The Evaluation of COVID Medications' Impact on the Liver Enzymes: A Study on Patients in Al-Ramadi Hospital, Iraq

Mohammed Hashim Mohammed[1], Bilal Jasir Mohammed Aldahham[2*] and Hussein Salim Abed[1]

[1] Department of Medical Laboratory Techniques, Al-Maarif University College, Iraq

[2] Department of Applied Chemistry, College of Applied Sciences, University of Anbar, Iraq.

* Corresponding author: bilalaldahham@uoanbar.edu.iq

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Abstract

This research aims to evaluate the liver enzymes in patients who have recovered from COVID-19 compared to healthy controls. The sample included 69 COVID-19 survivors with liver failure, aged 26 to 66 years (mean age 47.61 ± 11.69). 67 healthy adults aged 19 to 62 years (mean age 36.33) were compared. Pearson correlation (with some differences from Spearman's method) was used to determine the relationship between liver failure and the drugs used during treatment (ceftriaxone, azithromycin, levofloxacin, and remdesivir). The results showed significant differences in ALT, AST, and ALP levels ($p<0.001$), between the two groups. In recovered patients, ALT is associated with ceftriaxone ($R = 0.443$, $p<0.001$) and remdesivir ($R = 0.441$, $p<0.001$). AST levels are similarly associated with ceftriaxone ($R = 0.529$, $p<0.001$), remdesivir ($R = 0.455$, $p<0.001$), and azithromycin ($R = 0.366$, $p<0.001$).

Keywords: Liver enzymes, COVID-19, ceftriaxone, ALT, AST.

Introduction

Studies have shown that coronavirus can affect various organs and vital systems in the human body, especially the heart, lungs, kidneys, liver, nervous system, and blood vessels. However, its effect on fertility and the possibility of vertical transmission are controversial [1-4]. COVID-19 patients with liver disease from the recently emerged SARS virus have recently received special care during their hospitalization [5]. Previous studies have reported the prevalence of chronic liver disease in COVID-19 patients at 2% - 11% [6, 7].

Conditions like hepatitis B or C, lean liver disease, hypertension, and liver transplantation may lead to different outcomes depending on the clinical setting. Be careful when managing people with infectious COVID-19. Approximately 40% of SARS-CoV-2 patients develop hepatitis. During the COVID-19 pandemic, the extent of liver damage and associated clinical features were unclear, and liver disease has been the leading cause of death among COVID-19 patients [8-10]. Furthermore, the adverse effects of COVID-19 are more severe in people with preexisting conditions, making the global crisis even more severe [11].

Research works on the impacts of COVID-19 on liver and lung function include many studies on the effects of drugs on these diseases. Some studies suggest that some treatments may cause liver damage and death in COVID-19 patients [12,13]. We hypothesize that the excessive overuse of many antibiotics may have adverse effects on liver function. Therefore, this study aims to evaluate liver enzymes in individuals who have recovered from COVID-19 by comparing different liver function tests with healthy controls. In addition, this study

investigated the relationship between drug use and liver enzyme tests.

Materials & Methods

Patients

This study included 146 samples divided into two groups: 69 people who have recovered from COVID-19 and 67 healthy people as a control group. The research period to collect the samples is from October 2021 to March 2022. Laboratory analysis has been carried out at the Biochemistry Department of Al-Ramadi Teaching Hospital and Al-Shafaa Specialized Laboratory (private facility).

Ethical Consideration

The Institution's Ethics Committee gave its permission before any subjects had been enrolled. The goals and specific steps involved in drawing blood and doing imaging. Participants in the study were informed of their eligibility for this research. It was emphasized that taking part in this study was optional. Forms of written consent were acquired from every subject who consented to participate in the research.

Blood Sample Collection

Peripheral venous blood samples (5 ml) were collected using disposable syringes into EDTA tubes and the tubes were centrifuged for (10) minutes (1500 xg). Plasma has been collected and stored at -20°C until use.

Methods:

Blood samples have been analyzed for enzymes to test liver functions. Aspartate aminotransferase AST, Alanine aminotransferase ALT, and Alkaline phosphatase ALP levels had been estimated (Cromatest Linear chemicals S.L.U. Barcelona Spain), with code numbers B1105-2/0901, B1109-2/0901, and B1102-2/0901 respectively.

Statistics:

Data have been analyzed by one-way analysis of variance, Pirate City's Graph Pad prism 8 has been used to calculate statistical significance. A p-value of less than 0.05 is required for significance ($p \leq 0.05$).

Results and Discussion:

This study compared liver function markers, specifically liver enzymes, between two groups: 69 people recovered from COVID-19 and 67 healthy control samples.

The findings showed that ALT levels have increased between COVID-19 patients and healthy controls ($p<0.0001$), as shown in Figure 1. The standard ALT range is 4-36 U/L [14,15]. Table 1 shows the relationship between high ALT levels in COVID-19-recovered patients, and some drugs used in treatment. It is noteworthy that ceftriaxone, azithromycin, and remdesivir were associated with increased ALT (correlation coefficients $p<0.001$, $p<0.01$, and $p<0.001$ are stronger than Levofloxacin). Some antibiotics can directly cause hepatotoxicity, hence damaging liver cells in the liver lobules, and causing cell apoptosis and necrosis. The findings of elevated ALT and its association with ceftriaxone are consistent with previous studies [16].

Azithromycin may initially cause liver injury, which rapidly resolves after discontinuation of the drug. Although azithromycin-induced cholestatic liver injury is well known, this is only the third case of direct hepatocellular injury [17]. Our observations of azithromycin-induced increases in ALT levels are consistent with previous studies [18]. The results are consistent with those of Kim et al. (2021) who have reported that remdesivir use was associated with an increase in ALT levels, likely due to its direct effect on mitochondrial RNA polymerase inhibition [19, 20]. Despite some limitations, a pharmacovigilance review provides real-world data supporting an association between remdesivir and hepatobiliary adverse drug reactions (ADRs), such as elevated ALT and AST, despite the immediate risk of heart failure. It is important to pay close attention to liver and biliary health while taking remdesivir to avoid overdose.

Figure 2 compares the AST enzyme level in healthy controls and individuals who recovered from COVID-19 and shows that AST was higher in the recovered group ($p<0.0001$). Antibiotics and other treatments may increase the number [21, 22]. Table 1 shows the relationship between all drugs used in the study and AST level, as shown by the Pearson correlation coefficient.

According to previous studies, ceftriaxone has the best correlation with increased AST levels with a significance correlation of 0.592 ($p < 0.001$) indicating its effects on the liver [23]. Its ability to bind calcium can cause the formation of non-toxic stones in the gallbladder, leading to gallstone disease or gallstones. This phenomenon has also been observed in animal models, suggesting that it is not specific to humans. In addition, ceftriaxone calcium salt can accumulate in the urine, form sludge in the urine, and cause obstruction or stone formation in the kidneys and bladder. Acute cholestatic liver injury caused by ceftriaxone is rarely due to allergic reactions [24].

Additionally, remdesivir, azithromycin and levofloxacin have been associated with the increase of AST levels ($p<0.001$, $p<0.001$ and $p<0.05$, respectively), but the correlation coefficient for levofloxacin was lower at 0.212.

Figure 3 shows a statistically significant difference ($p<0.0001$) comparing the ALP levels of the two study groups. Differences between our findings and other references may be due to the fact that we measured total ALP instead of liver-specific isoenzymes [24, 25]. However, our results are consistent with those reported by Bloom et al. [26]. The alkaline phosphatase normal range is 30-120 IU/L, and some measurements are found outside this range. This may be due to increased levels of various ALP iso-enzymes, particularly those related to bone, as well as enzymes that are increased due to COVID-19 infection and drug use. According to the alkaline phosphatase correlation coefficient analysis, remdesivir alone was associated with increased ALP levels.

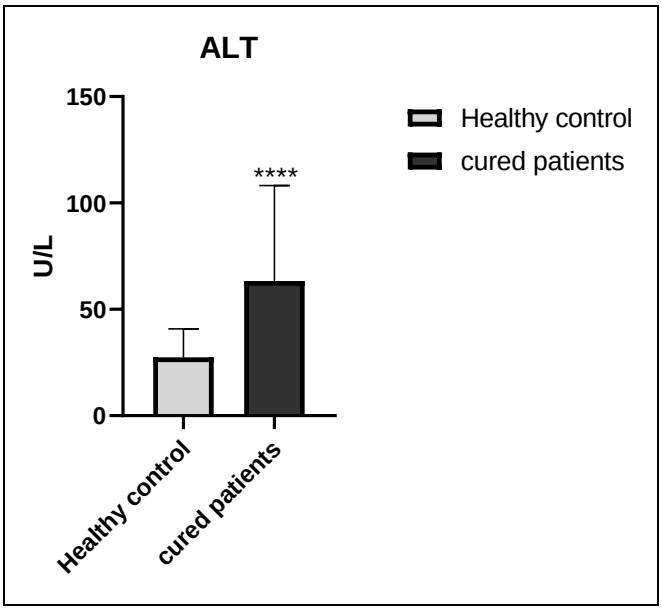

Figure 1: ALT concentration in study groups

Table 1: Pearson's correlation (r values) of enzymes with antibiotics.

	ALT	AST	ALP
ALT		0.832***	-0.27**
AST	0.832***		-0.282***
ALP	-0.27**	-0.282***	
Ceftrixone	0.443***	0.529***	-0.301***
Levofloxacin	0.158	0.212*	-0.111
Azithromycin	0.229**	0.366***	-0.322***
Remdesivir	0.41***	0.455***	-0.281***
* flag: p<0.05, ** flag: p<0.01, and *** flag: p<0.001			

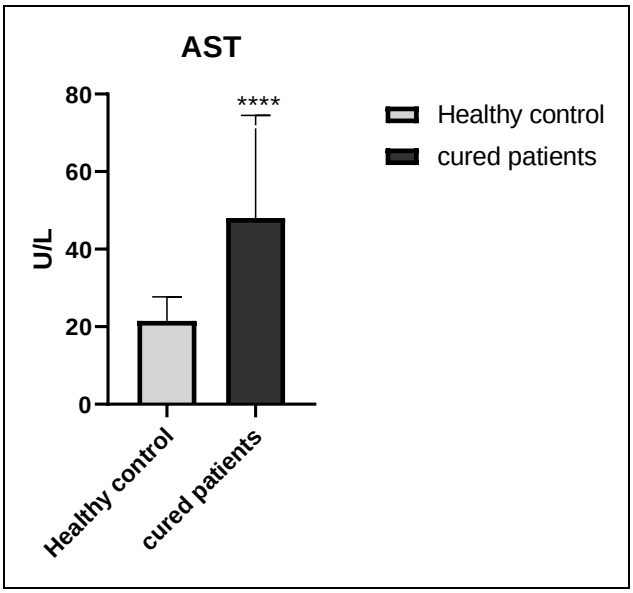

Figure 2: AST concentration in study groups

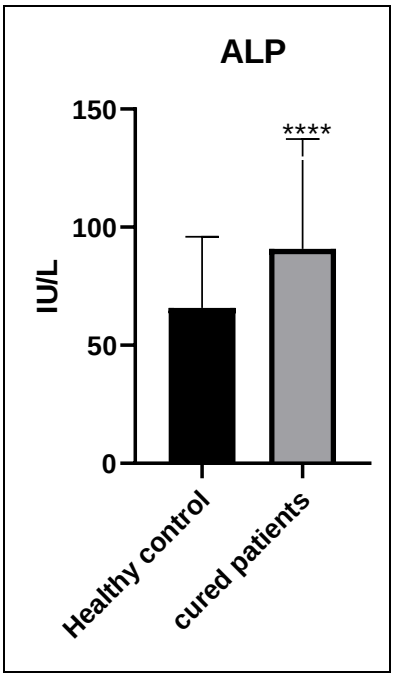

Figure 3: ALP concentration in study groups

Conclusions:

The use of many antibiotics may affect liver functions, especially liver enzymes such as ALT, AST, and ALP. Significant differences have been observed between individuals who have recovered from COVID-19 and healthy controls. Among the antibiotics studied, ceftriaxone had a high effect on liver enzymes, especially ALT and AST, while azithromycin had a small effect, hence, this variable should be regularly monitored during treatment.

Conflict of interest: None

Funding: None

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