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STUDY THE EFFECT OF MEDICATINS USED FOR COVID PATIENTS ON LIVER FUNCTION IN IRAQI PEOPLE

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Jun 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

STUDY THE EFFECT OF MEDICATINS USED FOR COVID PATIENTS ON LIVER FUNCTION IN IRAQI PEOPLE

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Master of Science in Chemistry

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ALDAHHAM Jun 2022

The aim of this study is to compare the liver functions of patients recovering from Covid-19 to those of a healthy control group. Additionally to discover the relationships between the recovered group's liver functions and the medications they were taking, For the safety of the liver from damage. The study comprised 69 persons recovering from Covid-19, with an age range of (26-66) years, and their liver functions were compared to a group of 67 healthy adults with ages ranging of (19-62) years. The Pearson correlation was used to evaluate the relationship between the parameters and the medications (Ceftriaxone, Azithromycin, Levofloxacin, and Remdesivir) that were taken by the persons in the group recovering from Covid-19, The results showed that there were significant differences in the levels of enzymes ALT, AST, ALP, LDH, and albumin between the two study groups ($p<0.001$), while the results did not show any significant differences in total protein concentration between the two groups ($p>0.05$). The ALT concentration had a significant $p<0.001$ correlation with ceftriaxone $R=0.443$ and remdisivir $R=0.441$ in the group of recovered patients, while the AST enzyme had a significant correlation $p<0.001$ with ceftriaxone $R=0.529$, remdesivir $R=0.455$, and Azithromycin $R=0.366$. While LDH had a high correlation with azithromycin ($\rho=0.566$), ceftriaxone ($\rho =0.517$), and remdesivir ($\rho =0.346$).

2022, 40 pages

Keywords: ALP, AST, ALT, LDH, Total bilirubin, Albumin, Covid-19

ÖZET

IRAK İNSANLARINDA KOVİD HASTALARINDA KULLANILAN İLAÇLARIN KARACİĞER FONKSİYONU ÜZERİNE ETKİSİNİN ÇALIŞMASI

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Haziran 2022

Bu çalışmanın amacı, Covid-19'dan iyileşen hastaların karaciğer fonksiyonlarını sağlıklı kontrol grubu ile karşılaştırmaktır. Ayrıca iyileşen grubun karaciğer fonksiyonları ile aldıkları ilaçlar arasındaki ilişkileri keşfetmek, karaciğerin hasar görmemesi için ve karaciğer fonksiyonları yaşları (19-62) arasında değişen 67 sağlıklı yetişkinden oluşan bir grupla karşılaştırılmıştır. Kovid-19 hastalığından iyileşen gruptaki kişilerin aldığı ilaçlar (Ceftriaxone, Azitromycin, Levofloksasin ve Remdesivir) ile biyokimyasal parametreler arasındaki ilişkiyi değerlendirmek için Pearson korelasyonu kullanılmıştır. ALT, AST, ALP, LDH ve albümin enzim seviyeleri iki çalışma grubu arasında anlamlı sonuçlar ($p<0.001$) bulunurken, iki grup arasında toplam protein konsantrasyonun anlamlı bir farklılık göstermediği tespit edilmiştir ($p>0.05$). ALT konsantrasyonu, iyileşen hasta grubunda seftriakson $R=0.443$ ve remdisivir $R=0.441$ ile anlamlı bir $p<0.001$ korelasyona sahipken, AST enzimi ile seftriakson $R=0.529$, remdesivir $R=0.455$ ve Azitromisin $R=0.366$. LDH, azitromisin ($\rho=0,566$), seftriakson ($\rho=0,517$) ve remdesivir ($\rho=0,346$) ile yüksek bir korelasyona sahip olduğu tespit edilmiştir.

2022, 40 sayfa

Anahtar Kelimeler: ALP, AST, ALT, LDH, Total bilirubin, Albümin, Covid-19

PREFACE AND ACKNOWLEDGEMENTS

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Mohammed Hashim Mohammed MOHAMMED
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LIST OF SYMBOLS

%	Percent
±	Plus-minus
°C	Degrees Celsius
dL	Deciliter
g	Gram
IU	International unit
L	Liter
mg	Milligram
mL	Milliliters
ng	Nanogram

LIST OF ABBREVIATIONS

ALP	Alkalin Phosphatase
ALT	Alanine aminotransaminase
AST	Aspartate aminotransferase
LDH	Lactate dehydrogenase
LFT	Liver funcion tests
T Bil	Total bilirubin
TP	Total protein

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1. INTRODUCTION

The SARS-Cov-19 epidemic has been a severe public health threat since 2019 (Hu *et al.* 2020). There were roughly 37 million laboratory-confirmed COVID-19 infected persons globally by the end of October 12th, 2020, with over 3 million of them dead. The total case fatality rate was above 7%, with higher rates among the elderly, males, and those with basic illness (Chen *et al.* 2020, Huang *et al.* 2020). Multiple organs and systems in the human body, including the lungs, heart, kidneys, liver, neurological system, and blood system, have been shown to be damaged by the corona virus (Sahu and Siddiqui 2020, Fan 2020).

However, the impact on the reproductive system and whether or not vertical transmission occurs between people are still debated (Dashraath *et al.* 2020). If patients with diabetes, high blood pressure, cancer, heart disease, nephropathy, or liver infection catch coronavirus, they are more likely to develop many symptoms and have a difficult time recovering or dying. Furthermore, they must assess the risks and benefits of providing therapy against the possibility of infection, particularly for cancer patients (Jindal *et al.* 2020). Based on the previous SARS epidemic's experience, COVID-19 patients with liver infection have lately received extra treatment during hospitalization (Li *et al.* 2021). COVID-19 individuals with underlying chronic liver problems were shown to have a prevalence of 2%–11% in previous research (Zhang, Shi, and Wang 2020). COVID- Because chronic hepatitis B or C, nonalcoholic fatty liver disease, liver cirrhosis, and liver transplantation have different clinical outcomes depending on the clinical setting, 19 patients with liver problems should be carefully handled (Lui *et al.* 2020). Hepatic problems have been observed in around 40% of SARS covid-19 patients.

The incidence of liver damage and associated clinical features in the current COVID-19 outbreak are unknown. COVID-19 people have died as a result of liver illness (Phipps *et al.* 2020), and the negative effects of COVID-19 are harsher in people who have liver infaction or damage, leading in the global pandemi (Pawlotsky 2020). Acute increases in ALT and AST levels after hospitalization are the most common signs of hepatic

function injuries (Fu *et al.* 2020). The study of the side effects of corona virus on liver and lung function necessitated thousands of hours of research on the effects of drugs and tablets used to treat corona virus on the liver and lung functions. Some studies claim that some protocol treatments caused liver damage and death in corona virus patients. The follow-up investigation is critical for a better knowledge of the sickness, especially in terms of observing issue recovery and recurrence. For this experiment, we used 150 covid-19 patients who had recovered and left the alrmadi hospital education-iraq.

We hypothesize that overuse of antibiotics, as well as the use of many types of antibiotics, has a deleterious influence on liver function in general. As a result, the purpose of this study is to evaluate liver function in individuals who have recovered from a covid-19 attack and compare their parameters related to liver function to a control group of healthy people. Researchers looked at the overall relationship between liver functioning as well as the relationship between drugs used and each indicator.

1.1 Aim of Study

1. Evaluate the proper course of antibiotic given through covid-19 attack
2. Assesment the use of other medications on liver function.
3. Prospect of liver function recovering from injury.

2. LITERATURE REVIEW

2.1 Coronavirus Disease 2019

Acute respiratory syndrome with severe symptoms Coronavirus 2 is a virus that causes an infectious sickness (SARS-CoV-2) (Hsu *et al.* 2020).

Coronaviruses belong to the Nidovirales order's Coronaviridae family (Pyrc *et al.* 2004). At the end of 2019, a run of pneumonia cases with unknown reasons emerged in Wuhan, China (Lu *et al.* 2020). The World Health Organization (WHO) classified Covid-19 a global pandemic on March 11, 2020, due to its rapid spread (Guan *et al.* 2020). Coronavirus is named from the crown-like spikes that appear on the virus's surface (Erener 2020). The Covid-19 is the third novel coronavirus to cause a wide-ranging epidemic in the twenty-first century, following the Severe Acute Respiratory Syndrome (SARS-CoV) outbreak in southern China in 2003. The Middle East Respiratory Syndrome and the year 2012 in Saudi Arabia (MERS-CoV) (Alanagreh *et al.* 2020). The coronavirus family is organized into four subgroups as shown in Figure 2.1: alpha (α), beta (β), gamma (ɤ), and delta (δ). Only alpha and beta coronaviruses can infect humans. The genomic analysis showed that SARS-2 belongs to the Beta coronavirus group (COVID 2020).

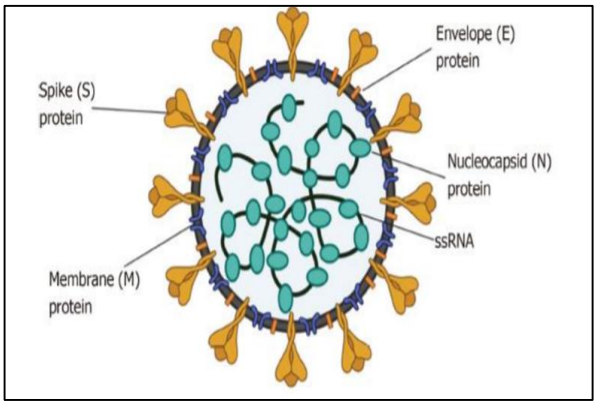

Figure 2.1 Schematic diagram of the structural features of coronavirus (Galanopoulos Doukatas and Gazouli 2020)

Coronaviruses are a group of Viruses that cause respiratory and gastrointestinal illnesses in both Animals and Humans. (Dong *et al.* 2019). These viruses typically affect the upper respiratory system, resulting in Mild to severe illnesses such as the Common cold or, in more Severe cases, pneumonia. To far, seven human coronaviruses have been discovered, including the three epidemic viruses of SARS-CoV, MERS-CoV, and the newest, SARS coronavirus 2. (SARS-CoV-2) (Niu *et al.* 2016). More than half of the genomic sequences of these three pandemic viruses are almost identical. (Lu *et al.* 2020). A rash of pneumonia cases of unknown origin began to spread in Wuhan, China's capital, in December of this year. The virus, now known as SARS-CoV-2, has infected around 300,000 people worldwide by March 2020. (Jia *et al.* 2019). The WHO has designated the coronavirus infection (COVID-19) a pandemic, citing hundreds of deaths and hospitalizations around the world. While the majority of COVID-19 cases are minor, some severe cases have resulted in respiratory failure, septic shock, and/or multiple organ dysfunction. (Wu and McGoogan 2020). More clinical and epidemiological characteristics must be uncovered as this infectious disease spreads in order to better understand the virus's true reach, improve diagnostic and treatment capabilities, and reduce overall morbidity and mortality. COVID-19's impact on other organs has recently been revealed, with multiple publications claiming that more than half of COVID-19 patients had varying degrees of liver dysfunction. (Chau *et al.* 2004). According to a new study, the SARS-CoV-2 virus may bind to cholangiocyte angiotensin-converting enzyme 2 (ACE2), causing cholangiocyte dysfunction and triggering a systemic inflammatory response that ends in liver injury (Chai *et al.* 2020). As of March 10, 2020, seven major hospital-based research had uncovered the clinical characteristics of COVID-19 patients, as well as some insights into other factors that may contribute to COVID-19-induced liver damage (Chen *et al.* 2020, Huang *et al.* 2020). In these studies, the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found to be high, ranging from 14 percent to 53 percent (Yang *et al.* 2020). Furthermore, a histological study of liver biopsy specimens from a COVID-19 patient revealed significant microvesicular steatosis as well as modest lobular and portal activity, showing that SARS-CoV-2 was responsible for the liver damage. However, data on further liver enzymes and clinical characteristics of liver failure in COVID-19 people is limited. As a result, the goal of this study was to

chronicle the clinical course of COVID-19 patients admitted to Shenzhen's only referral hospital, as well as the results of liver tests. With a greater understanding of pathophysiology, more tailored treatments and holistic care approaches could be developed to help COVID-19 patients avoid severe liver disease or failure (Xu *et al.* 2020).

2.1.1 Coronavirus genome structure

Coronavirus has a positive-sense RNA genome, an envelope, and a helical capsid. Their genomes are the largest of any RNA viruses, ranging in size from 27 to 32 kb (Li 2015). The genomic structure of Covid-19 has at least six open reading frames (ORFs) (Amini Pouya *et al.* 2020). The first ORFs (ORF1a/b) encode polyprotein1a,b and are found near the 5 end of the genome, around two-thirds of the way down (pp1a, pp1b) (Alanagreh *et al.* 2020) (Amini Pouya *et al.* 2020). At least four structural proteins are coded for by ORFs on three ends: Spike (S), membrane (M), envelope (E), and nucleocapsid (N) (Huang *et al.* 2020). The spike (S) protein recognizes host cell receptors, while the envelope (E) protein is in charge of virions' construction and release. The membrane (M) protein is responsible for viral shape, whereas the nucleocapsid (N) protein is involved in RNA genome packing and virions (Figure 2.2), as well as acting as an interferon (IFN) inhibitor (Pyrc *et al.* 2004, Gennaro 2020, Erener 2020).

Figure 2.2 Schematic representation of the genomic structure of Covid-19 (COVID 2020)

2.1.2 Angiotensin-converting enzyme (ACE2)

Angiotensin-converting enzyme is expressed in a variety of human organs and tissues, including alveolar and intestinal epithelia, as well as vascular endothelial cells in the heart, kidney, and lung (ACE2) (Leonu and 2017). The initial step in viral infection is to infect host cells. A spike glycoprotein in the coronavirus's envelope can attach to specific receptors on host cell membranes. According to research, SARS-CoV has a separate functional receptor termed ACE 2 (Ni *et al.* 2020). The gastrointestinal and respiratory tracts, which both have high ACE2 levels, could be the main entrance points for SARS-CoV-2 infection. Males have higher ACE 2 expression, and ACE 2 is detected in diabetes and heart failure (Abassi *et al.* 2020).

2.1.3 The life cycle of SARS-CoV-2 in host cells

The virus's life cycle begins when the Spike (S) protein binds to the cellular receptor ACE 2. After interacting with the ACE2 receptor, the Spike protein undergoes a conformational change that aids viral envelope fusion with the cell membrane via the endosomal pathway. Following that, SARS-CoV-2 injects genomic RNA into the host cell (Amini Pouya *et al.* 2020). Viral clones Polyproteins 1a (pp1a and 1ab) are translated into RNA, which is then broken down by viral proteinases into minute fragments. The polymerase manufactures a series of sub genomic mRNAs, which are eventually translated into viral proteins, by discontinuous transcription. In the endoplasmic reticulum (ER) and Golgi, viral proteins and genomic RNA are gathered into virions, which are then transported and released out of the cell via vesicles. (Huang *et al.* 2020, COVID 2020).

2.1.4 Liver function tests

The liver is a multipurpose organ that serves as the body's metabolic hub, producing and excreting bile. Bilirubin, cholesterol, hormones, and medicines are also secreted. It is involved in fat, protein, lipid, and carbohydrate metabolism, as well as the storage of

glycogen, vitamins A, D, B12, and minerals. Albumin and clotting factors are examples of plasma proteins. Blood cleansing and detoxification (Fu *et al.* 2021)

Liver Function Tests are one of the commonly requested examination blood tests. Total protein, ALT,AST, L-lactate dehydrogenase, Bilirubin, Alkaline phosphatase (ALP), Albumin, total protein, L-lactate dehydrogenase (LDH) (Hall and Cash 2012).

2.1.5 Alanine aminotransaminase

This enzyme is found mainly in kidney and highest concentration in liver cells. The body uses ALT to metabolize protein and breakdown food to product energy. Normal Serum ALT value is (7–56) U/L. Any kind of injury to liver cells lead to increase ALT enzyme level (Gitonga *et al.* 2015). In the liver, the ALT enzyme catalyzes the transfer of amino groups from L-alanine to ketoglutarate, resulting in L-glutamate and pyruvate (TCA). This action requires pyridoxal phosphate, a coenzyme (Liu *et al.* 2014)

2.1.6 Aspartate aminotransferase

AST is an enzyme that is found in larger amounts in the muscles, kidneys, liver, and heart. When the liver is harmed, the AST enzyme might escape into the bloodstream. The normal range for serum AST is 0 to 35 U/L. High mitochondrial AST is seen following myocardial infarction, severe tissue necrosis, and acute liver disorders like liver tissue degeneration and necrosis (Giannini *et al.* 2005).

When sickness or injury to human tissues or organs like the liver or heart occurs, more AST and ALT are released into the bloodstream, resulting in higher levels of the enzymes. As a result, AST and ALT blood levels are proportional to tissue injury severity. After a serious injury, AST levels climb 10 to 20 times higher than normal, whereas ALT levels rise significantly higher (up to 50 times higher than normal) (Huang *et al.* 2006).

2.1.7 Alkaline phosphatase

Your liver, digestive system, kidneys, and bones all contain the enzyme alkaline phosphatase. A high ALP level may indicate liver disease, sickness, bone disease, or a plugged bile duct. A high ALP is usually only a brief and minor worry. ALP levels may be higher in children and teenagers than in adults. ALP levels can be reduced with a combination of medications (Sharma *et al.* 2014).

The typical range of ALP varies by age and pregnancy status. ALP levels are higher in children because their bones are still growing, and they rise during pregnancy as the placenta develops and delivery approaches (Mutua, Njagi, and Orinda 2018). Children (under 350 U/L), Adults (40 to 14 U/L), Pregnacy (First trimester) (17– 88 U/L), Pregnacy (second trimester) (25– 126 U/L), Pregnacy (Third trimester) (38– 229 U/L) (Verma *et al.* 2012). ALP levels that are outside of these ranges are deemed abnormal. Abnormal ALP readings are not diagnostic on their own, although they can hint at the underlying reason.

2.1.8 Bilirubin

Bilirubin is one of the end products of heme metabolism and is derived from the heme part of the hemoglobin molecule. It is a yellowish pigment. The liver plays a key role in bilirubin metabolism (Erlinger *et al.* 2014). It is insoluble in water after the heme of the hemoglobin molecule (unconjugated bilirubin) is broken down. It is transported from the spleen, which is the site of RBC and heme breakdown, to the liver for (conjugation) linkage to albumin. The enzyme glucuronyl transferase in the liver conjugates bilirubin with glucoronic acid. Bilirubin becomes water Eoluble after this conjugation, and it is excreted through the bile (Wang *et al.* 2006).

2.1.9 Covid-19 and LFT

The liver acts an important function in host defense versus microbes and it is participate in most systemic infections where it receives both the systemic and portal circulation. Hepatocytes and cholangiocytes are directly affected by some viruses. (Alqahtani and Schattenberg 2020). Since several investigations of coronavirus patients have proven the presence of the virus in liver tissues, virus infection of liver cells may induce liver damage in people with coronavirus infections (Ridruejo and Soza 2020). The presence of diarrhea in 2 to 10% of patients, as well as Covid-19 RNA in Covid-19 patients' blood and stool, suggests that the virus is contained in the liver. Angiotensin-converting enzyme 2 (ACE2) is a receptor for coronavirus entry in both liver and bile duct cells (Ali 2020). The release of transaminase due to skeletal and cardiac muscle breakdown is another factor that could cause abnormal liver tests in Covid-19. Covid-19 is now known to cause venous and arterial thrombosis, particularly in the liver, where it may play an important role in biochemistry (Marjot *et al.* 2021). Several antiviral medicines, antibiotics, and steroids used to treat moderate to severe disease in people with Covid-19 have been linked to liver damage. Liver infections can produce systemic immunological inflammation, which can contribute to disease development. In the majority of severe cases, the presence of high levels of proinflammatory cytokines such as Tumor Necrosis Factor alpha (TNF-), Interleukin 6 (IL-6) and Interleukin 1 beta (IL-1) shows cytokine storm syndrome, which may be linked to illness severity. Hepatic ischemia and hypoxia reperfusion dysfunction can be produced by COVID-19's hypoxia and shock (Amin 2021).

2.2 Acute-Phase Protein

The acute-phase response describes how the body reacts to infection, inflammation, or trauma. It comprises a variety of pathophysiological reactions such as fever, leukocytosis (an increase in the amount of white blood cells), hormone changes, and muscle protein depletion, all of which work together to limit tissue damage while promoting the healing process (Van Dijk *et al.* 2013). Acute phase protein classification: 1. Positive acute-phase proteins cause inflammation and contribute to

various immune system physiological processes. CRP, ferritin, and other proteins, for example, harm or limit the growth of microorganisms. 2. Reduced inflammation due to negative acute-phase proteins. Inflammation is indicated by a lack of these proteins. Albumin and other proteins are examples (Grönlund *et al.* 2005)

2.3 Albumin

HSA is a 585-amino-acid protein produced by a gene on chromosome 4 that has a higher acidic amino acid ratio than other proteins, giving it a negative charge and a pH of 7. Eight helices form a heart-shaped tertiary structure in serum albumin (Spinella *et al.* 2016). Hepatocytes produce albumin, which is rapidly secreted into the bloodstream at a rate of 10 to 15 grams per day. The liver stores a limited amount of albumin, and the rest is discharged into the bloodstream (Moman and Varacallo 2018). Insulin, cortisol, and growth hormone enhance albumin production, while interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) inhibit it (TNF-) (Caraceni *et al.* 2013).

Serum albumin acts as an important modulator of oncotic pressure of plasma and a carrier of endogenous (cholesterol, fatty acids, bilirubin, thyroid hormones) and exogenous (drugs and toxins), Nitric oxide gas and transition metal ions. Also antioxidant and anti-inflammatory actions (Nicholson *et al.* 2000).

2.3.1 Covid-19 and albumin

One of the most common laboratory abnormalities in Covid-19 infection patients is hypoalbuminemia (>32 g/L), which was more obvious in severe cases than lightmoderate infections. The mechanism of hypoalbuminemia and its relationship with respiratory system impairment and clinical result yet needs to be illustrated (Bassoli *et al.* 2021). Hypoalbuminemia is a common lung illness symptom that can be detected early on. It is linked to inflammatory symptoms and clinical outcomes. Otherwise, the cytokine storm that followed in Covid-19 states that were hospitalized could cause severe hypoalbuminemia (Karakoyun *et al.* 2021). Acute hypoalbuminemia is linked to

a poor prognosis and necessitates medical treatment. As a result, understanding how Covid-19 viruses affect hepatic hepatocyte protein production is crucial. One possibility is that Covid-19 damages the liver and causes hepatitis (Huang *et al.* 2020).

2.4 Lactate Dehydrogenase

Lactate dehydrogenase is a cytoplasmic enzyme that catalyzes the anaerobic reversible conversion of pyruvate to lactate. Because of its widespread distribution in human tissues, the activity of this enzyme rises dramatically in blood after cell injury caused by a variety of clinical conditions (Buonocore *et al.* 2016). Lactate dehydrogenase (LDH) is an enzyme involved in glucose metabolism. LDH can be found in all cells, but it is especially abundant in cardiac and skeletal muscles, kidneys, liver, and red blood cells. LDH is composed of five isoenzymes: LDH1, LDH2, LDH3, LDH4, and (LDH5). Electrophoresis can be used to separate these LDH isoenzymes (Alkhatib and Alrakaf 2019). Lactate dehydrogenase, a common cellular enzyme, is elevated in the blood after tissue damage. As a result, elevated serum LDH levels are observed in a wide range of clinical situations, such as hemolysis, cancer, sepsis and acute infections, Meningitis, encephalitis, and infarction of the brain (brain inflammation), Infections and infarctions of the lungs, liver disorders, pancreatitis is the inflammation of the pancreas (pancreas inflammation), Myositis and muscle injury, Hematologic cancers, HIV infections, and a variety of other conditions (Erez *et al.* 2014).

2.4.1 Lactate dehydrogenase and Covid-19

On arrival to the hospital, higher lactate dehydrogenase (LDH) values were associated to the severity of Covid-19 infection. Neuophilia, organ failure, and coagulation dysfunction (as seen by high lactate dehydrogenase levels) have all been linked to mortality in individuals with acute respiratory syndrome (SARS). The presence of lactate dehydrogenase in the blood indicates tissue injury, necrosis, and hypoxia. In sepsis patients, high LDH levels may be a crucial predictor and indication of mortality (Vidal-Cevallos *et al.* 2021). When you have acute lung injury or an interstitial lung infection, your LDH level rises. Increased LDH levels in Covid-19 patients who are

severely sick can indicate an increase in the activity and severity of lung damage (Tjahyadi *et al.* 2020) However, the critical mechanism underlying the relationship between LDH and the development of Covid19 illness is yet unknown. In most studies, serum LDH levels rise as a result of significant tissue and organ damage caused by viral attack or inflammation (Prenissl *et al.* 2019).

3. MATERIALS AND METHODS

3.1 Subjects

In the present study we take 150 sample into tow groups, 75 patients have Covid-19, and 75 subjects as healthy control group for comparison. The study was throughout the period since from oct 2021 to March 2022. The samples of Covid-19 patients were collected from Al-rmadi education Hospital. The laboratory examination was carried out in the laboratory of biochemistry unit in Al-rmadi Teaching Hospital and also in Al shfaa Specialized Laboratory in Al-shfaa specialized hospita province.

3.2 Instruments and Tools

Table 3.1 lists the study's tools, along with the business and country of origin.

Table 3.1 The tools used in the current study

NO.	INSTRUMENTS	COMPANY	SOURCE
1	Centrifuge	Kokusan	Japan
2	Vortex	Cypress Diagnostics	Belgium
3	stop watch	Sories	China
4	Incubator	Yamato	Japan
5	Spectrophotometer	Erba	German
6	Mini-vidas	BioMerieux	France

Table 3.1 lists the study is tools, along with the business and country of origen.

Table 3.2 Instruments used in the current study

NO	TOOLS	COMPANY	SOURCE
1	disposable syringes	Sterile	China
2	Micropipette 100 µL	Watson Nexty	Japan
3	Micropipette 1000 µL	Watson Nexty	Japan
4	EDTA coated tubes	ALS	China
5	gel tubes	ALS	China
6	Plain tubes	ALS	China

3.3 Methods and Procedures

3.3.1 Blood samples collection

A venous blood sample (5-7 mL) was withdrawn by a medical syringe from people, and the blood sample was divided into:

1. (1-2) mL of blood was deposited in tubes treated with the anticoagulant agent EDTA (ethylene diamine tetra acetic acid) and used to do a complete blood count after being gently shaken to prevent blood clotting.
2. (5-6) mL from the blood was placed in a gel tube for the purpose of separating the serum and process biochemical analyzes and Left it for 15 minutes for clotting. The serum was separated by centrifugation at 3000 for 15 minutes, then stored at (-80 °C) until the study's assays were performed.

3.4 Biochemical Markers

3.4.1 Alanine amino transferase

The alanine aminotransferase catalyzes the conversion of the alanine amino group to oxoglutarate, resulting in glutamate and pyruvate. Then, in the presence of decreased nicotinamide adenine dinucleotide, lactate dehydrogenase (LDH) converted pyruvate to lactate (NADH) (Schumann *et al.* 2002).

$$\text{L-Alanine} + \text{2-Oxoglutarate} \xrightarrow{\text{ALT}} \text{L-Glutamate} + \text{Pyruvate} \qquad (3.1)$$

$$\text{Pyruvate} + \text{NADH} + \text{H}^{+} \xrightarrow{\text{lactate dehydrogenase}} \text{Lactate} + \text{NAD}^{+} \qquad (3.2)$$

Calculations: Δ A/min x 3333 = U/L ALT

3.4.2 Aspartate amino transferase

Principle: Alanine aminotransferase catalyzes the transfer of the amino group from Aspartate to oxoglutarate, yielding glutamate and oxaloacetate. In the presence of decreased nicotinamide adenine dinucleotide, malate dehydrogenase (MDH) converted oxaloacetate to malate (NADH) (Schumann *et al.* 2002).

$$\text{Aspartate} + \text{Oxoglutarate} \xrightarrow{\text{AST}} \text{Glutamate} + \text{Oxaloacetate} \quad (3.3)$$

$$\text{Oxaloacetate} + \text{NADH} + \text{H}^{+} \xrightarrow{\text{malate dehydrogenase}} \text{Malate} + \text{NAD}^{+} \quad (3.4)$$

Calculations: Δ A/min x 3333 = U/L AST

3.4.3 Total bilirubin

Method: Modified Jendrassik

The reaction with diazotized sulphanilic acid determines T Bil in the presence of dimethylsulphoxide (Westwood 1991).

3.4.4 Lactate dehydrogenase

Principle: this method is described by SFBC (French Society of Clinical Biology) (Huijgen *et al.* 1997).

$$\text{Pyruvate} + \text{NADH}^{+} \xleftrightarrow{\text{LDH/PH7.5}} \text{Lactate} + \text{NAD}^{+} \quad (3.5)$$

Calculations: Δ A/min x 8095 = U/L LDH

3.4.5 Albumin

The indicator 3, 3', 5, 5'-tetrabromo-m cresol sulphonephthalein was employed to assess serum albumin's quantitative linkage (Bromocresol green, BCG). At 578 nm, the albumin BCG complex absorbs, and its absorbance is proportional to the albumin concentration in the sample (Doumas *et al.* 1971).

Calculation:

$$\frac{A(Sample)}{A(Sample)} * \text{standard concentration} = (g/L \text{ or } g/dL) \text{ Albumin concentration} \quad (3.6)$$

4. RESULTS AND DISCUSSION

This study have been carried out by comparing the status of liver function regarding to liver enzymes, total bilirubin, and total protein between recovering from covid-19 which were 69 persons and healthy control people, they were 67 persons.

4.1 Laboratory Parameters

1. Liver function fests : ALT, AST, ALP, LDH, as well as Total bilirubin.
2. Albumin and Total protein.

4.1.1 Liver function tests

The findings revealed a highly significant difference in ALT levels ($p<0.0001$) between those who recovered from the Covid-19 virus and healthy control people. Figure 4.1 illustrates the differences in ALT level of study groups. The normal range of ALT is (7-55 mg/dL) (Kang *et al.* 2011) and alt-blood-test.

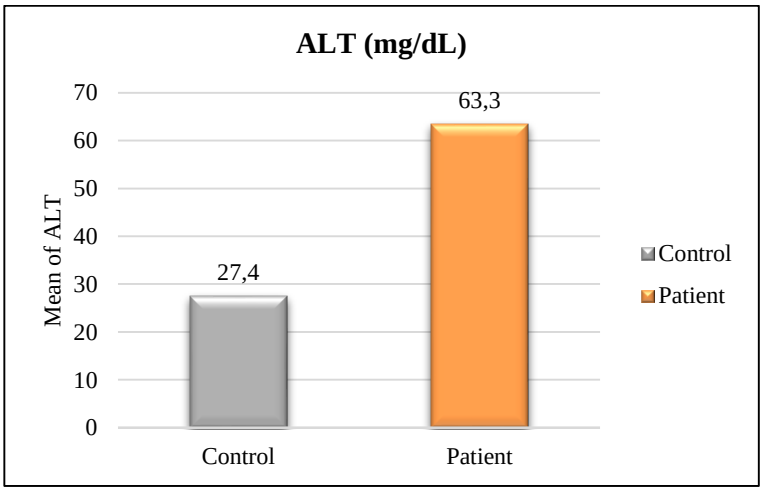

Figure 4.1 Showing ALT concentration in study groups

Table 4.1 reveals a correlation between the increase in ALT enzyme in people recovering from Covid-19 virus infection and some of the medications employed in the

treatment protocol. Ceftriaxone, azithromycin, and remdesivir all demonstrated a significant correlation with an increase in ALT concentration ($p<0.001$, $p<0.001$, and $p<0.01$), Ceftriaxone and remdesivir had a greater effect than azithromycin, according to the correlation coefficient values. Some antibiotics cause direct toxic damage to hepatocytes across the hepatic lobule, causing apoptosis and necrosis in varying degrees (Avila 2015). Our findings on raised ALT enzyme concentration and its connection to ceftrixone are consistent with those of (Abdelaziz *et al.* 2022).

When azithromycin was first started, it caused a potentially serious liver injury that went away rapidly after it was stopped. While cholestatic injury caused by azithromycin has been well documented, this is just the third incidence of direct hepatocellular injury to be published (Ellison and Blackwell 2021).Our findings on higher ALT levels and their association to azithromycin are in line with (Rodríguez-Molinero *et al.* 2020). What we saw with an increase in ALT is compatible with the usage of remdesivir by (Kim *et al.* 2021), who discovered that remdesivir causes an increase in the ALT enzyme, which could be attributed to a direct influence on the inhibition of RNA polymerase in mitochondria (Hoofnagle 2013). Despite these flaws, our large-scale pharmacovigilance investigation provides international real-world evidence that remdesivir use is linked to hepatobiliary ADRs like elevated blood ALT, AST, and bilirubin, as well as sudden liver failure. When taking remdesivir, it's important to keep an eye on your liver and biliary system to make sure you're not overdoing it.

Table 4.1 The relationship between liver enzymes and people recovering from Covid 19 infection and some drugs used in the treatment protocol

PARAMETERS	HEALTHY	PATIENTS	L.S.D.	P-VALUE
ALT	27.4 ± 13.4	63.3 ± 44.9	11.3	<.0001
AST	21.5 ± 6.18	48.0 ± 26.5	6.57	<.0001
ALP	65.76 ± 30.22	90.8 ± 46.46	9.21	<0.001
Alb	3.65 ± 0.562	4.21 ± 0.672	0.210	<.0001
T Bil	0.679 ± 0.360	1.656 ± 2.17	0.531	0.0004
LDH	185 ± 32.2	426 ± 256	62.4	<.0001
Total Protein	6.822 ± 0.511	6.796 ± 0.621	0.193	N.S.**
** N.S.: Non-Significant at probability value (P≤0.05)				

4.1.2 Aspartate aminotransferase

The levels of the AST enzyme were compared in Figure 4.2 between the healthy control group and the Covid-19 infection recovery group, as statistical analysis revealed significant differences in the enzyme's elevation among the infected ($p<0.0001$). It's possible that antibiotics and other drugs are to blame (Ejike *et al.* 2008, Park *et al.* 2021).

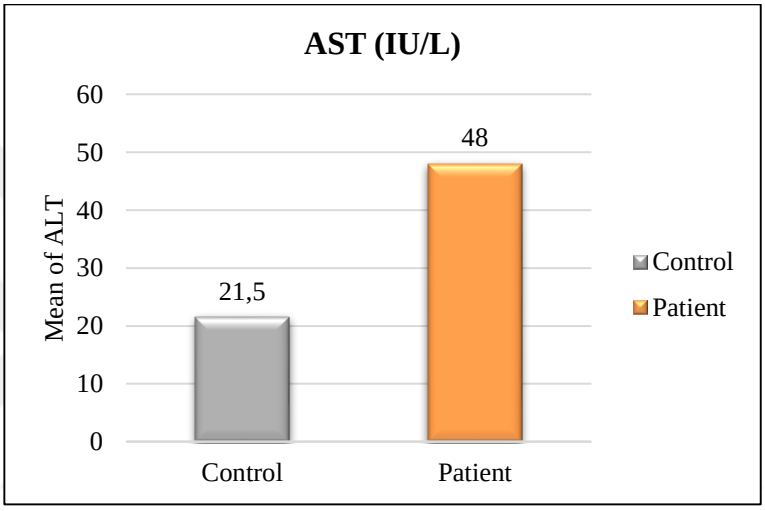

Figure 4.2 Showing AST concentration in study groups

All of the medications utilized in the study samples have a substantial association with the presence of the difference in significance and the values of the Correlaetion Coefficient, As shown in Table 4.2, 4.3, which displays the Pearson method correlation relations. Ceftrixone had the strongest link between high levels of AST and the drugs that the patients were taking, with a correlation coefficient of 0.592 and a high significance of $p<0.001$, which could be related to ceftrixone's effects on liver tissue, as indicated by (Oakes *et al.* 1984). Ceftriaxone's penchant for binding calcium and forming insoluble crystals in bile in the gallbladder, resulting in biliary sludge or outright stones, appears to be the mechanism of biliary sludge production during ceftriaxone therapy. Animal models show that this problem is not exclusive to humans. Ceftriaxone's calcium salts can precipitate in urine, forming sludge in the ureters or bladder, causing urinary blockage or symptomatic kidney and bladder stones.

Hypersensitivity is likely to blame for the rare, sporadic acute cholestatic liver damage linked to ceftriaxone. (Hoofnagle 2013). The medications Remdesivir and Azithromycine, as well as Levofloxacine, had substantial connections with high levels of AST enzyme p <0.001, p <0.001 and p <0.05 Respectively, however the Correlation coefficient of Levofloxacine was only 0.212.

Table 4.2 Pearson correlation r values

-	**ALT**	**AST**	**ALP**	**ALBUMIN**	**TOTAL PROTEIN**
ALT		0.832***	0.27**	-0.207*	-0.029
AST	0.832***		0.37**	-0.282*	0.014
ALP	0.27**	0.37**		0.013	0.028
Albumin	-0.207*	-0.282*	0.013		-0.197*
Total protein	-0.029	0.014		-0.197*	
Ceftrixone	0.443***	0.529***	-0.029	-0.301***	0.057
Levofloxacin	0.158	0.212*	0.179	-0.111	-0.082
Azithromycin	0.229**	0.366***	-0.117	-0.322***	0.012
Remdesivir	0.41***	0.455***	0.478***	-0.281***	0.047
* means p<0.05, **means p<0.01, and *** means p<0.001					

Table 4.3 Pearson's r correlation values in treatments

-	**CEFTRIXONE**	**LEVOFLOXACIN**	**AZITHROMYCIN**	**REMDESIVIR**
ALT	0.443***	0.158	0.229**	0.41***
AST	0.529***	0.212*	0.366***	0.455***
ALP	-0.029	0.179	-0.117	0.478***
Albumin	-0.301***	-0.111	-0.322***	-0.281***
Total protein	0.057	-0.082	0.012	0.047
Ceftrixone		0.273**	0.373***	0.198*
Levofloxacin	0.273**		-0.185*	0.122
Azithromycin	0.373***	-0.185*		0.257**
Remdesivir	0.198*	0.112	0.257**	
* means p<0.05, **means p<0.01, and *** means p<0.001				

4.1.3 Alkaline phosphatase

The levels of ALP in the two study groups are compared in Figure 4.3, based on statistical analysis, demonstrating that there are significant differences (p<0.0001). The

fact that what was evaluated in our study was the ALP enzyme in general rather than its isoenzyme counterpart associated to the liver could explain why our results contradict what has been stated in numerous references (Bilski *et al.* 2017, Henry *et al.* 2020). Our results are consistent with that of Bloom et al. (Bloom *et al.* 2021). The normal range of alkaline phosphatase is (30-120 IU/L) so some of our data was higher upper limits that because there are numerous ALP isozyme, the most important of which is related to bone, and the enzyme's concentration rises because of infection with Covid-19 and various medicines. The usage of Remdesivir alone has a strong link with elevated ALP concentrations, according to correlation coefficient alkaline phosphatase.

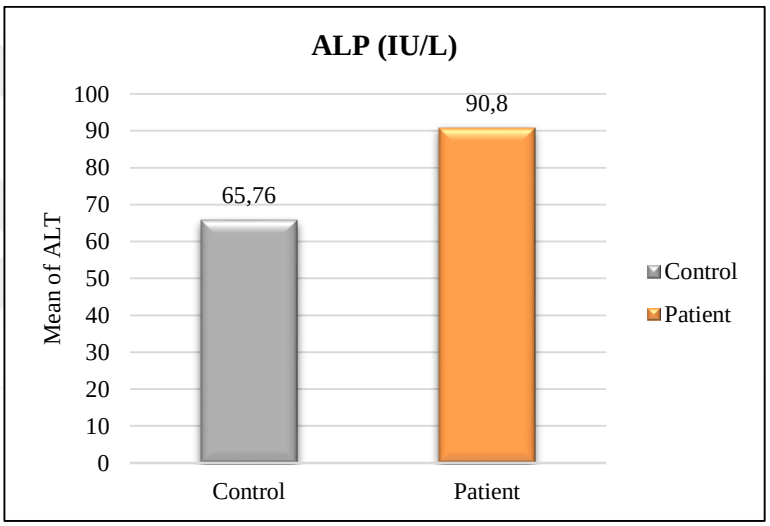

Figure 4.3 Showing ALP concentration in study groups

4.1.4 Lactate dehydrogenase

Lactate Dehydrogenase (LDH) levels were compared as an important factor in liver function and one of the most notable variables impacted by COVID-19 infection. Figure 4.4 shows the comparison's outcomes, Results show that the increase in LDH among individuals recovering from Covid infection differs significantly ($p<0.0001$). The normal value of LDH is 105 to 333 IU/L, so our results indicated that the cured people has strongly elevated levels of enzyme compared to normal range as well as the healthy control persons. As demonstrated in Table 4.1, the increase in LDH concentration is related to drug use in the group of recovered patients.

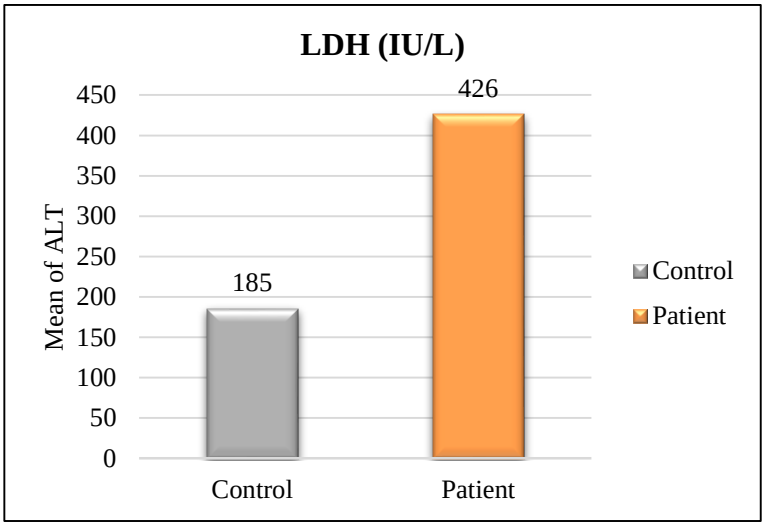

Figure 4.4 Showing LDH concentration in study groups

According to the Pearson correlation, there is a significant relationship between the rise in LDH among people recovering from Covid-19 infection and the usage of ceftriaxone, azithromycin, remdesivir, and then levofloxacin in the order of correlation strength ($p < 0.001$, $p < 0.001$, $p < 0.01$, and $p < 0.05$, respectively). The link between the rise and the usage of medicines suggests that specific side effects of these drugs contributed to the rise's persistence, especially given the enzyme measurements were done after the injury, which matches what we found in the data. However, the correlation between the rise and the use of medicines indicates that certain effects of these medicines led to the continuation of the rise, which corresponds to what we obtained from the results, compared to other sources that measured during the injury (Henry *et al.* 2020, Serrano-Lorenzo *et al.* 2021). LDH levels have been used to assess the effects of medications, particularly antibiotics, and they have been found to have negative impacts on liver function, which is consistent with other references (Castro-Filice *et al.* 2014, Bloom *et al.* 2021). Other references have established a link between the usage of ceftrixone and the negative effects on liver function, which is consistent with our findings (Wiesli *et al.* 2021, Kumar *et al.* 2020).

4.1.5 Total bilirubin

Total bilirubin was studied as an important supplement to the study and its levels were compared between the two study groups, as shown in Figure 4.5, which indicates clear differences, statistically significant p<0.001, in total bilirubin rise In the group recovering from Covid -19 infection Compared to the healthy as a group in charge. Because bilirubin levels are not normally distributed, the Spearman method (Table 4.4) was employed to examine the correlation, which reveals the relationship between the rise in total bilirubin and all of the medicines studied at different rates. The differences are significant, despite the low ρ values as a correlation coefficient.

Table 4.4 Spearman correlation ρ values

	LDH	Bilirubin	Ceftrixone	Levofloxacin	Azithromycin	Remdesivir
LDH		0.522***	0.517***	0.272**	0.566***	0.346***
Bilirubin	0.522***		0.367***	0.191*	0.421***	0.194*
Ceftrixone	0.517***	0.367***		0.273**	0.373***	0.198*
Levofloxacin	0.272**	0.191*	0.273**		-0.185*	0.122
Azithromycin	0.566***	0.421***	0.373***	-0.185*		0.257**
Remdesivir	0.346***	0.194*	0.198*	0.122	0.257**	
* means p<0.05, **means p<0.01, and *** means p<0.001						

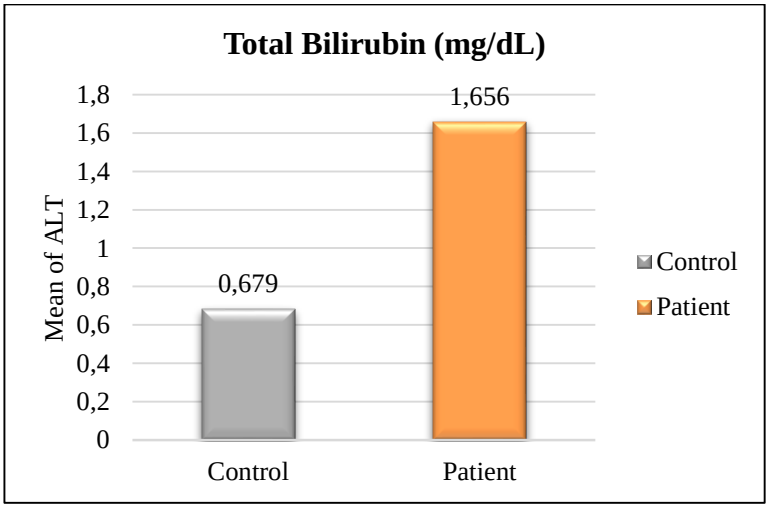

Figure 4.5 Showing total bilirubin concentration in study groups

The results correspond with other references (Hwang *et al.* 2019, Li *et al.* 2017) for the rise in total bilirubin after taking drugs (Table 4.5), and the rise may exceed the upper limit of the normal range, which is between 0.1 and 1.2 mg/dL (Creeden *et al.* 2021).

Table 4.5 Mechanisms of hyperbilirubinemia in sepsis

NO	HEMOLYSIS	HEPATIC DYSFUNCTION
1	In normal red cells	Decreased bilirubin uptake
2	In RBCs with red cell enzyme defects (G6PD)	Decreased canalicular transport
3	Pathologic changes to RBCs secondary to infection	Decreased clearance of conjugated bilirubin
4	Drug-induced hemolysis	Hepatic ischemia
5		Hepatocellular injury (mild reactive hepatitis to overt hepatocellular necrosis

Despite their similarities, the processes responsible for toxicity might range dramatically within a pharmacological class. Table 4.4 indicates the correlations of total bilirubin with different medications used in this study in a significant manner but with light variations. Ceftriaxone can produce biliary sludge, and symptoms might appear as soon as a few days after commencing treatment (Khurram *et al.* 2015), Macrolide-induced hepatotoxicity causes pruritus and jaundice, which usually appear three weeks after exposure. These clinical characteristics were shared by four of the five patients, and the majority of them were similar in age and symptom onset and resolution. Patients' total and daily azithromycin doses varied. While current guidelines debate the dose's appropriateness, as well as the selection and reasoning for additional antibiotics, The type of liver damage caused by azithromycin appears to be idiosyncratic and independent to dose or duration. Other characteristics that set the five apart (Brown and Desmond 2002, Lockwood *et al.* 2010).

4.1.6 Albumin

The difference in mean SD between the two study groups is shown in Figure 4.6, and this difference is statistically significant ($p<0.001$). Albumin concentrations rise as a

result of its important role in delivering chemicals in the blood stream, which could explain why the group taking drugs had a higher concentration than the healthy people. Except for Levofloxacin, albumin has a strong connection with the medicines studied in Table 4.1. The most prevalent protein in plasma, human serum albumin (HSA), can reversibly attach to a range of endogenous and exogenous compounds, assisting in storage and transport (WANG *et al.* 2017).

According to studies (Feng *et al.* 2019, China *et al.* 2021), A high quantity of albumin in the blood serum has been linked to the use of some medicines. The high levels remained within the normal range of 3.3-5.4 g/dL despite the disparities between the two study groups.

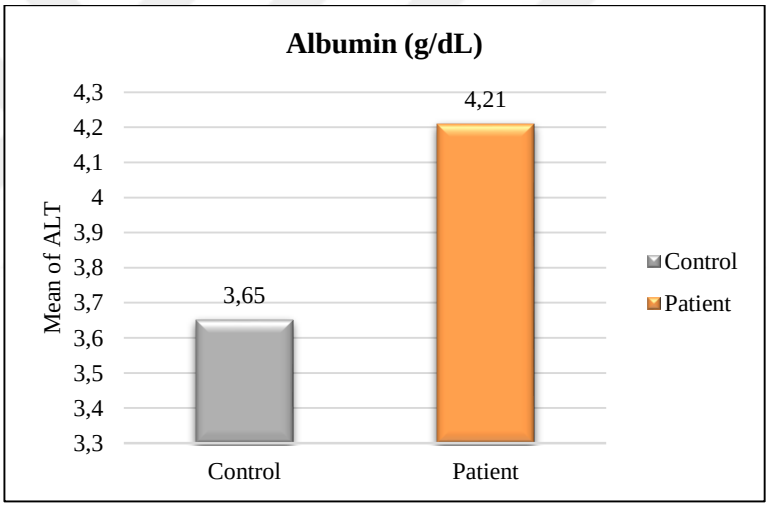

Figure 4.6 Showing albumin concentration in study groups

4.1.7 Total protein

Figure 4.7 illustrates the total protein comparison for the two research groups, which indicates no significant changes $p>0.05$ based on statistical analysis, which is consistent with prior findings. Furthermore, there is no significant association between total protein and the drugs investigated, as indicated in Table 4.1. The typical range for total protein concentration is 6.0 to 8.3 g/dL. The findings contradict those of earlier research (Nie *et al.* 2020, Schoergenhofer *et al.* 2020), which found that infection with Covid-19

can cause a rise in total protein in patients' blood due to the immune system's activity in creating high amounts of immune proteins. While our research depended on patients who utilized some medications that may affect liver function. This might imply that the cellular metabolism of proteins is regular, as the overall protein content remained within acceptable limits (Xu *et al.* 2021).

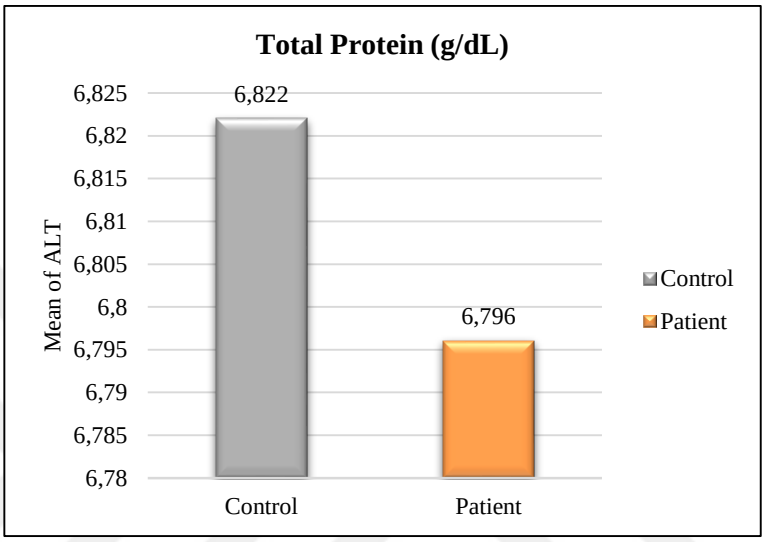

Figure 4.7 Showing total protein concentration in study groups

This study is notable for focusing on connecting variables in a novel statistical method to determine the effect of the inappropriate and unjustifiable use of several antibiotics on liver functioning. The researchers want to come up with key recommendations that will help doctors pay attention to the treatment course's quality. It should be noted that Corona virus infection has a serious impact on the respiratory system and thus the rest of the organs' safety, but the beneficial treatment must be described and not interfere with additional treatments that cause significant damage to the liver, which is the most important organ for metabolic activities. The enzymes that transport the amino group, and to a lesser extent, the LDH enzyme, are the earliest indicators of liver function. The significance of the variables is ordered, but when all of them are described, including total albumin and total protein in addition to bilirubin, and the link of each variable to the drugs used by persons recovering from coronavirus infection, this suggests complementarity. The graph depicts the percentages of each enzyme's rising or

reduction, as well as the statistical correlations that follow. It would have been worthwhile to investigate the measurement of the gamma glutamyl transferase (GGT) enzyme in order to determine all of the medications' harmful effects, but time constraints and high measurement costs precluded this. The need of monitoring the liver functions of all persons receiving antibiotics, especially when using more than one class, was revealed by statistical connections examining the correlation of more than one kind of medicine with variables according to a statistical model. The results show that Ceftrixone and Azithromycin are the most often used medicines that alter liver function and have substantial effects and connections. As a result, persons who are receiving these two medicines must be monitored, especially if they are given at the same time.

5 CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

From the findings, it can be concluded that:

1. Liver functions are affected by the use of different types of antibiotics.
2. In terms of liver function Test (ALT, AST, ALP, LDH, total bilirubin, and albumin) ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.01$, and $p < 0.001$ respectively) there are evident significant differences between recovering from COVID-19 and healthy people.
3. Total protein concentrations in the two research groups do not differ statistically significantly ($p > 0.05$), and the correlation relationships suggest that total protein concentration and any of the drugs taken by persons recovering from Covid-19 infection have no relationship.
4. The antibiotic ceftriaxone has the greatest impact on liver function, particularly the enzymes ALT and AST, whereas the antibiotic azithromycin has a smaller impact.
5. Antibiotic usage affects albumin protein in Covid-19 patients, necessitating continuous monitoring of this variable during treatment.

5.2 Recommendations and future work

1. For a thorough and accurate characterization, we advocate combining the variables indicating liver function with additional nonparametric variables.
2. Evaluate GGT enzyme activity, comparable to ours, as a comparison between the two groups and correlations.
3. Creation of a cohort study with precise therapeutic amounts to follow up on patients in order to discover the best treatment technique without causing harm to their liver function.
4. 4. Patients with Covid-19 should have their liver functions, as well as the types and doses of antibiotics they're taking, checked.

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