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### Original Research Article

## Investigating the Effects of Chemical Drugs on Clinicopathological and Survival in Hepatocellular Carcinoma; A systematic Review

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#### ABSTRACT

In this article we Investigate the Effects of Chemical Drugs on Clinicopathological and Survival in Hepatocellular Carcinoma. Hepatocellular carcinoma (primary liver cancer) arises from liver cells and is different from secondary liver cancer, which originates from other parts of the body and spreads to the liver. Hepatocellular carcinoma is classified in different ways. A classification is made by the Barcelona Clinic Liver Cancer Group (BCLC), which classifies cancer based on how long a person is expected to live. This classification depends largely on the size of the cancer, the number of cancers in the liver, how well the liver is functioning, and whether the person's activities are affected by the cancer. Patients with intermediate-stage hepatocellular carcinoma have large and multiple cancers, but they do not have complete liver failure. The cancer is confined to the liver, and there is no limitation in the patient's daily activities. There is considerable uncertainty in the management and treatment of patients with intermediate stage hepatocellular carcinoma. Apart from using standard Cochrane methods that allow comparison of only two treatments at a time (direct comparison), planned to use an advanced method that allows comparison of many different treatments that are compared separately in trials (meta-analysis). An increase in liver enzymes can be a sign of inflammation or destruction of cells in the liver. Inflamed or damaged liver cells release larger amounts of certain chemicals, including liver enzymes, into the bloodstream, which can lead to increased liver enzymes in blood tests. Elevated liver enzymes that are often seen include alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma glutamyl transpeptidase.

**Keywords:** *COVID-19, Liver Enzymes, Patient, Drug, Blood Lipids.*

## Introduction

These days, the corona virus has become one of the major crises for the health of the world, and there are many unknowns and uncertainties about it. One of the groups at risk of contracting this virus are people with underlying diseases [1-3]. Regarding this virus, the question has been raised whether having a fatty liver can increase the possibility of contracting the corona virus or worsen the patient's condition?

The liver is one of the vital organs of the body and has two lobes, which is located under the chest and on the right side of the abdomen [4]. This organ plays important and different roles in the body. Among these roles, it is possible to mention participation in body metabolism activities such as digestion, metabolism of drugs and cleansing the body of various toxins. Liver diseases can be hereditary or caused by various environmental factors [5]. Other diseases that commonly cause elevated liver enzymes include metabolic syndrome, hepatitis, drug or alcohol abuse, heart failure, and cirrhosis of the liver. Some fewer common diseases can also cause an increase in liver enzymes, including: autoimmune hepatitis, celiac disease, liver cancer, hemochromatosis, cytomegalovirus infection, mononucleosis, liver cancer, sepsis or blood poisoning, Wilson's disease, and polymyositis. Also, the use of some drugs, such as some painkillers and statins, can also increase liver enzymes [6]. The results showed that those who have diseases such as diabetes, blood pressure, fat and obesity are more exposed to fatty liver disease. In addition, family history of the disease can increase the percentage of the disease. It can also be said that most of the diseases related to the liver are without any symptoms, and most of the patients are those whose disease has progressed and they have found liver failure and had to undergo a liver transplant. Over time, damage to the liver can lead to cirrhosis, which ultimately ends in liver failure, and this process is a life-threatening condition [7-9]. Symptoms related to liver diseases include yellowing of the skin and eyes (jaundice), abdominal pain, swelling in Different parts of the leg, itchy skin, dark urine, bloody or black stools, chronic fatigue, nausea, vomiting, loss of appetite and tendency to bruise. Liver diseases have many causes, which can be mentioned as follows:

**1- Infection:** A number of viruses have the ability to infect the liver, which causes inflammation of the liver and eventually leads to a decrease in the function of this organ. Viruses that cause liver damage can be spread through blood or contaminated food and water [10-13].

**2- Immune system disorder:** diseases in which the immune system attacks certain parts of the body are called autoimmune diseases. Autoimmune hepatitis is a chronic disease in which the immune

system attacks the liver and affects the function and tissue of the liver.

**3- Genetics:** Like many other diseases, genetics play a significant role in liver disorders. In fact, it is possible that a defective gene inherited from a parent can lead to acute or chronic liver failure. Genetic liver diseases include hemochromatosis, Wilson's disease, hype oxalosis and cancer.

**4- Other common causes of liver dysfunction:** alcohol abuse (alcoholic hepatitis), accumulation of fat in the liver (non-alcoholic fatty liver disease) are among other things that lead to inflammation and liver failure. Factors that may increase the risk of developing liver diseases include:

- ✓ Alcohol abuse and drug injection using shared needles and tattoos.
- ✓ Exposure to blood and body fluids of infected people or certain chemicals or toxins.
- ✓ Diabetes and obesity [13].

Due to the different causes of liver problems, the complications of liver disease are different. For example, in people with autoimmune hepatitis and liver cirrhosis, there is a high risk of developing liver cancer. Untreated liver disease can eventually lead to liver failure.

Hepatocellular carcinoma is the most common type of liver cancer. This type of cancer often occurs in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C diseases [14].

### **Search strategy and selection of articles**

Search in Scopus, Google scholar, PubMed databases and by searching with keywords such as "Chemical Drugs" and "Clinicopathological and Survival" and "Hepatocellular Carcinoma" to obtain articles related to the selected keywords [12]. Case report articles, editorials, and articles that were not published or only an introduction of them were available, as well as summaries of congresses and meetings that were in languages other than English, were ignored. Only the original research articles that evaluated the effectiveness of different drugs in the treatment of COVID-19 using standard methods were studied (figure 1).

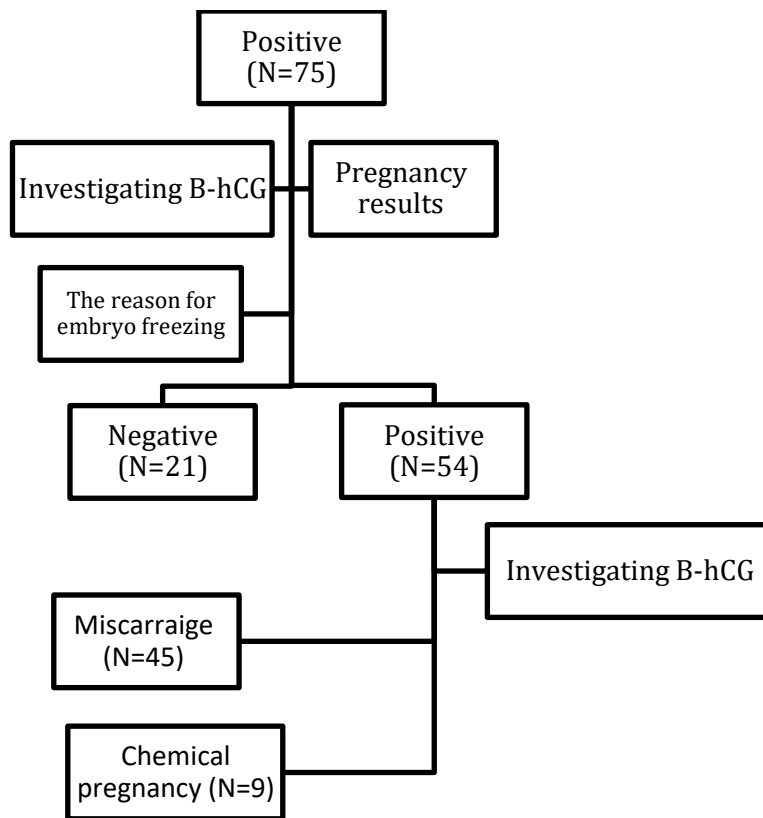


Figure 1. Flow chart of included subjects

**Risk factors of hepatocellular carcinoma**

The risk of hepatocellular carcinoma, which is the most common type of liver cancer, is higher in people with long-term liver diseases. Hepatocellular carcinoma is more likely to occur in people (Figure 2) whose liver is scarred by hepatitis B or hepatitis C, who drink large amounts of alcohol, or who have severe accumulation of fat in the liver [15].

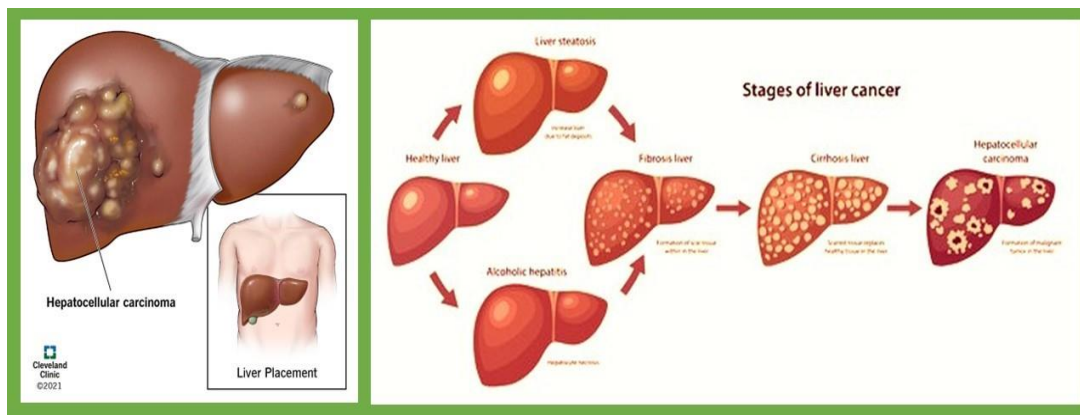


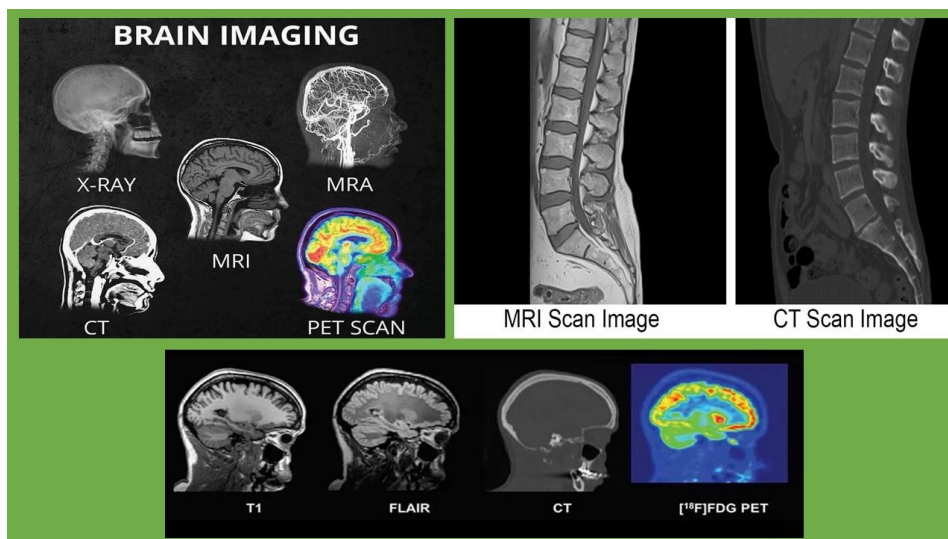
Figure 2. Risk factors of hepatocellular carcinoma

### Diagnosis of hepatocellular carcinoma

The tests and methods used to diagnose hepatocellular carcinoma are: Blood tests to assess liver function Imaging, such as CT and MRI (Figure 3) in some cases, liver biopsy to test for hepatocellular carcinoma Treatment of hepatocellular carcinoma The best treatment method for each person is selected according to the size and location of hepatocellular carcinoma, liver function and general health of the person. Hepatocellular carcinoma treatments include:

- Treatment of hepatocellular carcinoma
- Hepatocellular carcinoma surgery.

Usually, in surgery, cancerous tissue and the margin of healthy tumor tissue are removed. Also, this method can be a suitable treatment option for people who are in the early stages of liver cancer, but the liver has still maintained its normal function [16].



**Figure 3.** CT and MRI

Hepatocellular carcinoma liver transplant surgery. Surgery to remove the entire liver and replace it with a donor's liver is one of the treatment options for hepatocellular carcinoma. which can be helpful for people whose liver cancer has not spread to other tissues [17]. Killing cancer cells using heat or cold. For people who cannot undergo surgery, ablation methods are recommended to kill cancer cells in the liver using extreme heat or cold. These methods are ablation by radio frequency waves (radio waves), cryoablation and ablation using alcohol or microwaves [18]. Chemotherapy or direct radiation therapy of cancer cells. Doctors introduce chemotherapy drugs into the liver by passing a catheter through the blood vessels (chemoembolization), sometimes small radioactive glass spheres

(radioembolization) are used to directly deliver radiation to liver cancer cells. Radiotherapy of hepatocellular carcinoma. If surgery is not possible for any reason, radiation therapy using X-ray or proton radiation is recommended. Stereotactic body radiotherapy (SBRT) is a special type of radiation therapy that simultaneously focuses a large number of beams on one point of the body. Targeted drug therapy of hepatocellular carcinoma [19]. Targeted drugs attack certain weak points in cancer cells and reduce the progression of hepatocellular carcinoma in people with advanced liver cancer. Hepatocellular carcinoma immunotherapy. Immunotherapy drugs use the body's immune system, which fights microbes, to attack cancer cells [20]. Immunotherapy can be an option for the treatment of advanced liver cancer. Clinical trials of hepatocellular carcinoma. Clinical trials give people the opportunity to experience new liver cancer treatments. Ask your doctor if you are eligible to participate in a clinical trial [21].

### Laboratory diagnosis of liver diseases

**1- Examining the general condition and function of the liver:** The general condition of the liver is performed by testing liver enzymes including AST(SGOT), ALT(SGPT), ALP and  $\gamma$ GT.

**2- Checking the state of the coagulation system:** The coagulation system of the body is checked by PT tests (INR and PTT) [22].

**3- Investigating a person's hepatitis B status:** Hepatitis B virus identification tests include the identification of surface antigens of the virus, such as HBs Ag and HBe Ag tests, as well as the HBV RT PCR molecular test, which is highly accurate.

**4- Investigating a person's hepatitis C status:** HCV RT PCR molecular test and HCV Ab test are used to identify the hepatitis C virus.

**5- Examining the immune status against hepatitis:** Following the person's vaccination against the hepatitis B virus, the HBs Ab test is performed to measure the person's immunity against the mentioned virus.

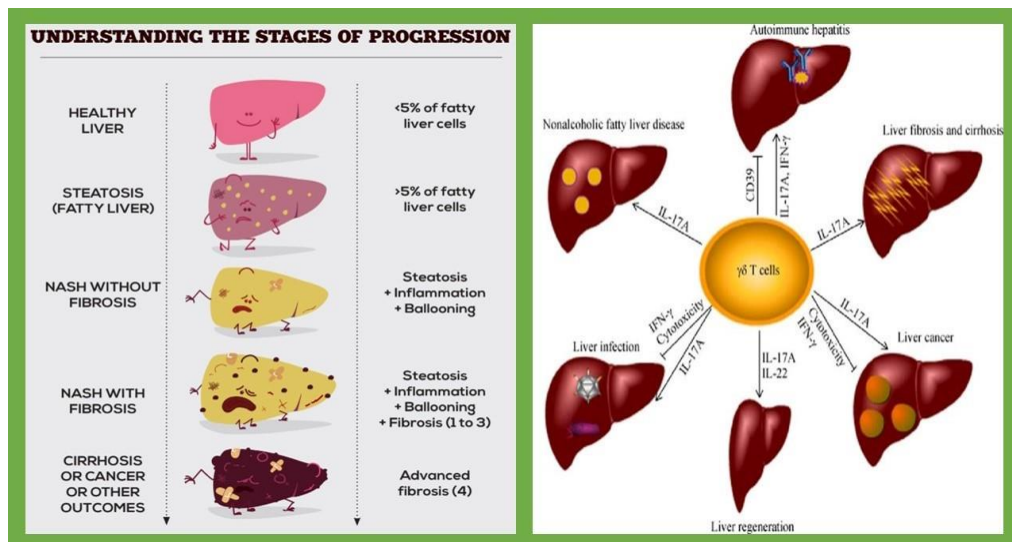
**6- Examining the presence of immune system disorders:**

- ✓ Test (Anti-liver/kidney Microsomal Antibody (anti-LKM).
- ✓ Anti-Mitochondrial Antibody Test (AMA).
- ✓ Test (Anti-smooth muscle antibody (ASMA).
- ✓ Test (Anti-nuclear Antibodies (ANA).

**7- Examining the status of liver cancer:** Liver cancer is determined by various tests such as Alpha-fetoprotein blood (AFP) test [23].

**8- Investigating the condition of fatty liver:** This condition is diagnosed by testing the level of liver enzymes including AST(SGOT), ALT(SGPT), ALP and  $\gamma$ GT. Liver function tests, also known as liver chemistry (Figure 4), help determine the health of the liver by measuring the level of proteins, liver enzymes and bilirubin in the blood [23]. Liver function tests are often recommended in the following situations:

- ✓ To investigate damage caused by liver infections such as hepatitis B and hepatitis C.
- ✓ To monitor the side effects of certain medications that affect the liver.



**Figure 4.** Laboratory diagnosis of liver diseases

### The presence of various underlying diseases

- ✓ Checking the status of hemochromatosis disease is done by serum transferrin and serum ferritin tests.
- ✓ Wilson's disease status is checked by serum Copper and urine Copper tests and serum Ceruloplasmin test [24].
- ✓ Alpha-1 antitrypsin ( $\alpha$ 1AT) deficiency test is performed.
- ✓ Examining the condition of hyper oxalosis disorder is determined by serum and urine oxalate level tests.

Many tests can be done on the liver. Specific tests can reflect different aspects of liver function. Tests



commonly used to check for liver abnormalities include:

- ✓ Alanine transaminase (ALT).
- ✓ Aspartate aminotransferase (AST).
- ✓ Alkaline phosphatase (ALP).
- ✓ Albumin and bilirubin.

ALT and AST tests measure enzymes that your liver releases in response to injury or disease. Albumin test measures the amount of albumin production in the liver, while bilirubin test measures the amount of bilirubin excretion, ALP can be used to evaluate the bile duct system of the liver.

**1- Alanine transaminase (ALT) test:** Alanine transaminase is used by your body to metabolize protein. If the liver is damaged or not working properly, ALT can be released into the blood. This causes the ALT level to rise. A higher-than-normal result in this test can be a sign of liver damage. According to the American College of Gastroenterology, ALT above 25 IU/L in women and 33 IU/L in men typically requires further testing and evaluation [25].

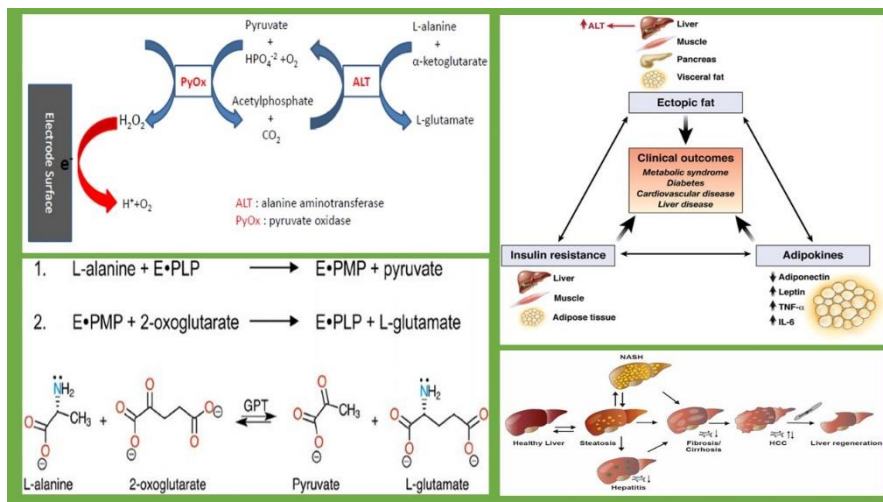


Figure 5. Alanine transaminase (ALT) test

**2- Aspartate aminotransferase (AST) test:** Aspartate aminotransferase is an enzyme found in several parts of the body, including the heart, liver, and muscles. Because AST levels are not as specific for liver damage as ALT, they are usually checked for liver problems along with ALT. When the liver is damaged, AST can be released into the bloodstream. A high result in the AST test indicates a problem in the liver. The normal range of AST in adults is up to 40 IU/L and may be higher in infants and young children [26].



- 3- Alkaline phosphatase (ALP) test:** Alkaline phosphatase is an enzyme found in bones, bile ducts and liver. An ALP test is usually prescribed in combination with several other tests. High ALP levels may indicate liver inflammation, bile duct obstruction, or bone disease. Children and adolescents may have high ALP levels. Because their bones are growing. Pregnancy can also increase ALP levels. The normal range for ALP in adults is usually up to 120 IU/L.
- 4- Albumin test:** Albumin is the main protein made by the liver that performs many important functions of the body. For example, albumin stops fluid from leaving your blood vessels, nourishes your tissues, and transports hormones, vitamins, and other substances into your body. The albumin test measures the quality of the production of this particular protein by the liver. A low result on this test could indicate that your liver is not working properly. The normal range of albumin is 3.5-5.0 g/dL. However, low albumin can also be caused by poor nutrition, kidney disease, infection and inflammation.
- 5- Bilirubin test:** Bilirubin is a waste product resulting from the breakdown of red blood cells. It is normally processed by the liver. Bilirubin passes through the liver before being excreted in the stool. A damaged liver cannot process bilirubin properly. This leads to abnormal levels of bilirubin in the blood. A high bilirubin test result may indicate a problem in the proper functioning of the liver. The normal range of total bilirubin is usually 0.1-1.2 mg/dL. There are certain hereditary diseases that increase the level of bilirubin, but the liver function is normal.

#### **What are the symptoms of liver disorder?**

- ✓ Weakness, tiredness or loss of energy and weight loss.
- ✓ Jaundice (yellowing of the skin and eyes), bruising or abnormal bleeding.
- ✓ Accumulation of fluid in the abdomen known as ascites.
- ✓ Bad body secretions (dark urine or light stools).
- ✓ Nausea, vomiting, diarrhea and abdominal pain.

Your doctor may prescribe liver function tests if you see symptoms of liver dysfunction. Various liver function tests can also monitor the progress or treatment of the disease and test the side effects of some medications. Your doctor will give you complete instructions on how to prepare for the blood sample. Certain medications and foods may affect the levels of enzymes and proteins in the blood [27].

**Discuss**

Hepatoma (HCC) is a malignant tumor in the liver, which is called liver cell cancer. This cancer starts from functional liver cells. 75 to 85% of liver cancers are related to this malignant type. Other times, liver cancer may start in blood vessels, small bile ducts, or immature liver cells. But the most common type of cancer is hepatoma or liver cell carcinoma. This type of cancer is more common in people with chronic liver diseases. Diseases such as liver cirrhosis, hepatitis B and hepatitis C increase the risk of developing this cancer. But about 25% of patients with liver cell cancer do not have a history of any chronic disease. For this reason, everyone should pay attention to the symptoms of hepatoma. According to radiopaedia regarding the spread of liver cell cancer: Hepatocellular carcinoma is the fifth most common cancer in the world and the third most common cause of death from cancer (after lung and stomach cancer). The incidence of HCC is increasing, which is mainly attributed to the increase in hepatitis C infection. The incidence of hepatoma is strongly affected by areas where chronic hepatitis B infection is common. The highest rate of this risk factor is in Asia (Figure 6 & 7). In Western countries, this amount is lower and alcohol accounts for a greater share of risk factors.

**Figure 6.** Forest plot showed Heart rate



**Figure 7.** Forest plot showed Body temperature

HBV infection with (or without) liver cirrhosis is the most important risk factor for HCC in most

regions of the world, including Iran. HCC has a much poorer prognosis if detected early. One of the most important screening methods for this tumor in the community is the use of ultrasound and serum level measurement (AFP) periodically. In addition to the pulmonary system, the corona virus can cause conflicts in various organs of the body, including the digestive system, liver, heart and blood vessels. Although the symptoms of corona are different in different people, this virus can affect different organs of the body. The liver is one of the important organs that are involved in some corona patients. The liver can be involved along with the lungs, digestive system and other organs, or even this important organ of the body can be involved alone and people suffer from liver complications [28]. Gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhea are common in corona patients, and sometimes liver symptoms appear in the form of increased liver enzymes or even cases such as jaundice or liver failure, which can be due to direct involvement of liver cells. be with the corona virus [29].

Corona, like other viruses such as infectious mononucleosis, cytomegalovirus and hepatitis viruses, can cause damage and inflammation in the liver in addition to general symptoms such as fatigue, lethargy, body pain, fever and chills. Although the symptoms of corona are different in different people, this virus can affect different organs of the body. Experts believe that one of the important organs that are involved in some corona patients is the liver. Corona is one of the important reasons for the increase of liver enzymes [30]. Therefore, it is necessary for people with high liver enzymes to undergo medical examinations in terms of corona infection. According to experts, high liver enzyme is considered an underlying disease. This disease, along with other underlying diseases such as blood pressure, diabetes and kidney failure, increases the risk of contracting the corona virus [31]. People with underlying diseases are more susceptible to corona disease than others, and it is recommended that these people follow health principles, control the underlying disease with timely and regular use of medicines and be careful in their diet to strengthen their immune system. Take care not to get corona disease. Evidence shows that people with more severe symptoms of the corona virus also have higher liver dysfunction. Defects in liver function are common in people with corona, and some studies have stated that this defect is seen in 60% of patients with Sars [32].

Of course, the liver disorder caused in a number of these patients can be partially related to receiving effective drugs to treat this disease, but studies have shown that liver damage in corona patients may be directly caused by viral infections. Pathological studies in SARS patients have confirmed the presence of the virus in the liver tissue. A study in China has shown that there is no significant difference in the incidence of liver dysfunction among survivors and those who died from the

coronavirus [32]. Studies show that age, gender, co-infection, underlying diseases such as obesity, diabetes, heart, lung, kidney diseases and weak immune system are risk factors for corona viruses that can lead to severe disease. or death in infected people.

Exposure to vinyl chloride (a chemical used in the manufacture of some plastics) and thorium dioxide (a chemical formerly used in X-ray testing) may also increase the risk of liver angiosarcoma. In recent years, strict regulations regarding exposure to these chemicals have been put in place in the United States. Certain types of inherited metabolic diseases may cause cirrhosis and increase the chance of developing cancer. Genetic hemochromatosis (an excessive iron disorder that causes iron stores throughout the body, including the liver), tyrosinemia (increased levels of the amino acid tyrosine), alpha-1-antitrypsin deficiency, porphyria cutaneous tarda (deficiency of heme synthesis), glycogen. Storage disease and Wilson's disease (increased levels of copper in the liver) are rare diseases that may damage the liver and increase the risk of liver cancer.

A new study shows that people with fatty liver disease are more likely to be admitted to the hospital due to Corona, and on the contrary, it was found that metabolic surgery can help reduce the symptoms of obesity and, as a result, reduce the hospitalization rate [33]. Acute respiratory syndrome coronavirus spread in China since noon in December 2019. As of September 4, 2020, more than 26.2 million people have been infected and 866,000 people have died. Although there is still much to learn about this new pathogen, information is still not fully available. We have already identified the most important risk groups. Patients with diabetes are chronic diseases, heart patients, kidney patients and liver patients [34-36]. Osteohepatitis or non-alcoholic fatty liver disease increases the likelihood of hospitalization. Non-alcoholic fatty liver increases the possibility of hospitalization of corona patients [37-39].

Considering that the pathophysiology of Covid-19 has a strong relationship with inflammation, despite all this information, more investigations are still needed. For this reason, researchers from the University of Minnesota, the University of Miami, and the Johns Hopkins School of Medicine are investigating the risk assessment percentage of hospitalized patients [40]. In summary, this study shows that liver disease and osteo-hepatitis are risk factors for admission by analyzing a large database in the United States, as well as possible treatments to prevent this issue. Retrospective analyzes of patients admitted for treatment of fatty liver and obesity from 65 primary care clinics and 12 hospitals were followed [41].

In addition, researchers also believe that metabolic treatments for diabetic patients reduce their risk of severe corona infection, and this is not just one reason, but racial and gender risks also add to this

statistic. In summary, this study shows that the data and medical records of liver patients can help in identifying which patients are susceptible to the severe type of the disease [42-44]. In short, this study shows that patients who were hospitalized due to liver disease in the past include more statistics of corona patients hospitalized in the hospital. Promisingly, we have found that known treatments for metabolic syndrome reduce hospitalization rates for covid-19. Also, obese patients who have undergone surgery will also have a chance to stay out of the risks of worsening Corona [45-47]. There is a lot of uncertainty in the treatment of intermediate-stage hepatocellular carcinoma. This cancer is defined by the Barcelona Clinic Liver Cancer Center (BCLC) as follows: stage B large and multinodular hepatocellular carcinoma, Child-Pugh status, A to B, performance status 0 to 2, and no vascular obstruction or extrahepatic disease [48].

### Conclusion

Men aged 60 and older are more prone to liver cancer than women and young men. In fact, hepatocellular carcinoma is considered a relatively rare type of cancer. Hepatocellular carcinoma accounts for about 85 to 90 percent of primary liver cancers, meaning cancers that start in your liver and not elsewhere in your body. There are different types of liver cancer. Hepatocellular carcinoma is the most common form of liver cancer. Currently, there is no evidence from randomized clinical trials that people with intermediate-stage hepatocellular carcinoma benefit from systemic chemotherapy with sorafenib either alone or when arterial chemoembolization is used as a concomitant intervention (high-quality evidence very low). We need high-quality, randomized clinical trials designed to measure differences in important clinical outcomes (eg, all-cause mortality or health-related quality of life). According to the available evidence, it can be concluded that liver involvement may be caused by contracting the corona virus or by receiving medication to treat it, and considering the different results of the studies, it is not possible to reliably identify fatty liver as an underlying risk factor. To cause disease or to aggravate it. Of course, this virus is new, and it is necessary to conduct more research on its risk factors, and until then, all people, especially those with chronic diseases, should observe health and preventive measures. During the research conducted regarding the symptoms and complications of Corona, about 15 to 58% of the patients experienced an increase in liver enzymes. The exact cause of this complication is not known. Corona may directly damage the liver or this complication may be an inflammatory response. There is also a possibility that the level of enzymes will increase due to the use of corona drugs. Some experts believe that the new liver virus can be a trace of the complications of Corona. Besides, it is said that maybe because the children have been in

quarantine for a long time and now, they are out of this quarantine, they have been infected with viruses that they used to get.

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