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THE EFFECT OF COVID 19 ON LIVER ENZYMES: A FIELD STUDY ON THE PATIENTS OF AL-KINDI HOSPITAL IN BAGHDAD

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ANWER SABAH AHMED AHMED

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By Anwer Sabah Ahmed AHMED

May 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

THE EFFECT OF COVID 19 ON LIVER ENZYMES: A FIELD STUDY ON THE PATIENTS OF AL-KINDI HOSPITAL IN BAGHDAD

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Master of Science in Chemistry

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Recent studies have related to COVID 19 is a virus that spread in China at the end of 2019 and its first target is the respiratory system and spreads to the rest of the body, and its symptoms range from mild to severe, Where liver enzymes are evaluated in the laboratory to see what differences they will have. In this study, included 120 patients infected with COVID 19 who were confirmed to have a PCR test. As well as the other group called the control group was selected and they were not infected with the virus, as it was confirmed that they were not infected with a PCR test, the hospital's approval was obtained, as well as the patients. As result, we can imply that the results were compared between the group of patients and the control group, and it was found that liver enzymes rise in the case of infection with the virus. As ALP and AST increased in most patients, which is considered statistically significant while ALT increased in almost a third of patients, and the lowest test was the bilirubin, which increased in 10% Almost from patients, on the contrary, albumin decreased in two thirds of patients. While all examinations were normal in the control group. Where the risk of severe symptoms of COVID-19 increases in the elderly, as there is a role for age and some accompanying diseases such as diabetes, pressure, liver and kidney diseases, a role in the rise of these enzymes.

2022, 42 pages

Keywords: Covid 19, AST, ALT, Alkaline phosphatase, Albumin, Total bilirubin

ÖZET

KOVİD 19'UN KARACİĞER ENZİMLERİ ÜZERİNE ETKİSİ: BAĞDAT EL-KINDI HASTANESİ HASTALARI ÜZERİNDE BİR SAHA ÇALIŞMASI

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COVID 19 ile ilgili son araştırmalar, 2019'un sonunda Çin'de yayılan ve ilk hedefi solunum sistemi olan ve vücudun geri kalanına yayılan ve semptomları hafif ila şiddetli arasında değişen bir virüstür, Karaciğer enzimlerinin değerlendirildiği yerler laboratuvarda ne gibi farklılıklar olacağını görmek için. Bu çalışmaya, PCR testi olduğu doğrulanan COVID 19 ile enfekte 120 hasta dahil edildi. Kontrol grubu olarak adlandırılan diğer grubun yanı sıra virüs bulaşmadıkları ve PCR testi ile enfekte olmadıkları teyit edildiği için hastaların yanı sıra hastane onayı da alındı. Sonuç olarak hasta grubu ile kontrol grubu arasında sonuçların karşılaştırıldığı ve virüs ile enfeksiyon durumunda karaciğer enzimlerinin yükseldiği tespit edildiğini söyleyebiliriz. Çoğu hastada ALP ve AST arttığından, bu istatistiksel olarak anlamlı kabul edilirken, ALT hastaların yaklaşık üçte birinde yükselirken ve en düşük test bilirubin idi, bu da %10 arttı Hastalardan neredeyse tam tersine, albümin üçte iki oranında azaldı hastaların Kontrol grubunda ise tüm muayeneleri normaldi. Yaşlılarda COVID-19'un şiddetli semptom riskinin arttığı durumlarda, yaş ve buna eşlik eden diyabet, basınç, karaciğer ve böbrek hastalıkları gibi bazı hastalıkların rolü olduğu için bu enzimlerin yükselmesinde rol oynar.

2022, 42 sayfa

Anahtar Kelimeler: Covid 19, AST, ALT, Alkalin fosfataz, Albümin, Total bilirubin

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Anwer Sabah Ahmed AHMED

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CONTENTS

LIST OF SYMBOLS

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

LIST OF ABBREVIATIONS

ACE2	Angiotensin converting enzyme 2 receptor
AH	Hypertention
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
DM	Diabetes millitus
ES2	Endostatin
MERS-CoV	Middle east respiratory syndrome
RTPCR	Real time polymerase chain rate
SARS-CoV-2	Sever acute respiratory syndrome coronavirus 2
SAS	Statistical analysis system
TSB	Total serum bilirubin

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

COVID-19 infection was triggered by the discovery of SARS-CoV-2 (SARS-CoV-2) on December 31, 2019. Worldwide, the continuing COVID-19 epidemic poses a significant threat to healthcare systems. Pre-existing liver illness is a risk factor for severe COVID-19 infection, although little is known about how infection impacts liver function. Several medicines used to treat new coronavirus infection have been linked to liver toxicity (Holshue et al. 2020). However, gastrointestinal symptoms such as diarrhoea and vomiting are also reported by some individuals who have a fever and respiratory disease. The gastrointestinal tract's symptoms worsen as the illness progresses in severity. Patients with gastrointestinal symptoms had higher liver enzyme levels, lower monocyte counts, a longer prothrombin time, and more antimicrobial medication than those without gastrointestinal symptoms, according to several studies. lung diseases; But there is increasing data confirming damage to many other body systems, including the liver and the digestive system, where an increase in liver enzymes has been observed in many cases, and the appearance of gastrointestinal symptoms (diarrhea, anorexia, nausea, and vomiting) in about 60% of the injured (Schaefer *et al.* 2020).

The surface protein is an important product of this virus that binds to the cell via the ACE2 receptor, as this receptor is found on the surfaces of many cells of the body such as the liver and respiratory organs. The main reason why this virus is so much more contagious than its counterparts and is more easily transmitted between humans is the microscopic structure of this prominent surface protein. A recent study was published saying that this protein binds to the cellular receptor (ES2) more strongly and faster than similar viruses. Activation of the furin enzyme present in cells, which increases the strength and speed of its binding to cells The future and this protein is what they focus on and should produce vaccines (Lau *et al.* 2013). When the human body encounters a germ, the immune system usually attacks that "enemy" and then stops after completing the task. But sometimes this army of immune cells which fight invading viruses with molecular “weapons” get out of control, and their obedient soldiers turn into an unruly

horde. Exposure in the body to various types of infections or a defect in some genes, which is known as "autoimmune disorders". In all of these cases, the body thinks its tissues are forming foreign bodies and invaders, which is generally called a "cytokine storm," which, compared to dozens of glycoproteins, is used to deliver and transmit signals between the "immune army" in cells. One of them bears the name "cytokine". Increasing the number of "cytokine" proteins responsible for increasing the immune activity of cells, in a way that exceeds normal rates, may make the immune system unable to control or stop them. In this case, these proteins spread to different parts of the body, not just the affected areas. It begins by attacking healthy cells, devouring red and white blood cells, and destroying the liver. At that time, the walls of the blood vessels open to allow immune cells to enter the surrounding tissues. But these vessels leak so poorly that they can flood the lungs with fluid and lower blood pressure. In addition, blood clots form throughout the body, further blocking the bloodstream. And when the organs of the human body suffer from a lack of blood supply to them, that person may suffer a shock that threatens to cause permanent damage to this or that organ, or even death (Wong, *et al.* 2020).

Coughing or sneezing by an infected individual releases respiratory droplets, which are then spread via the air. A person's health might worsen if they are older or have extra comorbidities or illnesses. (Harapan and colleagues, 2020) In immune-compromised patients with chronic liver disease, the effects of immunosuppressive treatment on COVID-19 and the virus itself are not well known. The risk of SARS-CoV-2 infection did not seem to be increased by the use of immune-modulatory medications for other conditions, such as rheumatologic illnesses (Kushner and Cafardi 2020). There were concerns that individuals on immunosuppressive treatment may be more vulnerable to the new strain of the virus as the epidemic grew. Infections caused by common viral agents such as adenovirus and rhinovirus are more likely to be severe if these drugs impact the immune system and neutrophil function. Influenza and RSV are both respiratory illnesses (Kaltsas and Sepkowitz 2012). Increased viral load and a longer time to cure may be caused by high levels of immunosuppression, although the worsening of the illness is mostly due to an ineffective immune system. The frequency of COVID-19 in liver transplant patients was greater than in the overall population, but

the death rate was reduced, indicating that suppressed people may have a better evolutionary trajectory. Although everolimus and calcineurin antagonists had no effect on poor outcomes, the use of mycophenolate was connected to an increased risk of mortality. Solid organ recipients hospitalized with COVID-19 at two large New York academic facilities were shown to have much higher rates of severe illness, ventilator use, and mortality, while it is not apparent whether this was related to immunological state, immunosuppressive medicine, or underlying comorbidities (Colmenero *et al.* 2021).

1.1 Objectives of Study

1. It aims to assess the effect of the Corona virus on liver enzymes. This effect may be direct through the treatments used to treat infections or damage to certain organs, which in turn affect the liver and its enzymes.
2. This study aims to assess the effect of infection with the Coronavirus on liver enzymes.

2. LITERATURE REVIEW

2.1 Liver

One of the glands that play a significant part in regulating the body's functioning, each gland has a specific function. The digestive system includes the liver as one of its organs. Right beneath the diaphragm, it performs a crucial function in eliminating toxins from the body and discharging them after modifying their components. Located on the right side of the body (Darvish 2012). Liver between 1300 grams to 1700. The liver is divided into two main lobes and two sub-lobes: the right and left lobes are larger than the caudal and quadrat lob. The liver performs an important set of sensitive and important functions, on top of which is the withdrawal of toxins from the blood circulation and the production of bile juice known as bile. It also plays a major task in regulating blood sugar levels. The liver has an important role in analyzing the excess fat that the body needs, dismantling it, and converting it into cholesterol (Elias and Bengelsdorf 1952). The bile juice that it produces plays a major role in breaking up the excess fat that the body needs, which harms the body if its rates are higher than normal. The liver also absorbs sugar over the body's needs, stores it, and then re-releases it when the body needs it if blood sugar levels drop for any reason. The liver also controls the urea cycle. Through this cycle, the liver gets rid of harmful waste products such as ammonia, which it converts into urea. The liver has a unique function that no other organ can perform, which is to collect the old red blood cells and then get rid of them outside the blood circulation. In addition to all that, the liver tracks harmful germs and microbes and then breaks them and expels them out of the body (Tortora and Derrickson 2018). The liver plays an important role in the development of proteins that help stop blood clots, and all of these proteins are responsible for maintaining the fluidity of the blood, as the patient may be at risk of developing a blood clot if a high proportion of these proteins is present, or may be at risk of severe bleeding Which cannot be stopped if the liver's production of these proteins decreases. The liver is a complicated chemical plant because this transforms surplus sugar into animal starch so that it may be stored for long periods, even if the body requires it, before returning it to

its original building as sugar and pumping it back into the bloodstream. The liver may store minerals like copper and iron as well as fat-soluble vitamins (Chao *et al.* 2012).

2.2 Liver Enzymes

Liver enzymes are globular proteins that are spontaneously released in minute amounts from the liver and aid in the speeding up of critical bodily processes and the conversion of food into energy. The liver enzymes in the serum samples are raised when liver cells are destroyed. Depending on the elevated enzyme, the type of disease can then be determined. Causes of cell damage can be alcohol viral infections, tumors, or poisonin

2.2.1 Albumin

Albumin represents more than half of the proteins in the blood. It is synthesized in the liver from proteins and then excreted into the blood. Albumin has an important role as it protects the fluids in the blood vessels from leaking out and transports hormones, medications, vitamins, as well as bilirubin through the body (Center 2007). Therefore, the main symptom that indicates low levels of albumin is the accumulation of fluid in the tissues, and the appearance of edema in the feet, ankles, lungs, and abdominal cavity. One of the reasons for low albumin is that there may be damage to liver cells or a decrease in the consumption of amino acids. On the contrary, high albumin is uncommon and may indicate dehydration (Marc *et al.* 2021).

2.2.2 Alkaline phosphatase

The liver, bone, kidney, gut, and placenta all contain alkaline phosphatase. Electrophoresis may be used to separate the distinct isoenzymes found at each of these locations. Alkaline phosphatase in the liver is located on the surface of the duct and is, therefore, a sign of dysfunction of the bile ducts, the values of which can be increased up to 10 times in obstruction of the bile ducts, in infectious processes or their presence. from the masses. This enzyme is also increased during the third trimester of pregnancy

(Zhang *et al.* 2020). and the enzyme profile is slightly different in each tissue type. Isoenzymes or isozymes are the inch versions of the enzyme. When cells are injured, this enzyme is produced, as well as its level in the blood rises as a result. This enzyme is linked to the process of bone formation in the bones. In a numberseveralnal disorders and cirrhosis, the amount of the enzyme in the blood rises throughout growth, and the majority of the alkaline phosphatase present in the blood originates naturally from the liver and bone. In a normal individual, most alkaline phosphatase is composed of alkaline phosphatase from the liver and bone (Li *et al.* 2020).

2.2.3 Bilirubin

Is the major metabolite of the heme group of hemoglobin, myoglobin, and cytochrome,ome. About 250 mg to 350 mg of bilirubin is produced per day, 85% as a result of the destruction of old erythrocytes. Most of the bilirubin is transported bound to albumin (direct or conjugated) and only a small portion circulates freely (indirect or unconjugated). The direct fraction accounts for less than 20% of the total bilirubin. The increase in total bilirubin occurs along with the increase in direct bilirubin when there is necrosis and cholestasis, while the accompanying indirect increase in bilirubin is associated with hemolysis or Gilbert's syndrome (Cummings *et al.* 2020).

2.2.4 Transaminase

Hepatic necrosis is typically detected using the enzymes ALT and AST, which measure alanine and aspartate aminotransferase, respectively. They are abundant in hepatocytes, where they catalyze the transfer of amino groups to form pyruvic acid and oxaloacetic acid, with vitamin B6 acting as a cofactor in both reactions. When there is damage to the cell membrane of hepatocytes, these enzymes contained in the cytoplasm of the cells pass into the plasma, increasing their concentration in the circulation. Transaminases are sensitive but not very specific to liver cell damage, with ALT being more specific than AST, since it is found not only in the liver but also in skeletal muscle, the heart, the kidney, and erythrocyte (Luke *et al.* 2006). In a biochemical blood test, the AST and

ALT indicator is always taken into account, the deviations of these enzymes make it possible to clarify the violations occurring in a particular organ.

- AST is present in all tissues of the human body, but the heart muscle (myocardium) contains the most enzymes That is why the excess of this substance indicates diseases of the heart.
- The ALT enzyme is found in the highest quantities only in the liver, so a significant excess of its norm indicates a violation of the work of this parenchymal organ.

The ratio of AST and ALT in the medical language is called the de Ritis coefficient, therefore, with a biochemical blood test, it is possible to determine which organ is affected. With problems with the heart, the level of AST increases up to 8-10 times more than normal, while ALT increases by only 1.5-2 times more. With such indicators, the patient is diagnosed with a heart muscle infarction.

2.3 The Mechanisms of a Novel Coronavirus Infection's Liver-Damaging Effects

COVID 19 is a disease that affects the liver in a variety of ways. Liver damage from the novel coronavirus infection is being studied in many ways, including the direct toxicity caused by active virus replication in hepatocytes (direct toxicity) (Nan et al. 2015). Multiple organ failure in severe and life-threatening cases of immune-mediated liver injury in the sense of chemokine storm, COVID 19 related coagulopathy, and inflammatory syndrome (Magrone et al. 2020). Because of the virus's ability to clog airways, hypoxic hepatitis caused by anoxia is common in critically ill individuals with COVID 19. Liver damage in COVID-19 patients with respiratory failure and/or shock may be caused by severe hypoxia, anoxia, and hypovolemia. Cytolysis and changes in mitochondrial membrane permeability are typically seen in this liver injury. This liver damage is usually characterized by substantial cytolysis. Most of the COVID 19 liver damage that develops as a consequence of isotropic treatment for SARS-CoV-2 infection and underlies the pathophysiology therapy for COVID 19 is caused by drug-induced liver damage (Gerges Harb et al. 2020). When the SARS-Cov-2 pandemic initially broke out, doctors recommended antibiotics including azithromycin,

umifenovir, favipiravir, and recombinant interferon beta-1b, all of which have hepatotoxic hazards. In addition, chronic viral hepatitis B and C, which cause liver cirrhosis and non-alcoholic fatty liver disease in patients with metabolic syndrome (diabetes, obesity), should be taken into account because of the high frequency of these illnesses worldwide. People with COVID-19 may have liver damage as a result of these CKDs. SARS-CoV-2-induced liver damage may be more common in those with chronic renal disease. COVID-19 development may be influenced directly or indirectly by the time period before hepatic illness, but the information is inadequate at this time to draw any firm conclusions. & the converse is also true Multiple studies on COVID-19 patients found that 2-11 percent had CKD (Zong and Stanger 2011). Hypoxia and hypoxemia may lead to severe asthma or a cytokine storm in patients with CKD, who are more susceptible to COVID-19's clinical consequences. Topical medication is not to blame, but rather a lack of viral exposure or systemic disease. Aminotransferase levels in COVID-19 patients are the most common problem. AST is more often elevated than ALT, according to published statistics (Weiss and Leibowitz 2011). The presence of elevated alkaline phosphatase and bilirubin is unusual. gamma-glutamyltransferase (GGT) was found in approximately half of the individuals studied. Biochemical alterations in the liver are marked by an increase in aminotransferases after hospitalization for COVID-19 infection; these changes are more common in individuals with severe COVID-19. Hepatitis B and C have different patterns of liver damage, although at least one research identified a similar pattern in influenza A/H1N1 infection. During the last SARS outbreak in 2003, a similar pattern of liver damage was documented. When it comes to alcoholism-induced liver illness, elevated AST levels are more common than GGT rises, indicating aberrant hepatic biochemical processes. Late in the course of COVID-19 disease, an elevated alkaline phosphatase may indicate septic cholestasis, severe sickness, or a drug-induced impact (Weiss and Leibowitz 2011).

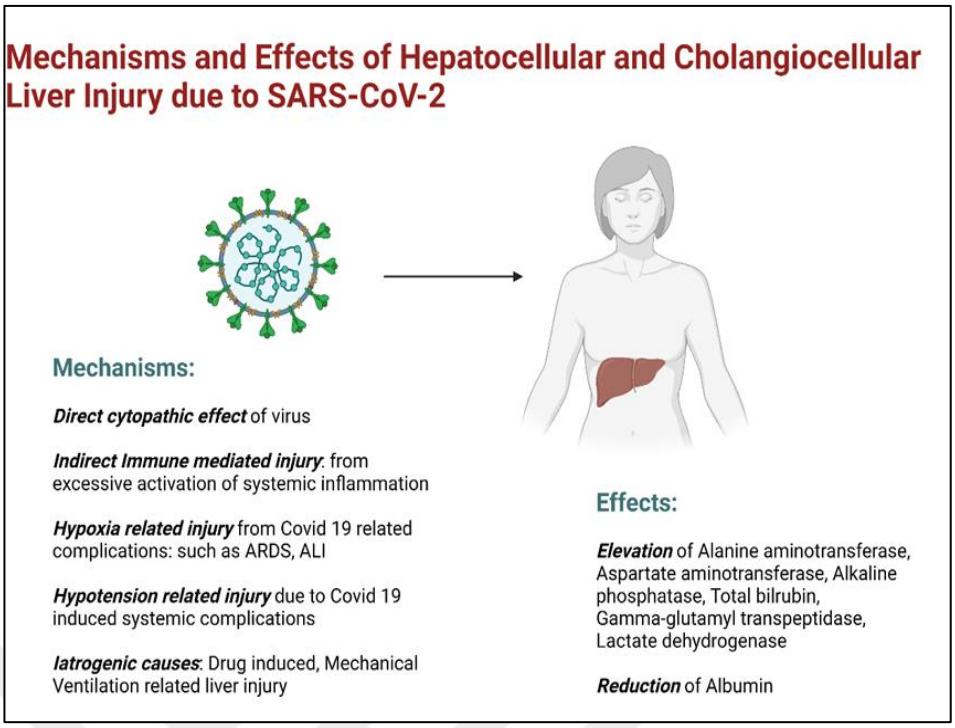

Figure 2.1 COVID 19 patients liver injury mechanism (Ghazanfar *et al.* 2022)

2.4 COVID-19 Histopathology of the Liver

Revealed the first post-mortem data of a patient who died with severe COVID-19. There were only mild inflammatory infiltrates in the liver lobule and portal system, as well as mild microvesicular steatosis, according to the liver histology in this study. At this point, it's not apparent whether these alterations are the result of the virus or the drugs. To put it another way: The number of CCR6+ Th17 CD4 T cells and cytotoxic granules on CD8 cells was significantly reduced in the peripheral blood, but the proinflammatory condition resulted in a hyper-reactive state of CD4 and CD8 cells, which might contribute to hepatocellular dysfunction. According to Tian S et al., 32 post-mortem liver samples from four COVID-19 patients showed mild sinusoidal dilatation and localized macrovesicular steatosis. Some lobular lymphocytic infiltration was seen although it was not significant in the portal regions. RT-PCR was used to recover SARS-CoV-2 RNA from liver tissue in one of the patients. No evidence was found to indicate that the epithelial cells of the gallbladder had been damaged by the presence of ACE2 receptors. As of 2020, Tian et al. When SARS-CoV spread in 2002, between

23% and 60% of those infected had liver impairment, yet only a few of people underwent a liver biopsy. Apoptosis, hepatocyte ballooning, and mild to moderate lobular lymphocytic inflammation were seen. Most notable were the high mitotic numbers, which indicated a rapidly growing state. There are roughly 0.45 to 1% of hepatocytes in chronic hepatitis C infection with a Ki proliferation value of 0.45 to 1. According to immunohistochemistry, the Ki proliferative index of hepatocytes was much higher during SARS-CoV infection than during chronic hepatitis C infection and liver regeneration. A cell cycle halt induced by SARS-CoV infection is the most plausible explanation for the high mitotic index. The etiology of COVID-19 is unknown (Chau *et al.* 2004).

2.5 Liver Damage in COVID-19

SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) have been found to induce liver damage in people who are sick (Xu et al 2020). Changes in the liver's functional characteristics were also discovered with COVID-19, and they were linked to the infection's development and severity. SARS-CoV-2 RNA in biological medium and antibodies in blood serum validate the diagnosis of COVID-19. Swabs taken from the throat, nose, and lungs, as well as cells from the parenchyma and vascular endothelium of several other organs, such as hepatocytes, were all used to identify the SARS-CoV-2 genome. In COVID-19, the cause of liver injury is unknown. Hypoxia, hypovolemia, hypotension during shock, medication hepatotoxicity, and viral-induced effects (the "cytopathic effect") are only a few of the many possibilities. Renewal or relapse of viral hepatitis (especially non-alcoholic steatohepatitis) and the advancement of metabolically related liver illnesses (such as liver cirrhosis) are all factors that increase the risk for CoV-2 infection in individuals (Ilchenko et al. 2020). Despite the fact that ACE2 expression in cholangiocytes is greater than in liver cells and similar to that of type 2 alveolocytes, the mechanism by which active replication of SARS-CoV-2 in hepatocytes causes direct cytotoxicity is still unclear. Cholangiocytes seem to be the primary source of liver injury in COVID-19. SARS-CoV-2 infection does not cause obvious cholestasis, which may imply that the virus enters the hepatocytes in other ways. Another possibility is that in COVID-19, the virus induces

cholangiocyte malfunction and, as a result, indirectly leads to hepatocyte injury or growth. No one can rule out the possibility of medication hepatotoxicity and liver damage as a result of chronic inflammation. Biochemical abnormalities in the blood of infected individuals were found in 14–53 percent of them before, and the emergence of COVID-19 was documented in 2–11% of patients with chronic liver disease (Chia et al. 2020). Alanine and aspartic aminotransferases (ALT/AST) activity increased, although not to the point of exceeding 1.5–2 norms from the upper limit of normal. Occasionally, the total bilirubin content increased. SARS-CoV-2-caused acute viral hepatitis has been documented in a few patients. It was shown that COVID-19 may be successfully resolved in a 59-year-old patient with metabolic syndrome who was receiving treatment for a human immunodeficiency virus infection (Wander et al. 2020).

Patients with severe COVID-19 had a greater rate of liver damage than those with moderate illness. However, even in the most severe and life-threatening stages of the illness, no cases of fatal liver failure were discovered (Cholankeril et al. 2020). Only in a few instances did the liver's ability to synthesize protein (albumin drop to 26.3-30.9 g/L) fail. SARS-CoV-2-infected individuals' intravital liver morphology has been little documented. However, autopsy studies on the liver morphology of individuals who died with COVID-19 are providing new insights. Focal necrosis in hepatocytes and microscopic vesicles in the liver tissue are all signs of microvesicular steatosis, whereas neutrophil predominance is shown in lobular and portal inflammation, as well as microthrombi in sinusoids. SARS-cytopathic CoV-2's action may be to blame for these histological abnormalities, although drug-induced liver damage cannot be ruled out. Here is an example of a patient COVID-19 who was effectively treated for drug-induced hepatitis (Hanley *et al.* 2020).

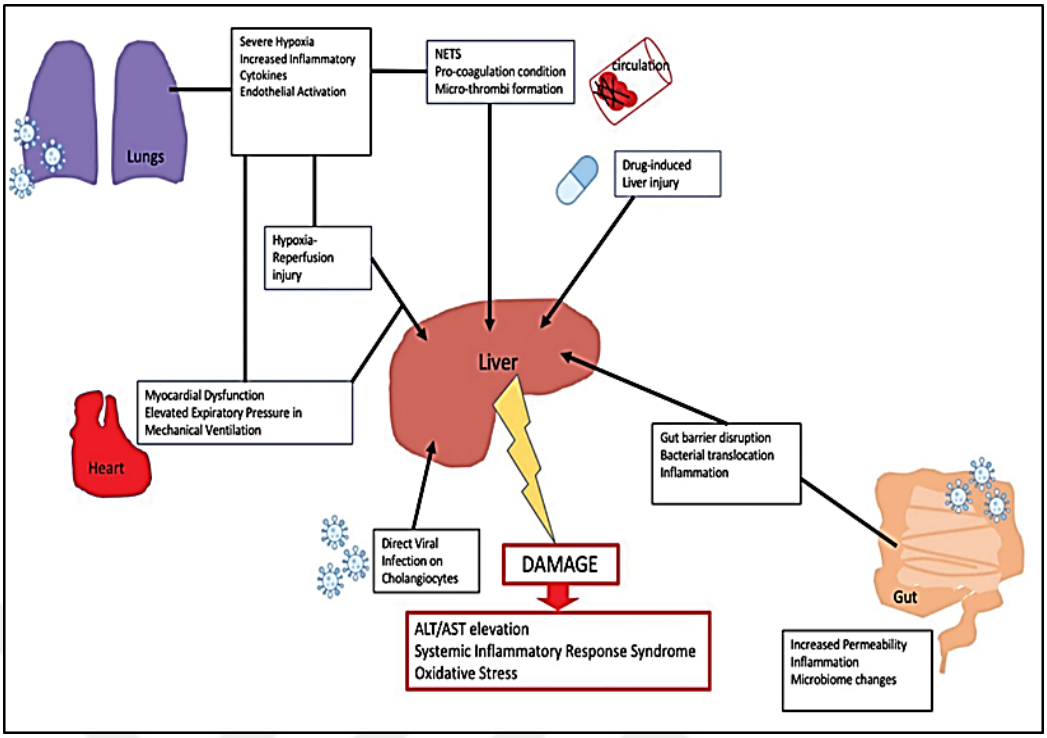

Figure 2.2 The physiological effects that affect the liver by infection with the corona virus damage (Luglio *et al.* 2020)

There was also a significant prevalence of severe and critical cases, as well as a high death rate, found in Wang and associates 2020's new research on 339 older patients with COVID-19, which was just published. Another 28.7% of patients had abnormal liver enzymes in addition to cardiovascular issues such acute cardiac injury, arrhythmia, and heart failure (Garrido et al. 2020). A new strain of the coronavirus has emerged in 2019, but nothing is known about its clinical course, severity, or long-term effects. In light of the lack of information, it's difficult to say anything about how COVID-19 affects the liver. Hepatic effects of COVID-19 include abnormalities of liver enzymes (particularly aminotransferases), followed by immediate liver injury and hypoproteinemia, according to the most current published evidence. When a patient is admitted, they often have elevated ALT, AST, and total bilirubin levels, as well as low albumin levels, which are all signs of liver disease (Gori et al. 2020). However, according to the results of a recent research, only 2% to 11% of COVID-19 patients had liver comorbidities. Patients with pre-existing liver illness who were tested with COVID-19 had worse outcomes, which researchers attribute to their immunocompromised status. A rise in the severity of

COVID-19 and its potentially disastrous outcomes has been related to acute liver injury. Aminotransferases are typically high in liver injury, and evidence shows that high levels of these enzymes are linked to an increased risk of severe disease and fatality. The activation of the coagulation and fibrinolytic cascades, decreased platelet count, increased neutrophil count, reduced lymphocyte count, and high ferritin levels are all connected to liver dysfunction in systemic disorders that impair innate immune regulation. Signs of liver dysfunction should be monitored more closely. patients in the hospital so that early and individualized therapeutic procedures may be used. Studies using COVID19 have shown increased transaminases and hypoproteinemia as well as a delayed prothrombin time to be signs of mild to severe liver damage, but nothing is known about the liver infection produced by SARS-CoV2. About 60% of those with SARS had liver issues, according to previous study. SARS genetic material was found in liver tissue. Although hepatocyte function was reduced, there was no evidence of fibrin buildup or fibrosis.. Hepatology. SARSCoV-1 or SARS-CoVV-2 infection is suspected to have caused the city to develop viral hepatitis or a side consequence of pharmaceutical toxicity from excessive use of antiviral medications, antibiotics, and steroids. ACE2 expression was significantly elevated in cholangiocytes (59.7% of cells) rather than hepatocytes (2.6%) as a consequence of an overactive immune system in Twoseparate cohort investigations, demonstrating that SARSCoV2 may directly damage intrahepatic bile ducts via the production of ACE2 (Kukla et al. 2020). For the most part, the expression of ACE2 was significantly elevated in the clusters (59.7 percent of cells). There was only 2.6% of hepatocytes that expressed ACE2, and this was 20 percent lower than the amount seen in hepatic cells on average. SARS and 2019-nCton's principal targets in the lung are alveolar type 2 cells, which display the same level of ACE expression as cholangiocytes. It is plausible that viruses like 2019-nCoV and SARS, which utilize ACE2 as a host cell receptor, might infect and damage the liver via the presence of high levels of ACE2 expression in hepatic cells. Infection of the liver with COVID 19 is a given. Retrograde liver damage may be caused by the presence of ACE2 receptors on the cholangicyte. Biopsies reveal the presence of viral RNA in liver tissue. Cell death with ballooning, acidophilic substances, and lobular inflammation were also seen, bolstering the idea that the virus directly harmed the hepatocytes (Zhao et al. 2020). COVID-19 individuals may also have liver damage

from routinely administered medicines known to induce liver harm, such as antibiotics, antiretrovirals, and NSAIDs (non-steroidal anti-inflammatory drugs).

2.6 Liver Infection in Patients with Coronavirus

Acute liver injury and increasing cirrhosis are also related with a higher risk of severe current Covid 19, and the increased risk is considerably more associated with decompensated cirrhosis or cirrhosis, according to current knowledge. The acute course of Covid19 is related with alcoholic or non-alcoholic fatty liver disease. According to a study, patients with moderate infections had a death rate of around 43%, while those with severe infections had a mortality rate of about 74.4%. The autopsy of a coronavirus patient revealed viral particles in the lungs, certain organs, and the liver. MERS-CoV genome was detected in liver tissues by RTPCR assay Regarding whether the new coronavirus causes changes in the liver, because of the receptors that the virus uses to invade cells are also present in the liver and therefore the liver is a potential target for infection with the new coronavirus. Coronavirus particles are found in hepatocytes, therefore poor liver function tests in these individuals may be directly related to this virus; furthermore, because of an immune system reaction to the virus; and finally, since the current treatment for Covid 19 is hepatotoxic. If a patient has been diagnosed with Covid 19 and has bad liver function tests, they are at greater risk of developing severe illness than if they have good liver function tests. Severe acute hepatitis cases are very uncommon, occurring almost exclusively in patients using Covid 19. Covid 19 may impair liver function tests, but these impairments are generally modest and transitory, so no special treatment is necessary (Shi *et al.* 2020).

2.7 Albumin Regulation on ACE2 and COVID19

Albumin is one of the proteins that make up 60% of the blood content, and it is responsible for carrying 250 types of nutrients and vitamins and transporting them from the intestines to the rest of the body. As in the case of COVID 19 infection, a strong inflammatory storm ensues in the body because of viral infection, and this storm leads to a rise in oxidative stress, so albumin interacts with free crack compounds and

succeeds in combating and removing them, but it suffers severe damage(Rabbani *et al.* 2018). Changes in the body's structure and function occur because of a strong reaction, changing its role in controlling blood clotting, increasing the body's vulnerability to clots, and raising the patient's risk of mortality. The seriousness of COVID 19 is related to the occurrence of these three complications, which are called the triangle of terror, which are: cytokine (inflammatory) storm, oxidative stress, and blood clotting. The technology is very advanced, and a relationship has already been found between higher mortality rates in COVID 19 patients during the first 10 days of admission to intensive care and an increase in the severity of protein damage. The half-life of albumin is about 19 days, and its production decreases when the elderly are over 50 years old, as the albumin is freely present in a very large percentage and performs many functions, including transporting hormones, fatty acids, etc., and most importantly, the Coronavirus and many medicines, as the lack of albumin is an indicator of infection with the virus as well as bad Nutrition and other diseases.(Johnson *et al.* 2020) We often notice a lack of albumin in patients with diabetes, hypertension, and heart disease. Patients who suffer from a lack of albumin have more death rates. The work of albumin is similar to that of heparin, as it includes anticoagulant properties. ACE2 receptors are controlled by albumin, which enhances arterial oxygen level, and because albumin deficit increases mortality, therapy with albumin is becoming possible, as the body needs a lot of albumins when infected with pathogens, notably respiratory viruses because of increased capillary permeability as a consequence of inflammation leads to albumin escapes. to the interstitial environment(Liu *et al.* 2009).

2.8 COVID-19 and Impairment

In order to know never infection with covid19. Most likely, the liver is affected directly as a result of COVID 19 cellular disease, or as a result of medication, septic blood, or immunologically as a result of the body’s immune reaction. In addition, this virus may cause an increase in the death rate due to aggravation of the liver where there are receptors Many bile cells called ACE2 make the liver a target for this virus (Hoffmann *et al.* 2020). Where the risk increases in patients who suffer from severe diseases and led to poor results. It is not clear whether the virus has a direct effect on the liver, or is a

result of other factors such as treatments used against the Coronavirus of drugs or chronic diseases. The clinical significance and prevalence of liver dysfunction associated with Covid-19 disease are not entirely clear due to the paucity of available studies on the topic (Walayat *et al.* 2015). As a result, experts are trying to figure out if the sickness is to blame or if other factors like the body's inflammatory response or pharmacological disorders are to blame. Transient hepatitis is a condition that occurs when a systemic viral infection causes a transitory increase in liver biomarkers due to immunological activation without affecting liver function. In individuals with severe COVID-19 symptoms, particularly those with pre-existing liver issues, some scribed drugs used to ease some of the symptoms might strain the liver. Taking antivirals, antibiotics, antipyretics, and pain killers, for example, might severely worsen hepatopathy (Stockman et al. 2006). Chronic and acute liver failure may occur in patients with cirrhosis of the liver who have COVID-19. A condition known as mild lipids, or the buildup of extra fat in the liver, has been seen in cases of COVID-19 patients' livers. As a result of their predisposition to comorbid conditions such diabetes, obesity, and cardiovascular disease, patients with non-alcoholic fatty liver disease are at greater risk of developing severe forms of COVID-19. Hepatocyte macrophages (with an elevated percentage of M1 pro-inflammatory and M2-suppressive macrophages) demonstrated some kind of depolarization or activation in nonalcoholic fatty liver patients, which may have a role in infection with the covid-19 virus. Non-alcoholic fatty liver disease patients have an increased chance of contracting Covid-19 virus infection and requiring more time to clear the virus and recover (Kapuria et al. 2020). It is also difficult for people with liver illness to fight against COVID-19 because of the compromised immune system. Patients with weaker immune systems, such as those with autoimmune liver disease, organ transplant recipients, or those with liver cancer who are receiving immunosuppressive medication, are more likely to get COVID-19 when they become infected with the virus (Wu *et al.* 2020).

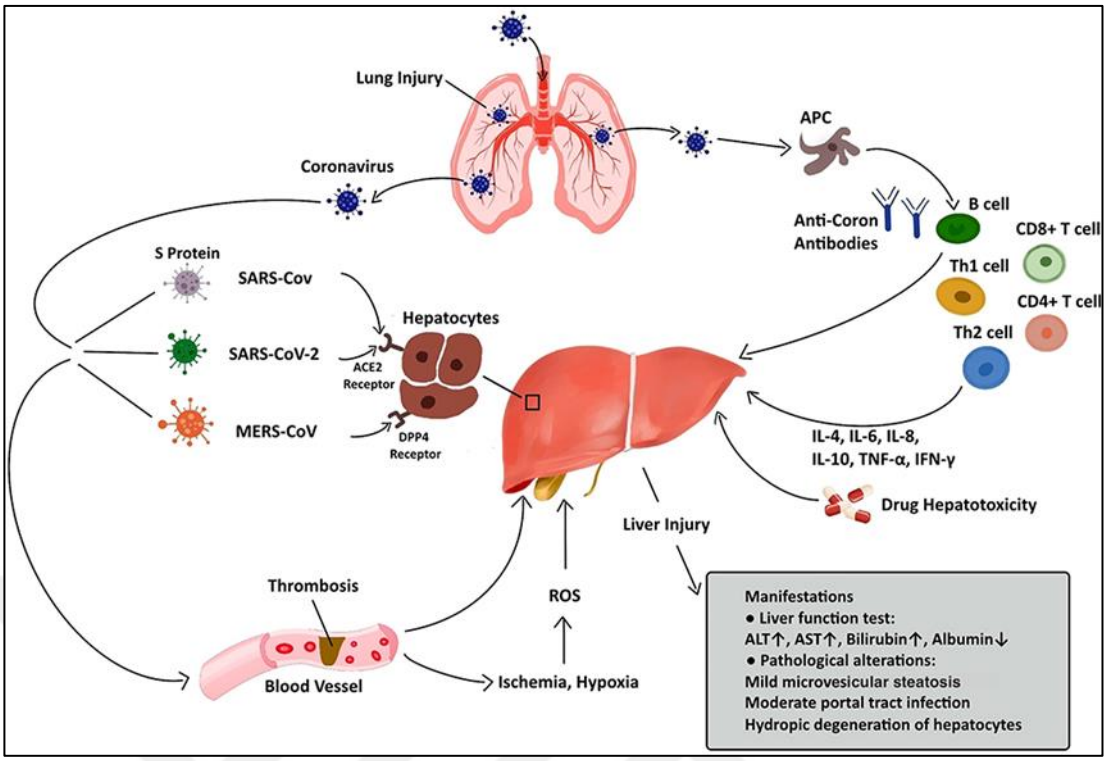

Figure 2.3 Coronavirus infection causes liver damage(Wang *et al.* 2021)

2.9 Hepatotoxicity of COVID-19 Antiviral and Anti-Inflammatory Therapies

According to the reports, the therapies used to combat the Corona virus might cause liver infection and damage. Most patients will have symptoms after a week of infection, and around half of those individuals will have atypical symptoms within a week following infection (Fan et al. 2020). Coronavirus-related medications, such as ritonavir, may be to blame for elevated alanine, aspartate, and plipropene, as well as acetaminophen and hydroxychloroquine treatments, which may cause imbalances in liver markers, as well as medicines that have been shown to treat the virus. As a result of its angiotensin-converting enzyme inhibitor, the coronavirus also raises liver enzymes. Patients infected with the Coronavirus may be treated with dexamethasone, a corticosteroid, since it has been demonstrated to lessen the incidence of infection in the event that the virus causes higher stimulation. Because of the overstimulation of this system, patients' lives are affected as these steroids block this overstimulation and ultimately antibiotics are the most prevalent cause of liver damage (Cai et al. 2020).

"Dexamethasone" and "Remdesivir" are two of the most often utilized antiviral medications in the treatment of "Covid-19" patients in the hospital, and they both target particular viral enzymes or weak points in the virus's reproduction inside human cells. Other studies have demonstrated that the common treatment of malaria and Rheumatoid Arthritis with hydroxychloroquine is harmful to persons with Covid-19.. For Ebola patients in clinical trials, Remdesivir is an antiviral medicine that might cause stomach difficulties and nausea, but it is being administered secretly in covert trials (Montastruc et al. 2020).

lopinavir and ritonavir, which suppress the protease enzyme and have proved successful therapies against the coronavirus in addition to numerous adverse effects on the liver and pancreas, are two further options for treating the infection (Atkins et al. 2006). Several liver enzymes were discovered to be elevated in the blood serum, and this results in an imbalance between the levels of external and internal calcium (Cao *et al.* 2010).

2.10 Vaccination against COVID-19 in Liver Disease Patients

Concerns have been raised about the effectiveness and safety of SARS-CoV-2 vaccinations in the general population as well as persons with concurrent diseases. Vaccine prophylaxis is particularly important for those with comorbidities in the case of a COVID-19 pandemic. Previous study has revealed that individuals with underlying liver problems may have a lower immune response to vaccinations against hepatitis A, hepatitis B, and seasonal flu. Patients with autoimmune hepatitis, who often use immunosuppressive medicines, had decreased vaccination responses (Härmälä et al. 2019).

The development of vaccines for SARS-CoV-2 has moved at such a rapid pace. According to the WHO COVID-19 vaccine tracer, 126 different vaccines have been tested in clinical trials since the beginning of the pandemic. For any new vaccination, there are always concerns about the possible side effects. Anaphylactic shock may occur in a very small proportion of cases following the first or second COVID-19

immunization; the most typical side effects include a rise in temperature and a general feeling of exhaustion (Chen et al. 2021). Another potential side effect of new vaccinations is autoimmune illness. Patients and doctors alike are worried about the risk of a return or worsening of autoimmune disorders due to a lack of available evidence. Vaccines used in this study have not provided conclusive evidence of a relationship (Genovese et al. 2018). It's important to note that vaccination clinical trials included people with persistent chronic liver disease. Patients with chronic liver illness may have a higher frequency or severity of adverse effects, although this has not been shown to be the case in studies using COVID-19 vaccines (Cornberg et al. 2021). Long-term evidence on the SARS-CoV-2 vaccine's safety is lacking, but the risk of gains and losses must be considered when deciding whether or not to take the vaccines in the first place. Patients with a high risk of COVID-19-related complications and death should be extra vigilant in this regard. SARS CoV-2 neutralizing antibody responses cannot be measured using a commercially available test at this time. It is because of this that we cannot say with certainty whether or not the vaccination is successful. There is still a lot of work to be done in this subject. As a side note, approved vaccinations' benefits far exceed their potential negative effects (Walsh *et al.* 2020).

2.11 Relationship Between COVID-19 and Renin-Angiotensin Converting Enzyme System

Co-morbidities and cellular storms may affect the severity of coronavirus infection, since COVID-19 enters organ cells through the renin-angiotensin system and is replicated inside human cells. This system regulates blood pressure, metabolism, and the body's ability to fight off disease (Watanabe et al. 2011). It has been shown that ACE-2, a receptor found on cells in the respiratory, renal, gastrointestinal, blood vessel, and liver systems, acts as a "portal" for viruses to enter the body. Patients with type 1 or type 2 diabetes have a considerably higher ACE2 level in their cells. Medications are often used to treat patients with diabetes (ACE inhibitors, also known as ACE inhibitors). Angiotensin converting enzyme is inhibited. On top of that, it includes the angiotensin-converting type I receptor and another key renin-angiotensin-system protein, ang II. Antihypertensive medications often include ACE-II and ACE-II receptor

blockers, which encourage the body's cells to produce even more ACE-2. Those on ACE/ACE inhibitors have very high levels of this enzyme, which puts them at a significant risk of severe MERS-CoV infection that may lead to death. Patients with cardiovascular disease, high blood pressure, or diabetes who are using ACE2 stimulant medications should exercise great care while taking these medications, according to the FDA (Benjamin *et al.* 2017).

2.12 COVID-19 and Associated Chronic Diseases

As a result of the severe acute respiratory syndrome caused by the coronavirus illness (COVID-19), more patients are admitted to the intensive care unit (ICU) and a larger number of people die (Guan et al. 2020). Many COVID-19 patients have recovered, however certain diseases have been linked to death and severe sickness. In fatal instances, hypertension (AH), diabetes mellitus (DM), coronary heart disease (CHD), stroke, and chronic bronchitis are the most common pathologies (Deng and Peng 2020). An increased risk of mortality has been linked to the combination of cardiovascular disease (CVD) and COVID-19 in acute COVID-19 patients compared to non-risk individuals, according to studies. What's the deal with this connection? Many chronic illnesses have characteristics with infectious diseases, such as inflammation and a compromised innate immune system. The production of proinflammatory mediators like interleukin-1 and tumor necrosis factor-alpha by overactive innate immune cells in metabolically active tissues causes insulin resistance and cell damage in diabetics (Odegaard and Chawla 2012). It is possible that thrombosis caused by MERS-CoV infection might lead to death, which can be verified by the presence of thrombosis by a rise in D-dime. When a patient died, lactic acid levels were found to be high. Lymphocytopenia is a common symptom of viral infection as well as acidosis. C. Huang and co-authors were the first to uncover that 32% of COVID-19 patients had comorbidities, such as cardiovascular disease, diabetes, hypertension, and chronic obstructive pulmonary disease, after examining the clinical features of 41 verified cases (COPD) (Huang *et al.* 2020).

2.13 The Relationship Between Age, Gender and COVID-19 Disease

According to health statistics, senior persons are more likely to die from the developing coronavirus than those under the age of 40. From a medical standpoint, this makes sense or appears self-evident, given that the elderly make up the majority of those suffering from ailments like diabetes, hypertension, and lung problems. It's also been suggested that the lungs of the aged have higher concentrations of enzymes that convert angiotensin II, which might explain why the elderly suffer from such severe illness. Add that the immune system weakens as we become older. For those who are older, the aging cells in the tissues of the body generate inflammatory compounds on their own since they experience a big change with age, which is why a person's innate immune system is continuously on alert and inflamed, which is not favorable to health. Immune system proteins like "cytokines," which cause inflammation, are more prevalent in those over 60 years old. Proteins of the immune system are more prevalent in the elderly than in the young, which contributes to an increased risk of disease in this population group. These developments are difficult to comprehend. Women are less likely to get infected than males because they have a smaller amount of ACE in their bodies, which prevents the immune system from reaching its intended target (Cai et al. 2020). Several variables, some biological and others entrenched in lifestyle, are working against males in the present pandemic since men are the weaker sex when it comes to a reaction to infection when they create an immune response. For example, women have two X chromosomes that include immune-related genes, unlike males who only have one X chromosome. Smoking rates may also be a factor, as is the function of estrogen in immunity. Only for males. Men have a higher rate of death. Men had greater ACE concentrations in the renin-angiotensin-aldosterone system in heart failure patients (Sama *et al.* 2020).

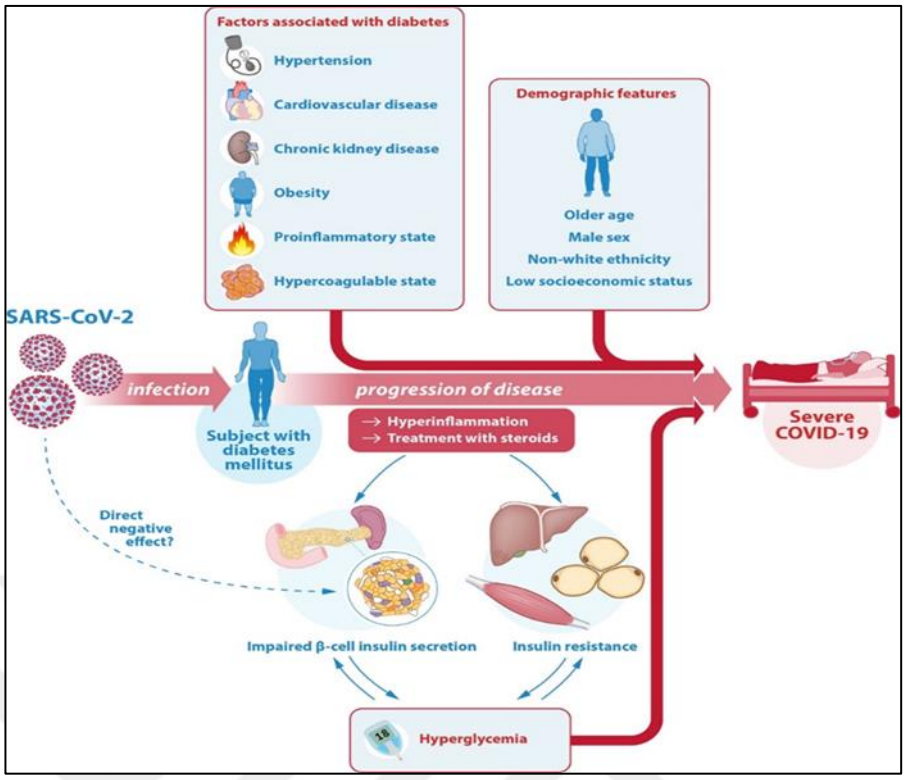

Figure 2.4 Diabetes and its relationship to infection with the corona virus (Landstra and de Koning 2021)

2.14 The Relationship Between Smoking and COVID19

Joan Smith *et al.* conducted research to determine why smokers are more prone to develop a range of viruses, including SARS-COV-2, which causes covid-19. As it is known, most people contract the new coronavirus in such a way that they either do not feel symptoms at all or transmit it easily. However, immunosuppressed people, the elderly, men, overweight, and smokers are more susceptible to infection.

In this study, scientists tried to find the main characteristic that makes smokers more susceptible to infection with the new Coronavirus. The group studied the activity of genes in the lungs and compared the results obtained in different age groups of both sexes, smokers and non-smokers (Smith *et al.* 2020). The scientist said: "When we put everything together and started the analysis, we noticed that both mice that inhaled tobacco and smoked had an increased amount of angiotensin-converting enzyme 2

(ACE2).” This is exactly the protein that the new Coronavirus uses to penetrate the cells of the human body, As it turns out, cigarette smoking boosts the creation of this protein in the lungs, implying that the virus aids in the infection of its own organ. Furthermore, smoking is a risk factor for many other non-communicable illnesses, including cardiovascular disease, cancer, respiratory disease, and diabetes, all of which are more prone to COVID 19 consequences (Van Zyl-Smit *et al.* 2020).

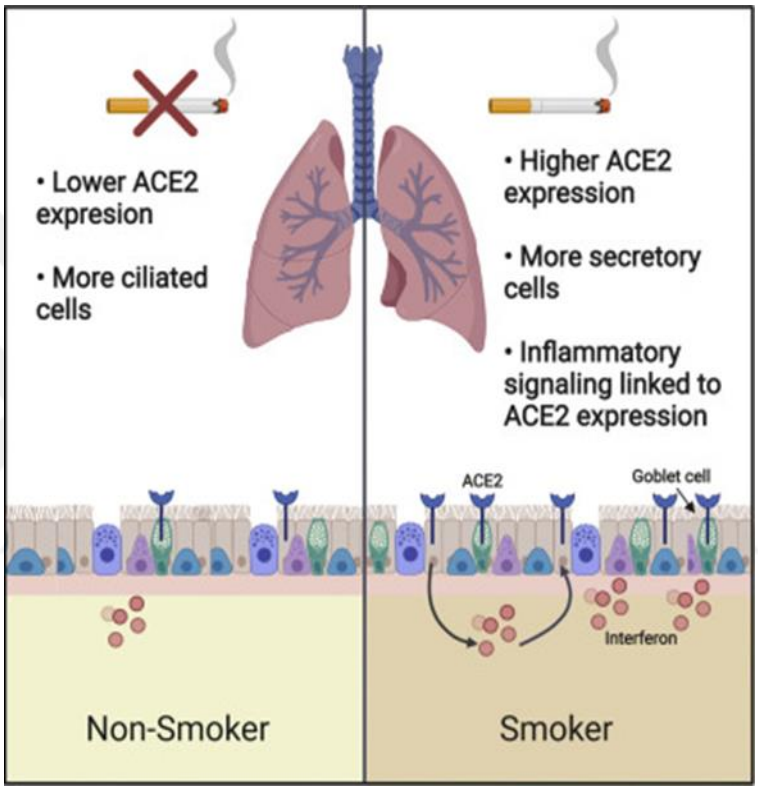

Figure 2.5 The coronavirus receptor ACE2 is found in greater abundance in the lungs of smokers (Smith *et al.* 2020)

3. MATERIALS AND METHODS

3.1 Study Design

The samples for this study were collected from December 2021 to February 2022 on 180 people, where the study consists of two groups, the first group consists of 120 patients infected with the corona virus, who were confirmed to have the PCR test, and the second group consists of 60 people. as a group officer. Where everyone agreed to participate in this study, the period of infection with the virus was postponed and was from one to three weeks, and none of the patients mentioned drug or alcohol abuse, and information was taken from patients such as age, gender, tobacco consumption, high pressure, diabetes, cancer, kidney and heart diseases because of their impact on the patient's immunity, or a direct or indirect effect on liver enzymes, as the study was conducted at Al-Kindi Teaching Hospital in the Iraqi capital, Baghdad..

3.1.1 Patients selection

Patients were selected according to the following criteria:

- The patient must be over 18 years old
- PCR swabs were taken from patients through the nose and oropharynx
- Taking information from patients about age, gender, smoking, vaccination and chronic diseases.

3.1.2 Sample collection

In order to detect the effects of corona on liver enzymes, 4 mL of blood was taken from a vein, placed in 6 mL chemical tubes with yellow caps, transported to the laboratory and centrifuged at 3500 rpm for 10 minutes, and blood serum was obtained. Where samples were taken at nine in the morning and transferred directly to the chemistry laboratory. Results were received 4 hours later and samples were examined using a

Cobas apparatus. Precautions such as wearing paws and face shields have also been taken to avoid contracting the virus.

3.2 Laboratory Equipment and Tools

Table 3.3 includes the precise and automated devices that were used in this study, as these devices are characterized by the accuracy of the results and the short time

Table 3.1 Laboratory materials and equipment

EQUIPMENT AND MATERIALS	ORIGIN	BRIEF SUMMARY
Cobas c 111 (4511)	Germany	Through this device, the results of the following tests were obtained: ALT,AST,Albumin and Alk. Phosphatase
ISE Deproteinize	Germany	Used as a cleaning solution for cleaning the probe, ion-selective electrodes
Activator	Germany	It is also used for the initialization of the ISE unit and for activating the probe.
Syringe	China	it was used to draw blood from patients and put it in tubes to perform the required analyzes
Pipettes	Germany	It is used to transfer blood serum to sample tubes as well as for measurements
Gel tube	China	It is used to separate blood as well as to store it.

3.3 The chemical kits used in our study

Biochemical reagents and kits It is included in this Table 3.2.

Table 3.2 Chemical tests and kits that were used in our study

KIT	LOT. NO.
Alanine aminotransferase	04718569
Aspartate aminotransferase	04657543
Alkaline phosphatase	04657373
Albumin	04657357
Total bilirubin	04255260

3.4 Methods

3.4.1 Procedure of ALT, AST, alkaline phosphatase and albumin by cobas c111

When the device is turned on and solutions are placed inside it, it heats the solutions to a limited temperature, and also checks the vessels for their quality and the required measurements. Check the support with water and cleaning fluids on each suction sample and each suction. When the blood separation is completed by means of a centrifuge, and the blood serum is obtained, where it is placed in the cuvettes, the required tests are determined through a screen in the device, and then the cuvettes are placed, where the jets are placed inside the device. Pump the air so that the sample is homogeneous with the solution. The device is washed until the completion of all the required examinations, then the required results are calculated through photoanalysis, and the result of the examination is distinguished in the event of a shortage or increase in the result, as well as stored in the device

3.4.2 Measurement of aspartate aminotransferase level in serum by cobas c111

Principle: This test has been improved for performance and stability by the recommendations of the International Federation of Clinical Chemistry. The reaction in the sample is accelerated by aspartate aminotransferase to form L- glutamate and oxaloacetate by transferring the amine group between L-aspartate and oxoglutarate. In the presence of malate dehydrogenase, oxaloacetate reacts with NADH to form NAD+. The enzyme pyridoxal phosphate ensures complete activation of the enzyme in the transaminase reaction. Aspartate aminotransferase is proportional to NADH.The method of measuring the decrease in the enzyme is done in absorbance.

3.4.3 Measurement alanine aminotransferase level in serum by cobas c111

Principle: This test has been improved for performance and stability by the recommendations of the International Federation of Clinical Chemistry, where the

reaction between oxoglutarate and alanine is catalyzed by L- alanine aminotransferase and by NADH, pyruvate formed in the reaction catalytic to form NAD + and lactate is reduced by the enzyme lactate dehydrogenase, and the rate of oxidation between alanine is directly proportional to the rate of oxidation between alanine and NADH. The method of measuring the decrease in the enzyme is done in absorbance.

3.4.4 Alkaline phosphatase

Principle: The colorimetric assay is carried out according to the standard method. Whereas p-nitrophenol phosphate is divided in the presence of zinc and magnesium ions and by phosphatase into p-nitrophenol and phosphate. The catalytic activity of alkaline phosphatase is proportional to the released p-nitrophenol, and in the end, the increase is calculated by absorbance.

3.4.5 Albumin

Principle: After agglutination resulting from antigen reaction with anti-albumin immunoassay. Consequently, antigen and antibody complexes that are measured by the turbidity method are formed as a result of this agglutination

3.4.6 Principle of total bilirubin

The color-based diazo method, in which bilirubin binds with 3,5-dichlorophenyl diazonium ion in the presence of a well-dissolved agent, and this process takes place in a strong acidic medium, and this process can be determined photometrically by matching the colors of the red azo dye with the bilirubin

4. RESULTS AND DISCUSSION

Corona virus is one of the viruses that affect the respiratory system and cause many symptoms that led to the death of approximately 3% of those infected with it and affects many organs, including the liver. From August 2021 to February 2022, 120 people infected with the virus were confirmed with a PCR test, and the second group, which is a control group consisting of 50 people, were also examined by the same test mentioned above, where their enzymes and albumin were studied at Al-Kindi Hospital in the capital, Baghdad.

4.1 Results of Age

The results of our study showed that the mean age of the patient group was 61.44 ± 17.72. While the results in the control group were 38.36 ± 14.769. This study helps to compare the age and differences that occur in liver enzymes from infection with the corona virus. As shown in Table 4.1 and Figure 4.1

Table 4.1 Age-specific patient and control group data

PARAMETERS	**MEAN ± SD**
	Age (year)
Patients group	61.44 ± 17.72
Control group	38.36 ± 14.769
T-test	8.105
P-value	0.495
* (P≤0.05), ** (P≤0.01).	

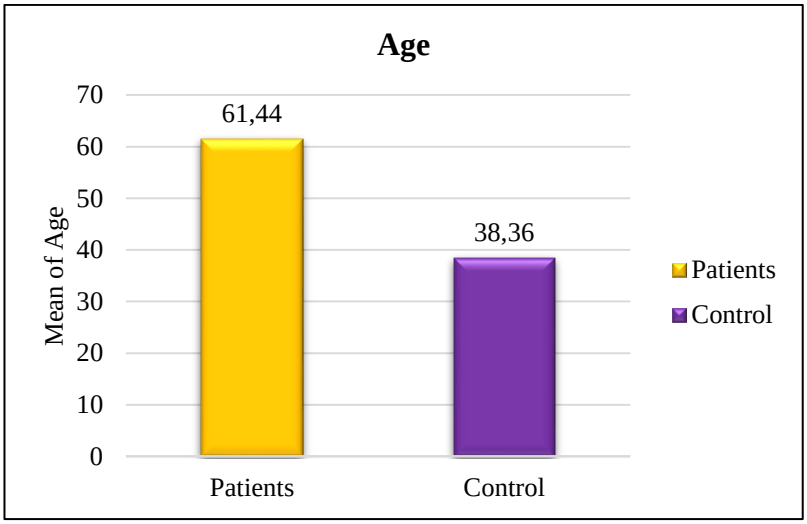

Figure 4.1 The mean age in patient and control group

4.2 The Results of ALT, AST and AST

In the Table 4.2 and Figure 4.2, the levels of ALP, ALT and ASP were compared in patients and the control group.

In our study for ALP the mean was (129.22 ± 88.97) and the noramal value (53-128 U/l), it was found that these enzymes were elevated in patients compared to the control group, and age or having one of the chronic diseases may have a role in this. While the control group was (72.70 ± 19.05). The showed result corona virus to icrease in level ALP. The patient not suffer from any diseases from before infection with corona virus.

While the mean ALT was (36.20 ± 40.49) and the normal value was (Up to 45 mg/dL), where it was found that this enzyme is high in about a quarter of the patients, and most of these patients had diseases, including kidney and liver diseases and others, and it may be a role for these diseases in the rise of this enzyme compared to the control group Whereas, the average height in the control group is (21.74 ± 11.20).

As for AST, the average AST was (62.05 ±49.66) and the normal value was (Up to 45 mg/dL), it was found that this enzyme was elevated in approximately one third of the

patients, and most of these patients had diseases, including kidney, liver, diabetes and other diseases, and there may be a role for these diseases in the rise of this enzyme compared to the control group. Whereas, the mean height in the control group is (7.60±18.34) Our study agrees with many studies, including this study (Wang *et al.* 2021).

Table 4.2 Comparison of patient and control group in ALT, AST and ALP

PARAMETERS	**MEAN ± SD**		
	ALP	ALT	AST
Patients Group	129.22 ± 88.97	36.20 ± 40.49	49.66 ± 62.05
Control Group	72.70 ± 19.05	21.74 ± 11.20	18.34 ± 7.60
T-test	4.442**	2.482**	3.551**
P-value	0.0001	0.001	0.0001
* (P≤0.05), ** (P≤0.01).			

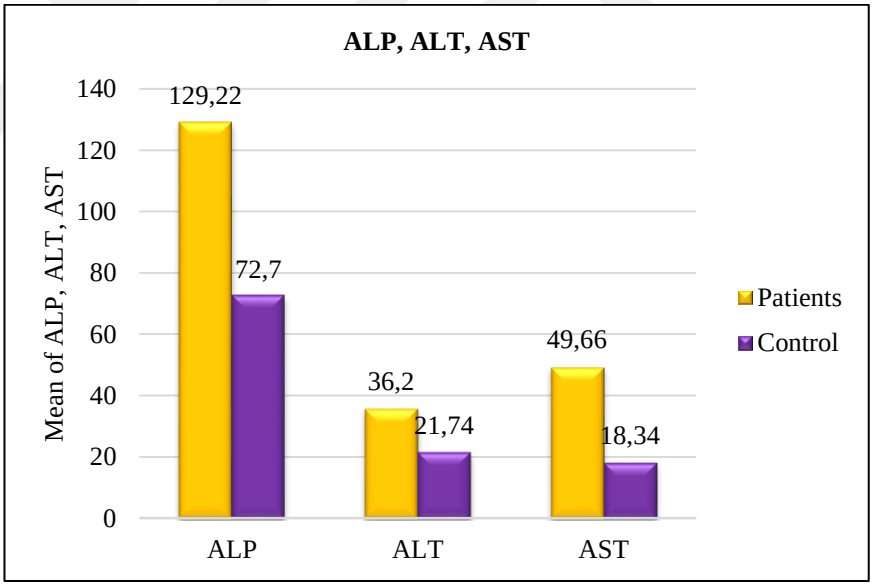

Figure 4.2 Mean ALT, AST, and ALP in the patient and control group

4.3 The Results of TSB and ALB

In this Table 4.3 and Figure 4.3, ALB and TSB levels were compared in patients and the control group.

In our study of albumin, the mean was (2.41 ± 3.35) and the normal value was (3.2 - 5.2 mg / dL), where it was found that albumin was statistically significant as it decreased in more than half of the patients, compared to the control group in which albumin was not affected, whose average was (0.34 ± 4.11) Our study agrees with many studies, including this study (Huang *et al.* 2020, Turcato *et al.* 2022).

While in our study for the TSB test, where the mean was (1.27 ± 0.75) and the norm value was (0.3-1.2 mg/dL), this test was not as it was statistically significant compared to the control group that was not affected by bilirubin whose mean was (0.17 ± 0.46) this study agreement with many study and conformed this state (Chen *et al.* 2020).

Table 4.3 Comparison of patient and control group in TSB and ALB

PARAMETERS	**MEAN ± SD**	
	TSB	S. Albumin
Patients group	0.75 ± 1.27	3.35 ± 2.41
Control group	0.46 ± 0.17	4.11 ± 0.34
T-test	2.45**	-3.321**
P-value	0.016	0.001
* (P≤0.05), ** (P≤0.01).		

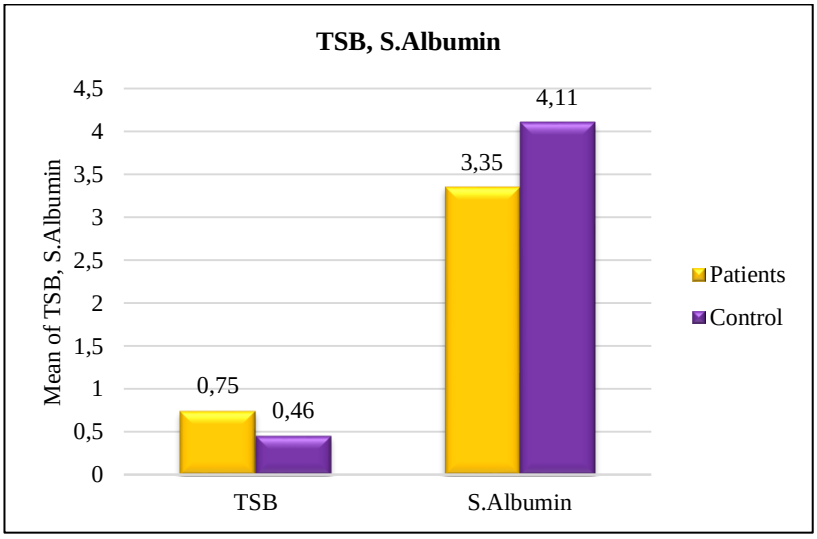

Figure 4.3 Mean ALB and TSB in the patient and control group

5. CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

The aim of our study was to find out the effect of COVID 2019 on liver enzymes as well as albumin for age. It was statistically significant, as the elderly are most affected by infection, and most of those admitted to hospital are elderly, especially those with comorbidities such as diabetes, hypertension, heart and kidney disease. As for the tests that were made, which included alkaline phosphatase, it was statistically significant, as it increased in about one third of the patients, and most of these patients had comorbidities, and its height was not very high. As for the alanine aminotransferase analysis, it had a simple statistical significance, about a quarter of the patients, but the aspartate was higher, reaching nearly half of the patients, on the contrary, the albumin decreased in about two thirds of the patients, and the least affected test was the bilirubin, which It increased in 10% of patients.

For the control group, not all analyzes were affected by this, and their number was 50 people. and the treatment used against the COVID 19, as well as other treatments, such as those used to reduce the temperature, may have a direct or indirect effect on liver enzymes, and it is known to us that the first key to contact COVID 19 with human cells is the "receptor of the angiotensin-converting enzyme-2" (ACE2), which has been monitored for several studies as this receptor is present in the bile ducts as well as the liver, and according to studies, it is present in men more than women. It is worth noting that most of the infected are men, and the virus's association with it leads to liver damage and thus an increase in its enzymes. Albumin deficiency is the most important statistical evidence in our study, as it decreased in a significant portion of patients. This could be explained by some putative mechanisms including sepsis and kidney disease, or by cytokines generated by inflammatory processes that in turn lead to their decrease. The most important reason is that albumin is made in the liver.

5.2 Recommendations

1. Include a gamma-glutamyl transferase (GGT) test to enhance the study.
2. Make patients of two groups young and old group.
3. Further study of the relationship between albumin and infection with the virus.

REFERENCES

Atkins, K. L., Cibulka, N., Lucco, K. L., Gase, D., Overton, E. T. and Gross, G. A. 2006. Kaletra: Viral Response and Pregnancy Outcomes in HIV Type 1 Infection. Obstetrics and Gynecology., 107(4): 80S.

Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R. and Gillespie, C. 2017. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. circulation., 135: e146-e603.

Cai, Q., Huang, D., Yu, H., Zhu, Z., Xia, Z., Su, Y. and Qu, J. 2020. COVID-19: Abnormal liver function tests. Journal of hepatology., 73: 566-574.

Cao, R., Hu, Y., Wang, Y., Gurley, E. C., Studer, E. J., Wang, X. and Zhang, L. 2010. Prevention of HIV protease inhibitor-induced dysregulation of hepatic lipid metabolism by raltegravir via endoplasmic reticulum stress signaling pathways. Journal of Pharmacology and Experimental Therapeutics., 334(2): 530-539.

Center, S. A. 2007. Interpretation of liver enzymes. Veterinary Clinics of North America: Small Animal Practice., 37(2): 297-333.

Chao, Y., Fan, C., Liang, Y., Gao, B. and Zhang, S. 2012. A novel serpin with antithrombin-like activity in Branchiostoma japonicum: implications for the presence of a primitive coagulation system. PLoS One., 7(3): e32392.

Chau, T. N., Lee, K. C., Yao, H., Tsang, T. Y., Chow, T. C., Yeung, Y. C. and Lai, S. T. 2004. SARS- associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology., 39(2): 302-310.

Chen, M., Yuan, Y., Zhou, Y., Deng, Z., Zhao, J., Feng, F. and Sun, C. 2021. Safety of SARS-CoV-2 vaccines: a systematic review and meta-analysis of randomized controlled trials. Infectious diseases of poverty., 10(1): 1-12.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y. and Wei, Y. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet., 395: 507-513.

Chia, P., Coleman, K., Tan, Y., Ong, S., Gum, M., Lau, S. and Lee, P. 2020. Singapore 2019 Novel Coronavirus Outbreak Research Team. Detection of air and surface contamination by SARS-CoV-2 in hospital rooms of infected patients. Nat. Commun., 11: 2800.

Cholankeril, G. Podboy, A. Aivaliotis, V. I. Tarlow, B. Pham, E. A. Spencer, S. P. and Ahmed, A. 2020. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: early experience from California. Gastroenterology., 159:775-777.

Colmenero, J., Rodríguez-Perálvarez, M., Salcedo, M., Arias-Milla, A., Muñoz-Serrano, A., Graus, J. and Cachero, A. 2021. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. Journal of hepatology., 74(1): 148-155.

Cornberg, M., Buti, M., Eberhardt, C. S., Grossi, P. A. and Shouval, D. 2021. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. Journal of hepatology., 74(4): 944-951.

Cummings, M. J., Baldwin, M. R., Abrams, D., Jacobson, S. D., Meyer, B. J., Balough, E. M. and Hastie, J. 2020. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. The lancet., 395(10239): 1763-1770.

Darvish, M. S. 2012. The identification and differentiation between normal and secondary colorectal cancer in human liver tissue using x-ray interaction techniques.

Deng, S.Q. and Peng, H.J. 2020. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. Journal of clinical medicine., 9: 575..

Elias, H. and Bengelsdorf, H. 1952. The structure of the liver of vertebrates. Cells Tissues Organs., 14(4): 297-337.

Fan, Z., Chen, L., Li, J., Cheng, X., Yang, J., Tian, C. and Cheng, J. 2020. Clinical features of COVID-19-related liver functional abnormality. Clinical Gastroenterology and Hepatology., 18: 1561-1566.

Garrido, I., Liberal, R. and Macedo, G. 2020. COVID- 19 and liver disease—what we know on 1st May 2020. Alimentary pharmacology and therapeutics., 52(2): 267-275.

Genovese, C., La Fauci, V., Squeri, A., Trimarchi, G. and Squeri, R. 2018. HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. Journal of Preventive Medicine and Hygiene., 59(3): E194.

Gerges Harb, J., Noureldine, H. A., Chedid, G., Eldine, M. N., Abdallah, D. A., Chedid, N. F. and Nour-Eldine, W. 2020. SARS, MERS and COVID-19: clinical manifestations and organ-system complications: a mini review. Pathogens and Disease., 78(4): ftaa033.

Ghazanfar, H., Kandhi, S., Shin, D., Muthumanickam, A., Gurjar, H., Qureshi, Z. A. and Budhathoki, P. 2022. Impact of COVID-19 on the Gastrointestinal Tract: A Clinical Review. Cureus., 14(3).

Gori, A., Dondossola, D., Antonelli, B., Mangioni, D., Alagna, L., Reggiani, P. and Rossi, G. 2020. Coronavirus disease 2019 and transplantation: a view from the inside. American Journal of Transplantation., 20(7): 1939-1940.

Guan, W.j., Ni, Z.y., Hu, Y., Liang, W.h., Ou, C.q., He, J.x. and Hui, D.S. 2020. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine., 382: 1708-1720.

Hanley, B., Lucas, S.B., Youd, E., Swift, B. and Osborn, M. 2020. Autopsy in suspected COVID-19 cases. Journal of clinical pathology., 73: 239-242.

Harapan, H., Itoh, N., Yufika, A., Winardi, W., Keam, S., Te, H. and Mudatsir, M. 2020. Coronavirus disease 2019 (COVID-19): A literature review. Journal of infection and public health., 13(5): 667-673.

Härmälä, S., Parisinos, C. A., Shallcross, L., O'Brien, A. and Hayward, A. 2019. Effectiveness of influenza vaccines in adults with chronic liver disease: a systematic review and meta-analysis. BMJ open., 9(9): e031070.

Hoffmann, M., Kleine- Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S. and Wu, N. 2020. H., Nitsche A., Müller MA, Drosten C., Pöhlmann S. Cell., 181: 271.

Holshue, M.L., DeBolt, C., Lindquist, S., Lofy, K.H., Wiesman, J., Bruce, H. and Tural, A. 2020. First case of 2019 novel coronavirus in the United States. New England Journal of Medicine., 119: 747–751.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y. and Gu, X. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet., 395: 497-506.

Huang, J., Cheng, A., Kumar, R., Fang, Y., Chen, G., Zhu, Y. and Lin, S. 2020. Hypoalbuminemia predicts the outcome of COVID- 19 independent of age and co- morbidity. Journal of medical virology., 92: 2152-2158.

Ilchenko, L.Y., Nikitin, I. and Fedorov, I. 2020. COVID-19 and liver damage. The Russian Archives of Internal Medicine., 10: 188-197.

Johnson, A. S., Fatemi, R. and Winlow, W. 2020. SARS-CoV-2 bound human serum albumin and systemic septic shock. Frontiers in Cardiovascular Medicine., 7: 153.

Kaltsas, A. and Sepkowitz, K. 2012. Community acquired respiratory and gastrointestinal viral infections: challenges in the immunocompromised host. Current Opinion in Infectious Diseases., 25(4): 423-430.

Kapuria, D., Upadhyay, S., Shekhar, R. and Torrazza-Perez, E. 2020. Alcoholic liver disease and COVID-19 pneumonia: a case series. Journal of clinical and translational hepatology., 8(4): 463.

Kukla, M., Skonieczna-Żydecka, K., Kotfis, K., Maciejewska, D., Łoniewski, I., Lara, L. and Koulaouzidis, A. 2020. COVID-19, MERS and SARS with concomitant liver injury-systematic review of the existing literature. Journal of clinical medicine., 9(5): 1420.

Kunutsor, S. K. and Laukkanen, J. A. 2020. Renal complications in COVID-19: a systematic review and meta-analysis. Annals of medicine., 52(7): 345-353.

Kushner, T. and Cafardi, J. 2020. Chronic liver disease and COVID- 19: alcohol use disorder/alcohol- associated liver disease, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, autoimmune liver disease, and compensated cirrhosis. Clinical Liver Disease., 15(5): 195.

Landstra, C.P. and de Koning, E.J. 2021. COVID-19 and diabetes: understanding the interrelationship and risks for a severe course. Frontiers in Endocrinology., 12: 599.

Lau, S.K., Lau, C.C., Chan, K.H., Li, C.P., Chen, H., Jin, D.Y. and Yuen, K.Y. 2013. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. Journal of General Virology., 94: 2679-2690.

Li, H., Chen, C., Hu, F., Wang, J., Zhao, Q., Gale, R. P. and Liang, Y. 2020. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia., 34(6): 1503-1511.

Liu, B.-C., Gao, J., Li, Q. and Xu, L.-M. 2009. Albumin caused the increasing production of angiotensin II due to the dysregulation of ACE/ACE2 expression in HK2 cells. Clinica chimica acta., 403(1-2): 23-30.

Luglio, M., Tannuri, U., de Carvalho, W.B., Bastos, K.L., Rodriguez, I.S., Johnston, C. and Delgado, A.F. 2020. COVID-19 and liver damage: narrative review and proposed clinical protocol for critically ill pediatric patients. Clinics., 75.

Luke, T. C., Kilbane, E. M., Jackson, J. L. and Hoffman, S. L. 2006. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Annals of internal medicine., 145(8): 599-609.

Magrone, T., Magrone, M. and Jirillo, E. 2020. Focus on receptors for coronaviruses with special reference to angiotensin-converting enzyme 2 as a potential drug target-a perspective. Endocrine, Metabolic and Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine and Metabolic Disorders)., 20(6): 807-811.

Marc, F., Moldovan, C., Hoza, A., Restea, P., Sachelarie, L., Romila, L. E. and Farcas, D. M. 2021. Evaluation of hepatic biochemical parameters during antiviral treatment in COVID-19 patients. Biology., 11(1): 13.

Montastruc, F., Thuriot, S. and Durrieu, G. 2020. Hepatic disorders with the use of remdesivir for coronavirus 2019. Clinical Gastroenterology and Hepatology., 18(12): 2835-2836.

Motamedi, H., Ari, M. M., Dashtbin, S., Fathollahi, M., Hossainpour, H., Alvandi, A. and Abiri, R. 2021. An update review of globally reported SARS-CoV-2 vaccines in preclinical and clinical stages. International immunopharmacology., 96: 107763.

Nan, X., Tamgüney, T. M., Collisson, E. A., Lin, L.-J., Pitt, C., Galeas, J. and Chu, S. 2015. Ras-GTP dimers activate the mitogen-activated protein kinase (MAPK) pathway. Proceedings of the National Academy of Sciences., 112(26): 7996-8001.

Odegaard, J.I. and Chawla, A. 2012. Connecting type 1 and type 2 diabetes through innate immunity. Cold Spring Harbor perspectives in medicine., 2: a007724.

Rabbani, G., Lee, E. J., Ahmad, K., Baig, M. H. and Choi, I. 2018. Binding of tolperisone hydrochloride with human serum albumin: effects on the conformation, thermodynamics, and activity of HSA. Molecular pharmaceutics., 15(4): 1445-1456.

Sama, I.E., Ravera, A., Santema, B.T., van Goor, H., ter Maaten, J.M., Cleland, J.G. and Ng, L.L. 2020. Circulating plasma concentrations of ACE2 in men and women with heart failure and effects of renin-angiotensin-aldosterone-inhibitors. European Heart Journal., 41: 1810-1817.

Schaefer, E.A., Arvind, A., Bloom, P.P. and Chung, R.T. 2020. Interrelationship between coronavirus infection and liver disease. Clinical Liver Disease., 15: 175.

Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J. and Zheng, C. 2020. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet infectious diseases., 20: 425-434.

Smith, J. C., Sausville, E. L., Girish, V., Yuan, M. L., Vasudevan, A., John, K. M. and Sheltzer, J. M. 2020. Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Developmental cell., 53(5): 514-529. e513.

Stockman, L. J., Bellamy, R. and Garner, P. 2006. SARS: systematic review of treatment effects. PLoS medicine., 3(9): e343.

Tian, S., Xiong, Y., Liu, H., Niu, L., Guo, J., Liao, M. and Xiao, S.-Y. 2020. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Modern Pathology., 33(6): 1007-1014.

Tortora, G. J. and Derrickson, B. H. 2018. Principles of anatomy and physiology: John Wiley and Sons.

Turcato, G., Zaboli, A., Kostic, I., Melchioretto, B., Ciccariello, L, Zaccaria, E. and Bonora, A. 2022. Severity of SARS-CoV-2 infection and albumin levels recorded at the first emergency department evaluation: a multicentre retrospective observational study. Emergency Medicine Journal., 39: 63-69.

van Zyl-Smit, R. N., Richards, G. and Leone, F. T. 2020. Tobacco smoking and COVID-19 infection. The Lancet Respiratory Medicine., 8(7): 664-665.

Walayat, S., Ahmed, Z., Martin, D., Puli, S., Cashman, M. and Dhillon, S. 2015. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. World journal of hepatology., 7(24): 2503.

Walsh, E. E., Frenck Jr, R. W., Falsey, A. R., Kitchin, N., Absalon, J., Gurtman, A. and Bailey, R. 2020. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. New England Journal of Medicine., 383(25): 2439-2450.

Wander, P., Epstein, M. and Bernstein, D. 2020. COVID-19 presenting as acute hepatitis. The American journal of gastroenterology., 115: 6255.

Wang, X., Lei, J., Li, Z. and Yan, L. 2021. Potential effects of coronaviruses on the liver: an update. Frontiers in Medicine., 8.

Watanabe, K., Arumugam, S., Thandavarayan, R.A. and Kodama, M. 2011. Experimental autoimmune myocarditis: role of renin angiotensin system Myocarditis., 309-320.

Weiss, S. R. and Leibowitz, J. L. 2011. Coronavirus pathogenesis. Advances in virus research., 81: 85-164.

Wong, S.H., Lui, R.N. and Sung, J.J. 2020. Covid- 19 and the digestive system. Journal of gastroenterology and hepatology., 35: 744-748.

Wu, H., Zhu, H., Yuan, C., Yao, C., Luo, W., Shen, X. and Xiang, Y. 2020. Clinical and immune features of hospitalized pediatric patients with coronavirus disease 2019 (COVID-19) in Wuhan, China. JAMA network open., 3(6): e2010895-e2010895.

Xu, L., Liu, J., Lu, M., Yang, D. and Zheng, X. 2020. Liver injury during highly pathogenic human coronavirus infections. Liver international., 40: 998-1004.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C. and Zhu, L. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine., 8(4): 420-422.

Zhang, Y., Xiao, M., Zhang, S., Xia, P., Cao, W., Jiang, W. and Zhang, H. 2020. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. New England Journal of Medicine., 382(17): e38.

Zhao, B., Ni, C., Gao, R., Wang, Y., Yang, L., Wei, J. and Xu, W. 2020. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein and cell., 11(10): 771-775.

Zong, Y. and Stanger, B. Z. 2011. Molecular mechanisms of bile duct development. The international journal of biochemistry and cell biology., 43(2): 257-264.

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