. Despite reports that patients with the condition were in a hypercoagulable state. Additionally, 25% of patients with severe COVID-19 experienced venous thromboembolism, while 30% of patients with COVID-19 had a pulmonary embolism diagnosis.[27,28]

A cytokine storm may occur as a result of high ferritin levels' direct pro-inflammatory as well as immunosuppressive effects.[29] Numerous researches on hospitalized COVID-19 patients have demonstrated that coagulopathy and overt disseminated intravascular coagulation both have a significant fatality rate. D-dimer elevation was the most efficient predictive predictor of mortality among the 191 cases studied. D-dimer levels are high in 91 nonsurvivors.[30]

The trial's findings revealed that nonsurvivors had considerably higher blood levels of the [d-d] and fibrin degradation products, expanded prothrombin times, and increased partial thromboplastin times than survivors.[31]

Han *et al.*[28] encountered a rise in the level of D-dimer in comparison with controls in 94 cases, Wu *et al.* found an increase in D-dimer levels in ARDS cases, Zhang *et al.* found an increase in D-dimer levels in severe cases in a study of 140 cases, and Gao *et al.* observed an increase in D-dimer quantities in severe cases in a study of 43 cases (28 mild and 15 severe).[21]

It's possible that SARS-CoV-2 enters hepatocytes more easily because it targets the hepatocyte protein ACE2. Furthermore, it has been demonstrated that the ACE quickly binds to the SARS-CoV-2 barbed protein. Our findings support past studies that showed biliary epithelial cells abundantly release ACE, but ALP abnormalities are less common.[32-34] An earlier study discovered that antiviral medications taken by COVID-19 patients may harm the liver, which would enhance the activity of liver enzymes in the blood during COVID-19.[16,35]

According to mean and SD, the difference in Serum Level of GPT (U-L) between females with COVID-19 infection and females who were not infected did not reach a significant level in the gender. Furthermore, there is no evident gender difference between groups of male-infected and noninfected individuals, and there is no obvious gender difference between groups of infected patients and noninfected individuals based on the mean and SE of ALP (U-L).[36]

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Conflicts of interest
There are no conflicts of interest.

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