



Comparison liver and kidney functions among COVID-19 infected patients, recovery period, and healthy subjects

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Authors:

Nidaa taha yassin¹

Mehdi Abbasnejad^{1*}

Saeed Esmaili-Mahani^{1, 2}

1. Department of Biology, Faculty of Sciences, Shahid Bahonar University of Kerman, Kerman, Iran
2. Laboratory of Molecular Neuroscience, Kerman Neuroscience Research Center (KNRC), Kerman University of Medical Sciences, Kerman, Iran

* Corresponding author:

Mehdi Abbasnejad, Ph.D.

P.O.Box: 76135-133

Fax: +98-34-33257432

E-mail: mabbas@uk.ac.ir

ABSTRACT

Introduction: Corona damage a wide range of organs and their functions So, the purpose of this study is to compare the function of kidneys and livers in COVID-19-infected people and people who were in the recovery phase after about five months from the onset of the infection.

Methods: This study was carried out in Samarra General Hospital (COVID-19 epidemic center) in Salahuddin province Iraq from the 1st of January 2022 till the end of December 2022. In The case-control study 100 subjects (men and women 20-80 years), 40 adult people as control with negative RT-PCR or CT-Scan for COVID-19 and no apparent chronic diseases, and 60 subjects (n=30). The blood urea, creatinine as markers of kidney function, alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase, and C-reactive protein (CRP) as markers of liver function by special kits were assessed.

Results: In COVID-19-infected subjects and subjects in the recovery stage, the markers of kidney function, blood urea, and creatinine increased significantly ($p < 0.001$), and in this regard, no difference was seen between the two genders. Similarly, the evaluation of compounds related to liver function, including ALT, AST, alkaline phosphatase, and C-reactive protein, was significantly higher in both affected and recovering patients ($p < 0.001$) compared to healthy individuals. In this case, there was no difference between the two genders.

Conclusion: It seems that not only in COVID-19-infected subjects but also in subjects who have recovered from corona, in both men and women, there are relatively permanent failures in the function of kidneys and liver.

Keywords:

COVID-19, Kidney, Liver, Inflammation.

Abbreviation list:

Alanine aminotransferase (ALT)/ Aspartate aminotransferase (AST)/ C-reactive protein (CRP)/ Angiotensin-converting enzyme 2 (ACE2)/ Renin-angiotensin-aldosterone system (RAAS)/ Glomerular filtration rate (GFR)/ Intensive care unit (ICU)/ Glutamic-oxaloacetic transaminase serum (SGOT)/ Alkaline phosphatase (ALP)/ Lactate-by-lactate dehydrogenase (LDH)/ Nicotinamide adenine dinucleotide (NADH)/ Malate-by-malate dehydrogenase (MDH)/ P-nitrophenyl phosphate (p-NPP)/ Kidney injury (AKI)/ Systemic inflammatory response syndrome (SIRS)/ Acute respiratory distress syndrome (ARDS)/ Acute-phase proteins (APPs)

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INTRODUCTION

Various inflammation agents, chemokines, and cytokines are released in COVID-19-infected subjects. The viral particles due to binding with the angiotensin-converting enzyme 2 (ACE2) receptors on the cell's surface, hyperactivate immune cells and lead to the release of chemokines and cytokines (1).

Urea is synthesized in the liver, and eliminated by the kidneys in the urine. Therefore, its normal concentration is a criterion for the health of these two organs, especially the kidneys (2). The coronavirus enters the kidney cells, duo to binding with ACE2, activates the renin-angiotensin-aldosterone system (RAAS), and changes the function of the organs (3). By

systemic effects it activates RAAS, leading to elevation of water and sodium absorption in the renal tubules, causing passive reabsorption, and secretion reduction of blood urea (4). Creatinine, as the product of the breakdown of creatine phosphate in muscles, is primarily synthesized in the liver and then transported to the skeletal muscle (5). Plasma creatinine concentration is the golden marker, as it filters through the glomerular membranes and does not reabsorbed again by the kidney tubules, for estimating the glomerular filtration rate (GFR) (6, 7). The main causative for kidney damage is an interplay between the coronavirus-induced hyperactive immune response, cytotoxic, and homeostatic reactions to balance the pulmonary hemodynamic response (8). Creatinine levels may be a useful parameter to quickly identify high-risk COVID-19 patients who require intensive management (9).

Alanine aminotransferase (ALT), as a hepatic tissue-specific enzyme, is majorly expressed in the cytoplasm of hepatocytes (10). A significant percentage of COVID-19-infected people show an acute increase in ALT and aspartate aminotransferase (AST) levels (11). AST, also called glutamic-oxaloacetic transaminase serum (SGOT), is released into the bloodstream as a result of a rupture in the cell membranes and an elevated level of AST is a symptom of liver damage (12, 13). 62% of patients with SARS-CoV-2 in the intensive care unit (ICU), and 25% in non-ICU show increased AST levels (14). Alkaline phosphatase (ALP) is present in high concentrations in the liver, bone, placenta, and intestinal epithelium (15). Furthermore, studies regarding COVID-19 patients have demonstrated that elevated levels of ALP show dependency on disease severity and increased mortality (16).

C-reactive protein (CRP) is an acute-phase protein produced in the liver that acts as an early marker of inflammation or infection. It is generally seen at blood concentrations of less than 10 mg/L. CRP levels rise fast during infectious or inflammatory disease states in the first 6 to 8 hours, peaking at 350–400 mg/L after 48 hours (17). CRP plays a role in the opsonization of infectious pathogens and dead or dying cells, it binds to phosphocholine on the surface of damaged cells, triggers the immune system's classical complement cascade, and modulates phagocytic cell action, is a useful marker for observing disease activity (18), CRP

can also produce by Non-hepatic cells (19, 20). Human pulmonary epithelial cells and alveolar macrophages produce CRP, it plays a role in pulmonary host defense and immunological response (21).

According to the mentioned introduction, it seems that the important markers of kidney and liver activity such as creatinine, ALT, AST, ALP, and CRP, are affected by COVID-19, and severity of the disease. Therefore, in the current research, we intend to compare the markers variation in the patient, recovered, and healthy people.

MATERIALS AND METHODS

Participants

This case-control (comparative) study was carried out in Samarra General Hospital (COVID-19 epidemic center) in Salahuddin province Iraq from the period starting the 1st of January 2022 till the end of December 2022. The study included 40 adult healthy people as control (20–80 years) with negative RT-PCR or CT-Scan for COVID-19 and no apparent chronic diseases, 60 adult patients (age 20–80 y) with positive RT-PCR for COVID-19 and/or CT-Scan positive divided into 2 (n=30 per group). Group 1: Patients with severe symptoms and Spo2 less than 93% had been admitted into the intensive care unit (ICU) in the hospital, (15 males and 15 females), group 2: patients with side effects after recovering from the infection over some time (about 5 months) divided into (15 male and 15 female, 20–80y). They had side effects after recovering from the disease throughout the time of patients. Subjects are selected according to questionnaire-basal data for controlling the demographic, confounding, and moderating variables. Blood was collected from patients and a questionnaire was filled, including (age, symptoms, spo2%, chronic illnesses, and CT findings), verbal consent was taken from everyone included in this study whether considered as a case or control. Blood samples were collected, and the tests were performed immediately after the sample was drawn. All experimental protocols were approved by the Ethical Committee of Shahid Bahonar University of Kerman, Kerman, Iran (Approval 4126-9067).

Determination of serum urea concentration

Urea is hydrolyzed by the enzyme urease to give ammonia and carbon dioxide, the

absorbance of the colored complex resulting from the reaction of ammonia with the reagent is measured. The analysis kit (Biolab, France) consists of the reagents, buffer solution (consists of 60 mmol/L of phosphate, pH=6.7), reaction enzymes (It consists of 2 mmol/L of EDTA, ethylene diamine tetra acetic acid, 60 mmol/L of sodium salicylate, and 32 mmol/L of sodium nitroprusside with 30,000 units/L of urease), standard solution (consists of 50 mg/100 cm³ of

standard urea), alkaline solution (consists of 40 mmol/L of sodium hypochlorite with 150 mmol/L of sodium hydroxide. The contents of the tubes were mixed and placed in a water bath at 37 °C for 5 minutes. The absorbance of both the sample and the standard was measured at a wavelength of 590 nm (23). The blood serum urea concentration was calculated according to the following equation:

$$\text{Conc. of urea (mg/dl)} = \frac{\text{A. Sample}}{\text{A. Stander}} \times \frac{\text{C. standard}}{50(\text{mg})/\text{dl}}$$

Determination of serum Creatinine concentration

The concentration of creatinine in the blood serum was estimated using a ready-made kit (Biolab France) based on the colorimetric method of Jaffe and Henry, which relies on the reaction of the creatinine present in the sample with picric

acid ions in a basic medium to produce a red-colored complex of creatinine picrate, which has the highest absorbance at a wavelength of 520nm (23).

Creatine concentration was calculated based on the following equation:

$$\text{Conc of Creatinine (mg/dl)} = \frac{\text{A2 sample} - \text{A1 sample}}{\text{A2 stand} - \text{A1 stand}} \times \text{C. standard}$$

Detectection of ALT

It was assessed by kit (Biolab, France), alanine aminotransferase (ALT/GPT) catalyzes the transfer of the amino group from alanine to oxoglutarate with the formation of glutamate and pyruvate. The latter is reduced to lactate-by-lactate dehydrogenase (LDH) in the presence of reduced nicotinamide adenine dinucleotide (NADH).

The reaction is monitored kinetically at 340 nm by the rate of decrease in absorbance resulting from the oxidation of NADH to NAD⁺, proportional to the activity of ALT present in the sample. After providing the solution according to the kit instructions absorbance of the solution and samples are read at a wavelength of 540 nm (23).

Detection of AST

Aspartate aminotransferase (AST/GOT) catalyzes the transfer of the amino group from aspartate to oxoglutarate with the formation of glutamate and oxalacetate. The latter is reduced to malate-by-malate dehydrogenase (MDH) in the presence of reduced nicotinamide adenine dinucleotide (NADH). The reaction is monitored kinetically at 340 nm by the rate of decrease in absorbance resulting from the oxidation of NADH to NAD⁺, proportional to the activity of AST present in the sample (22). AST level was assessed using a specific kit (Biolab, France).

Detection of ALP

ALP catalyzes the hydrolysis of p-nitrophenyl phosphate (p-NPP) with the formation of free p-nitrophenol and inorganic phosphate, acting as the alkaline buffer as a phosphate-group acceptor. The reaction is monitored kinetically at 405 nm by the rate of formation of p-nitrophenol, proportional to the activity of ALP present in the sample. The kit from (Biolab, France) was used for the evaluation of ALP in the sample (23).

Determination of CRP

The test of sandwich immune detection method was used, the detector antibody in buffer binds to antigen in the sample, forming antigen-antibody complexes, and migrates onto nitrocellulose matrix to be captured by the other immobilized antibody on the test strip. The more antigen in the sample forms the more antigen-antibody complex and leads to a stronger intensity of fluorescence signal on the detector antibody, which had been processed by the instrument for AFIAS tests to show CRP concentration in sample. Afias-6 CRP kit (Boditech, Korea) was used for evaluation of CRP concentration.

STATISTICAL ANALYSIS

Data are presented as mean ±SEM and were analyzed using one-way ANOVAs with statistical

significance set at ($p < 0.05$), the analysis was followed by Tukey's post hoc correction for multiple comparisons where applicable.

RESULTS

The effect of COVID-19 on kidney functions

The current results showed a significant

increase in the concentration of urea and creatinine in the blood ($P < 0.001$) of both male and female patients infected with COVID-19, as well as in the people with recovery period in comparison with control subjects Table 1.

Table 1. Comparison of the urea and creatinine blood levels between the experimental groups according to the male and female data. M: male, F: female. a, b, and c show significance.

parameter levels	GENDER	Control	Recovery period	Patients COVID-19
Urea (mg/dl)	M	26.95 ± 5.67 c	32.93 ± 7.13 b	38.61 ± 3.87 a
	F	30.30 ± 7.73 b c	41.93 ± 5.77 a	37.07 ± 4.00 a
Creatinine (mg/dl)	M	0.3700 ± 0.1031 c	0.4429 ± 0.2681 bc	0.6929 ± 0.3452 a
	F	0.3950 ± 0.0887 c	0.5933 ± 0.3432 ab	0.660 ± 0.3602 a

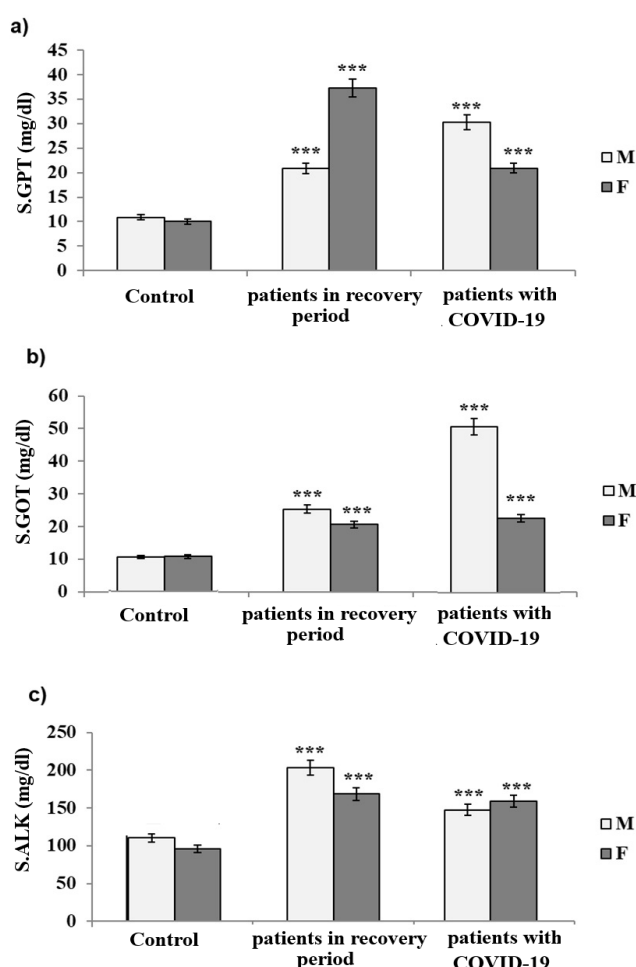


Figure 1. Comparison of the blood levels of SGPT(a), SGOT(b), and ALK (c) between the patients with COVID-19, patients in the recovery period, and control subjects according to the gender.

*** $P < 0.001$ as compared with the control group. M: male, F: female.

The effect of COVID-19 on liver functions

The current results showed a significant ($P < 0.001$) increase in the concentration of GPT (figure 1a), GOT (figure 1b), and ALP (figure 1c)

in the blood level of both male and female patients infected with COVID-19, as well as in people after COVID-19 who recovered from the infection in comparison with the control group.

The effect of COVID-19 on CRP

The current results showed a significant ($P < 0.001$) increase in the concentration of CRP in the blood of patients with COVID-19 (27.79 ± 3.29 mg/dl) and patients in the recovery period (30.31 ± 7.90 mg/dl), in comparison with the control subjects (4.43 ± 1.70 mg/dl) figure 2.

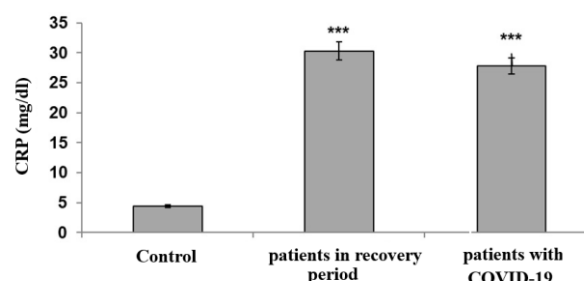


Figure 2. Comparison of the blood level of CRP in the patients with COVID-19, and the patient in recovery period with the control group.

*** $P < 0.001$ as compared with the control group.

DISCUSSION

Here comparison of the blood urea, creatinine, ALT, AST, alkaline phosphatase enzymes, and C-reactive protein of patients with COVID-19, patients in the recovery period, and healthy people showed a marked significant increase in the patients with COVID-19, and patients in recovery period. The changes were seen in both genders.

Previous investigations show the virus attacks the kidney cells directly, specifically the mitochondria of glomerular and proximal tubule

cells. On the other hand, the virus due to activation of immune cells leads to the release variety of inflammation and cytokines agents, the effect causing damage to the kidney, finally causing acute kidney injury (AKI) (24).

Previous studies report that both in subjects who have recently been infected with COVID-19 and in some people in the recovery period, the virus caused serious damage to some organs, especially the kidneys, and impaired their function (17). These results were consistent with the results of the current study. Application of mechanical ventilation for COVID-19 infection leaving the hospital care unit (26), and also certain medications and diuretics during the period (27) produce renal dysfunction.

A study by (Alimurzaeva 2023), indicates coronavirus can cause kidney dysfunction at all ranges ages actually, the blood urea concentration elevation dose not dependent on age (25). Here, we not only showed that the concentration of urea in COVID-19-infected people is high, but its concentration is also high in people in the recovery stage. Creatinine, as a nitrogenous metabolic waste compound, produces during metabolic processes and then excreted in urine, but in the case of infection with COVID-19, the kidneys will gradually lose their normal functions and will and excretion of waste compounds such as creatinine, which leads to an increase in its quantity in the blood. The elevation due to glomerular filtration rate (GFR) reduction and also muscle mass reduction show a significant dependency on age (15).

The current results are consistent with the results of a study by (Salman2023), COVID-19-infected subjects show significant liver dysfunctions associated with the infection (26). Several possibilities may produce an elevation in the liver enzyme concentration, including the pathophysiological effect of the virus Drug-induced liver injury in COVID-19 is possible, application of antipyretic drugs, acetaminophen, hepatotoxic drugs, lopinavir/ritonavir, oseltamivir, interferon, and antibacterial agents. However, checking the Liver function and monitoring were administered (27). Moreover, COVID-19-induced liver injury may be closely related to systemic inflammatory response syndrome (SIRS). The inflammatory cytokines storm induced by the virus leads to excessive immune response (28), and the release of

inflammatory cytokines triggers acute respiratory distress syndrome (ARDS) and SIRS. Such a vicious systematic inflammatory cytokines storm not only produces lung injury but also causes a marked liver injury. Vascular disease, coagulopathy, and thrombosis are other effects of coronavirus that can lead to liver malfunction (29).

Data from a study, show an increase in the levels of liver enzymes for both those infected and people after the recovery period. Data indicate a notable increase in the rate of enzymes in people after recovery, specifically the SGOT concentration rates, the enzyme is considered a very sensitive indicator (3). Both subjects infected by the virus especially people after the recovery period suffer from liver and heart problems and many of them have taken many medications during the period of infection. Therefore, there is a direct effect on the liver due to multiple medications because it is considered a major organ for ridding the body of toxins. This study and the results are consistent with heart studies (30).

In response to infections, the liver cells synthesize and release acute-phase proteins (APPs), such as CRP, an acute inflammatory protein, which is a highly sensitive biomarker for inflammation, tissue damage, and infection (31). CRP binds to microorganisms and promotes their removal through phagocytosis (32). The increased CRP concentration shows a significant link with the overproduction of inflammatory cytokines in severe patients with COVID-19. The Cytokines fight against the microbes but their overproduction can damage lung tissue. Thus, CRP overproduction is induced by inflammatory cytokines as well as tissue destruction in patients with COVID-19 (21). The study showed a significant elevation in CRP in patients even after a long period of recovery, here about five months after the onset of infection.

In conclusion, the results show that the blood urea, creatinine, ALT, AST, and alkaline phosphatase enzymes and C-reactive protein increased in both groups of people infected with COVID-19 during infection and after recovery and the appearance of secondary symptoms. Therefore, the measurement of the markers is not only important for evaluating the beginning of the COVID-19 disease, but also for long-term complications and in the recovery phase is very

important. However, the mechanism of virus action on the observed changes required additional studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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