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Review Article

Drug-Induced Liver Injury: A Literature Review

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Abstract

Drug-Induced liver injury (DILI) is a common harmful drug reaction of some medication which can cause the damage to liver cells, or might be a chance of death. In the western countries DILI is the main cause for acute liver failure. These reactions are very common because almost all drug regimens can cause injury to liver. Most of DILI cases are harmless and they get better after stopping the offending drug. These reactions are mainly due to some pharmacological remedies, traditional medications, herbal and nutritional supplements. Due to these harmful reactions, elevation is noticed in the liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate, total bilirubin) 2N from its normal value. Drug-induced liver injury includes 1,000 of pharmacological remedies or more. Here, we review the maximum current literature, so the treatment includes timely diagnosis and removal of the doubtful medication is the key. This paper explains the different causes, pharmacological medications responsible for drug-induced liver injury, effect of covid-19 on liver injury and future perspective. It is important to be aware of and remove the suspected agent as soon as possible. There are no specific risk factors for DILI, but existing liver disease and genetic factors may be a priority for some people. Treatment of liver damage caused by drugs and herbs includes immediate drug withdrawal and supportive care aimed at alleviating unwanted symptoms. Main purpose of this paper is to deliver the info about the DILI, which are dose related, identification and consideration of disease.

Keywords: Drug-Induced liver injury (DILI), Pathophysiology, Diagnosis, Treatment, Risk factors and effect of covid-19 on liver injury.

1. Introduction

Liver is the largest stable vital organ and gland, which is responsible for the metabolism of vitamins and excretion of waste metabolites, having four lobes: the quadrate, caudate, left and right. ¹⁻⁴ Hepatocyte plates, which make up the majority of the liver lobule, are among its constituents. ⁵

1.1 Drug-induced liver injury

Drug-Induced liver injury is a common harmful drug reaction of some medication which can cause the damage to liver cells, or even death. These reactions are very common and almost all drug regimens can cause injury to liver. In the western countries DILI is the main cause for acute liver failure. ⁶ A variety of reactions that develop as a result of exposure to any manufactured or unavoidably occurring chemical substance are referred to as drug-induced liver injury (DILI). When DILI occurs, it often manifests as a slight increase in blood transaminase levels that is noticed during routine biochemical laboratory testing and goes away once the offending chemical agent has been removed. Even though they are rare, symptomatic DILI episodes constitute a notable source of liver damage. In acute liver failure (ALF), also known as fulminant hepatic failure, is the sudden, unexpected, and potentially fatal liver malfunction that develops within 26 weeks of the start of an infection and results in coagulopathy and hepatic encephalopathy. ⁷⁻⁹

Most typically based on dose dependence and predictability, DILI is categorised into intrinsic and idiosyncratic reactions. Once a particular threshold concentration has been reached,

intrinsic hepatotoxicity is dose established and may eventually be predicted. Acetaminophen (APAP) overdose serves as the best evidence of this form of DILI. Contrarily, idiosyncratic DILI (iDILI) is assumed to be dosage independent, unable to be predicted by the drug's known pharmacological features, and ultimately unpredictable. However, it may not be as easy to distinguish between intrinsic and idiosyncratic DILI in terms of dose dependence as first thought. Although the exact mechanism of iDILI is not known, it is generally accepted to be complex and connected to environmental, chemical, and pharmacological variables. The liver is essential for medication metabolism. Hepatic damage may result from problems in the interaction of phase I, which involves the production of reactive drug metabolites, phase II, which deals with detoxification reactions, and phase III, which deals with cellular excretion. ^{10,11}

In terms of analysis and control, it is a rare clinical issue. Drug-induced liver injury is the most common cause of acute liver failure in most Western countries, accounting for more than half of cases, and accounts for 3 to 5% of hospital admissions for jaundice. It is anticipated that there will be 14 to 19 cases per 100,000 people, with jaundice being present in 30% of cases. Our knowledge of viral, autoimmune, and hereditary liver diseases, as well as methods for their prevention and treatment, have advanced, but developments on those fronts have been slow in the case of drug-induced liver harm. ^{12,13}

Three patterns of DILI had been identified: mixed, hepatocellular, and cholestatic. Alkaline phosphatase (ALP) values greater than twice the upper limit of normal (ULN)

and/or less than or equal to 2R (R is the connection between ALP and ALT) are used to identify the cholestatic pattern. In the mixed pattern, ALT is more than twice the ULN with R ranging from to 5. The hepatocellular pattern is defined as ALT ranges more than two times the ULN and/or more than 5R. Twenty to forty percent of DILI is caused by the cholestatic

pattern, forty to eighty percent by the hepatocellular pattern and twelve to twenty percent by the mixed pattern. Despite the fact that individuals with cholestatic presentations have a greater survival rate, patients' biochemical liver. ¹⁴

R= Patient's ALT/UNL of ALT/ Patient's ALP/UNL of ALP

R value determination for drug-induced liver injury fig 1:

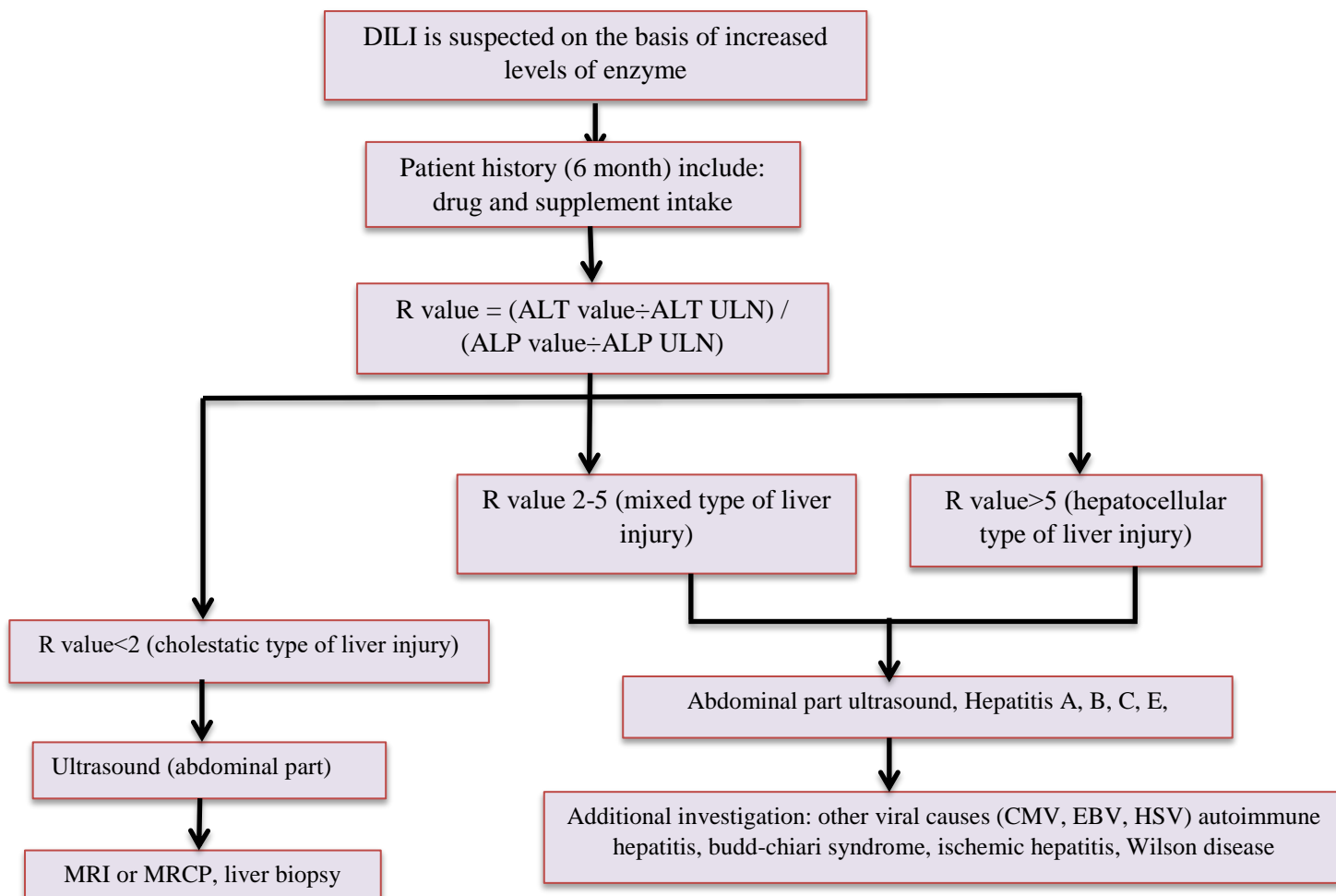


Figure 1: Diagnostic workflow for DILI and R value determination i.e. ALP-alkaline phosphatase, ALT-alanine aminotransferase, CMV-cytomegalovirus, EBV- Epstein-Barr virus, HSV- herpes simplex virus, MRCP-magnetic resonance cholangiopancreatography, MRI- magnetic resonance imaging, ULN- upper limit of normal range. ¹⁵ The diagnosis of DILI should be based on a comprehensive clinical trial, which includes a temporary relationship between illness and the administration of the underlying medication. The pattern of liver injury, which is a feature of the medication, also helps in the finding and removal of other causes of severe liver damage. ¹⁶

2. Epidemiology

Epidemiological data on DILI can provide essential information on the development of DILI mitigation strategies and its overall budget health care system. ¹⁷

- Drug-induced liver injury, which accounts for more than half of cases of acute liver failure in most Western nations, is the most common cause of 3 to 5% of hospital admissions for jaundice. It is anticipated that there will be 14 to 19 cases per 100,000 people, with jaundice being present in 30% of cases. ^{12,13}
- DILI is not well-defined in Asia. In China, because of largest population in the world, it has not been well studied. Up to 14–24 cases per 100,000 people have been observed, and 44,000 patients are predicted to acquire DILI each year.
- In India Antitubercular drugs are the major cause for developing DILI. TB treatment contributed to 58% of DILI

cases investigating acute liver failure in New Delhi; anti-tuberculosis drugs affected 5.7% of patients with ALF (70/1223), and 67% deaths.

- According to some recent demographic studies, there are 19.1 cases per 100,000 people in Iceland and 13.9 cases per 100,000 people in France per year, with hospitalization rates of 14% and fatality rates of 6%. i.e., 500 fatalities annually among the French populace.
- Although a number of medications have the potential to result in a DILI, antibiotics are the most frequently implicated, according to the DILI Network in the United States; they account for around 46% of all DILI cases. Similar findings were obtained in Spain and Iceland. The annual incidence of DILI was 4.1 cases per 100,000 people in an Italian case-control study. Women over 65 and those who have used antibiotics previously are affected. Trimethoprim sulfamethoxazole is another antibiotic that,

- because of its sulphonamide component, causes cholestatic damage in 60% of instances.
- NSAIDs are analgesic medications with gastrointestinal, renal, and cardiovascular side effects. Additionally, a small fraction of NSAIDs have an idiosyncratic hepatotoxicity that can have substantial, occasionally deadly, side effects. NSAIDs were a factor in (65/185) or 35.5% of cases. Nimesulide was the cause of 38.5 percent of cases, followed by ketoprofen (34%), diclofenac (15%), and ibuprofen (7%), while NSAIDs were combined with antibiotics in 17% of cases. In comparison to men, women made up about 50% of the population and had a higher frequency of hepatocellular and a lower frequency of cholestatic patterns. According to a recent multicentre study from Italy, there are roughly 4 occurrences of DILI for every 100,000 people, with the use of NSAIDs accounting for half of those cases. Nimesulide use is associated with an increased risk, then ibuprofen use and ketoprofen high dose.¹⁸
 - Statins such as simvastatin, rosuvastatin, atorvastatin, fluvastatin, and pravastatin were involved in 4.3 percent of patients (8/185), despite statins seldom causing DILI and having a history of liver toxicity.
 - The majority of psychiatric ailments, including anxiety disorders, depression, and epilepsy, are treated with antidepressant and antiepileptic medications. These drugs might cause hepatotoxicity even at therapeutic levels. On stopping the medicine, patients using paroxetine, citalopram, and venlafaxine exhibit reversible liver damage. According to published research, 7.6% of them (14/185) with psychiatric drug-related DILI were identified. Both on their own and in conjunction with other psychiatric medications, benzodiazepines were used.
 - In case of immunosuppressant, the main content responsible for hepatotoxicity is azathioprine (AZA). This is used to treat rheumatoid arthritis, IBD, and to avoid rejection following organ donation. However, there are numerous adverse consequences, including liver damage and a twofold increase in aminotransferases from the baseline. Only 20/185 cases (20/185) required immunosuppressive medicines; 75 percent of these cases used azathioprine, and 25% involved methotrexate.¹⁹
 - Hepatotoxicity brought on by dietary supplements and herbal products is already well-known. In comparison to Western nations, where it is lower, the prevalence is much higher in the Eastern globe, peaking at 70% (53.2-5 percent). About 12 percent of US patients receiving liver transplantation for DILI other than paracetamol may have HSD, according to estimates. The DILI reported a greater number, ranging from 10 to 20 percent.^{20,21}

3. Pathophysiology

Drug-induced liver damage (DILI) is a multistep process that includes some later inflammatory system activation.

Step1: DILI's first step is started when the drug metabolites are formed. During Phase I drug metabolism with the help of CYP450 these hepatotoxic byproducts (polymorphic cytochrome P450) are formed. These hazardous substances might have the potential to initiate the process of liver injury by conjugation during phase II metabolism.

Step2: Drug induced liver injury is then propagated through subsequent: cell stress, mitochondrial inhibition, and specific immune reactions.

- i. Direct cell stress can occur when metabolites attach to certain enzymes, lipids, nucleic acids, or other structures, or when glutathione levels drop.
- ii. Due to the inhibition of the mitochondrial respiratory chain brought on by the depletion of ATP and the buildup of reactive oxygen species, direct mitochondrial inhibition takes place (ROS).
- iii. When a medication or its metabolites attach to HLA proteins, which are further recognized as antigens, certain immune responses may be triggered. Neo-antigens are applied to these antigen-presenting cells, causing the antibodies to this cell structure to be activated. These auto-antibodies and reactive metabolites are insufficient to trigger an immunological response. Only when a second signal known as the Danger signal is present do additional reactions take place. These signals, which are caused by oxidative stress or immune-mediated liver injury, activate the signaling pathways.

The signals may come from a different drug or host components like bacterial or viral infection. A mild inflammatory reaction can also be the danger signals. Cell stress, direct mitochondrial inhibition, immunological responses, and mitochondrial permeability transition are the final three phases (MPT) As the permeability increases ATP synthesis gets disturb, which lead to expansion of mitochondrial matrix, also increased permeability of mitochondrial outer membrane. Cytochrome c and apoptotic proteins are consequently released into the cell cytoplasm.

Cell stress and immune reaction causes injury in one of the two ways:

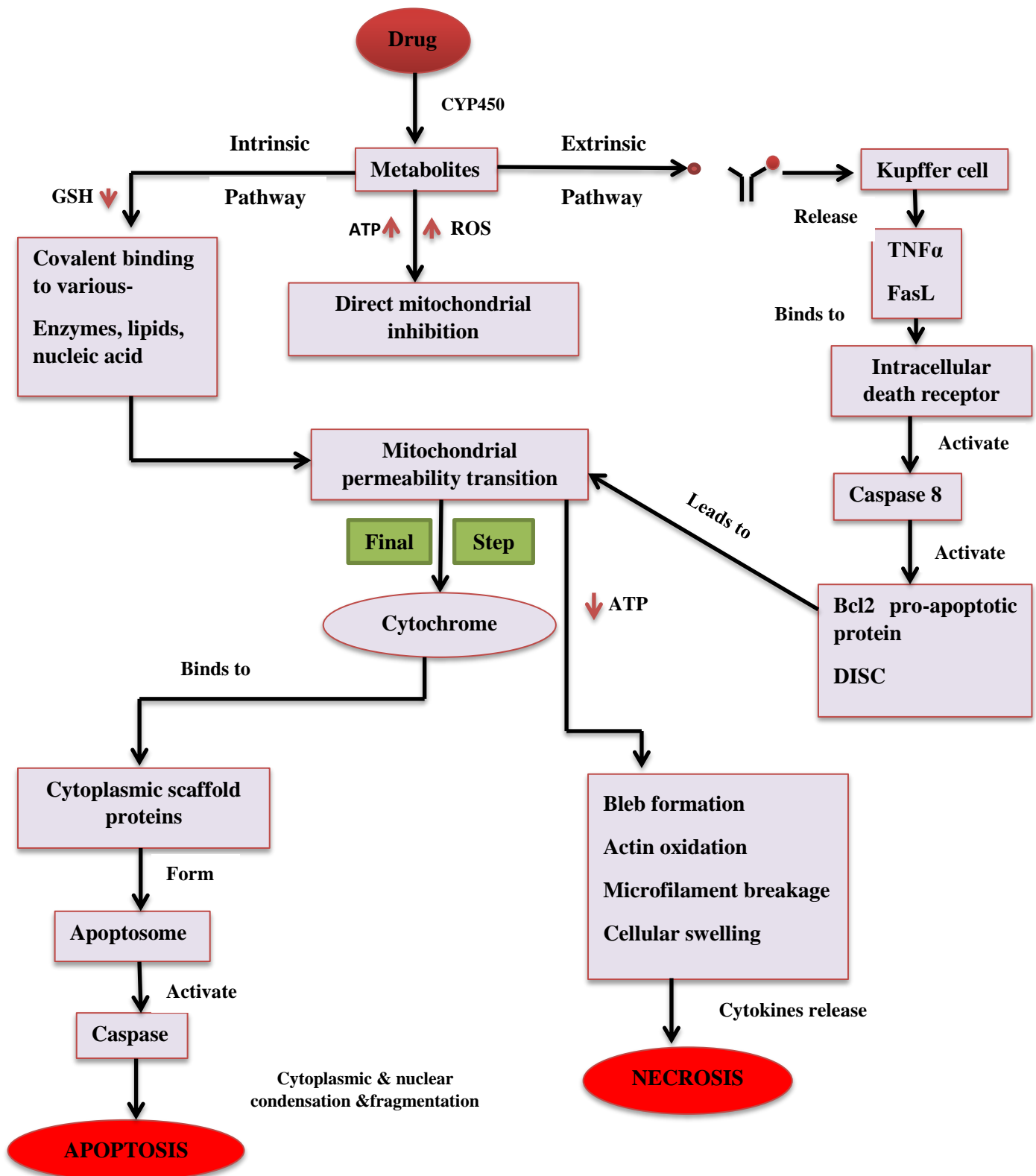
- Cell stress starts the direct pathway that leads to the activation of pro-apoptotic proteins and the inhibition of anti-pro-apoptotic proteins, which causes MPT to become active.
- When an immune response occurs, the extrinsic route is activated, causing Kupffer cells to release TNF and FAS ligand in response to antigen presentation (FasL). These TNF and FAS ligands connect to intracellular death receptor and death domain proteins, activate caspase 8, and create a complex that causes death (DISC). In addition, Caspase 8 activates the pro-apoptotic Bcl2 proteins, which when combined with DISC result in MPT.

Step3: Apoptosis or necrosis is the final step of injury:

When ATP is present, cytochrome C binds to cytoplasmic scaffold protein and pro-caspase 9 to create an Apoptosome, which activates the caspase and causes cytoplasmic and nuclear condensation and fragmentation. Apoptosis is an ATP-dependent mechanism that only happens when MPT does not occur quickly. Phagocytosis is used to remove the debris. Apoptosis doesn't result in a breakdown of plasma membrane integrity, which significantly reduces inflammation and the risk of secondary damage.

Necrosis develops as a result of MPT and ATP depletion impairing mitochondrial activity, causing severe disruption of cell processes that leads to the creation of bleb, actin oxidation, microfilament breakage, cellular swelling, and finally rupture of the plasma membrane.

The lysis process results in the production of cytokines, which harms the nearby hepatocytes.^{22,23,20,21}



Diagrammatic representation of Drug-induced liver injury (DILI)

Figure 2: In drug induced liver injury toxic metabolites are generated with the help of CYP450 which is a parent compound, causes mitochondrial impairment through one of the three pathways i.e., extrinsic, intrinsic, or direct mitochondrial inhibition. Mitochondrial permeability transition (MPT) which is a result of mitochondrial membrane disruption. Apoptosome is formed in the presence of ATP, and then cell is degraded by fermentation and apoptosis. Mitochondrial membrane permeability increases results in cell lysis, cytokines release and necrosis in ATP absences. ¹¹

If the liver injury is not diagnosed and treated timely, it may lead to severe liver disease which is irreversible and transplant is the only option which is shown in fig 3:

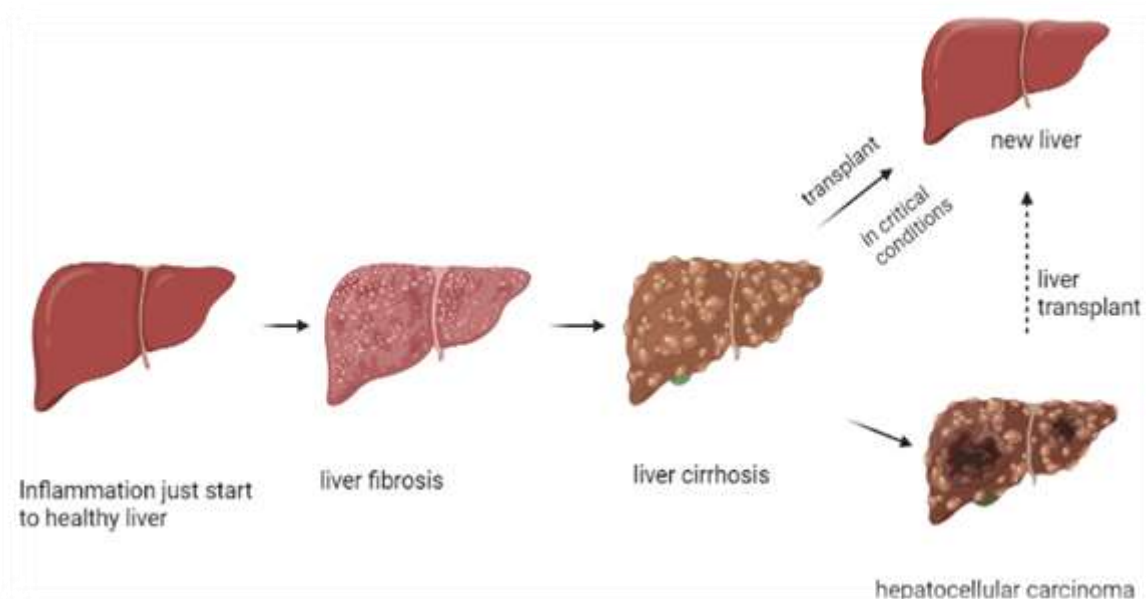


Figure 3: shows that the progress of liver disease, that the healthy cells of liver i.e., hepatocytes get inflamed which leads to fibrosis if it is not cured then it leads to cirrhosis and finally converted to cancer i.e., hepatocellular carcinoma and the only option remaining is liver transplant.

Stage1: Inflammation: At this stage, inflammation started to hepatocytes which damages the healthy liver cells due to many agents and diseases causes the liver to expand. Inflammation could lead to the scarring of healthy liver cells i.e., hepatocytes. Upper right corner of the abdomen is where the person feels pain. The illness can still be healed at this point. A yearly health examination, which should include a liver function test, is very important.^{26,27,24}

Stage2: Fibrosis: Fibrosis occurs when the inflammation gets converted into scarring. The scar tissue takes the place of healthy tissue of liver, yet scar tissue cannot perform the same functions. This can start to affect your ability to function properly. Fibrosis can be difficult to diagnose because symptoms are rarely found.²⁹ The most common kind of chronic liver illnesses are characterised by hepatic fibrosis, which is the excessive build-up of extracellular matrix proteins, including collagen. Cirrhosis, liver failure, and portal hypertension are side effects of advanced liver fibrosis, which frequently necessitates liver transplantation.^{30,31}

Stage3: Cirrhosis: Fibrosis is a reversible scarring reaction that manifests in nearly all chronic liver damage patients. Hepatic fibrosis eventually progresses to cirrhosis, which is characterised by nodule formation and organ contraction.³² Fibrosis is a prelude to liver cirrhosis, which is the end outcome of chronic liver disease. There is now no chance that the liver will heal itself because the scarring is complete.³³ In response to chronic liver injury, regenerating nodules that are encircled by fibrous bands are said to develop histologically as cirrhosis, which results in portal hypertension and end-stage liver disease.³⁴

Cirrhosis includes two categories: Compensated - this means that the liver is much scarred but still able to withstand damage and perform many of its functions, the vast majority of people with compensatory cirrhosis experience few or no symptoms. **Decompensated** - This means that the liver has a large scar and cannot function properly and the patients with degenerative cirrhosis develop a range of symptoms and complications of the disease.^{33,35,32}

Stage4: End stage liver disease (ESLD): As the cirrhosis advances, the liver starts to fail in one of two ways: Severe liver failure usually results from non-alcohol causes and develops within 48–72 hours. Alcohol misuse is a frequent cause of chronic liver disease, which takes a lot of time to develop. In addition to vomiting, nausea, diarrhoea, and appetite loss, the person also loses weight. A person's mental or cognitive health is also compromised, and they frequently experience confusion or complete confusion.²⁶

The only solution is to go for transplantation if we want to save the life of our patient.

Stage 5: liver cancer: Some medical professionals believe that there are only four stages of liver illness and do not consider liver cancer to be stage 5. This is due to the fact that liver cancer can arise at any moment and for causes other than liver illness (primary liver cancer). Or the liver can become infected with cancer from any other region of the body (secondary liver cancer). Additionally, it is not the last in a series and can develop in any of the first four categories. Unless the same liver or a portion of a healthy liver is placed in the body, liver cancer is fatal, similar to ESLD.²⁶

Primary liver cancer: Primary liver cancer is liver cancer that develops from inside the liver. There are various types of primary liver cancer, including

Hepatocellular carcinoma (HCC): Adults with this type of liver cancer are prevalent. It develops in many ways, with some beginning as a single plant that becomes enormous. In contrast to the first type, the second appears to begin with little areas of malignant tissue throughout the liver. Cirrhosis, a chronic liver injury that is the most prevalent kind in the US, is the condition in which this is most frequently observed. It's crucial to understand the rarity of one of these subtypes, fibro lamellar, which accounts for less than 1% of HCCs and is most frequently found in younger female patients. Typically, there is no liver disease throughout. Comparatively speaking, this subtype of HCC typically has a superior outlook.^{28,35,33}

Intrahepatic cholangiocarcinoma (bile duct cancer): Cholangiocarcinoma within the liver account for 10–20% of

liver cancer cases. The small bile ducts, which are tubes that deliver bile to the gallbladder inside the liver, are where these tumors begin to develop.³⁸

Angiosarcoma and hemangiosarcoma: Up to 2% of all primary liver tumors are hepatic angiosarcomas, an uncommon malignant vascular tumor. These are uncommon malignancies that develop in the cells that lining the liver's blood arteries. These malignancies are more likely to manifest in those who have been exposed to vinyl chloride or thorium dioxide (Thorotrast). Some cases are thought to be brought on by inherited hemochromatosis, exposure to radium or arsenic, or both. There isn't a clear cause in roughly 50% of cases. These tissues grow rapidly and spread widely then they can be surgically removed when they are found. Although the disease can be controlled with chemotherapy and radiation therapy, these malignancies are frequently very challenging to treat. These malignancies receive similar care as other sarcomas.³⁹

Hepatoblastoma: The primary malignant hepatic tumor that affects infants and children most frequently in the first two years of life is hepatoblastoma. This is an uncommon type of childhood cancer that often affects children under the age of four. Comparable to fetal liver cells are hepatoblastoma cells. With surgery and chemotherapy, about 2 out of 3 kids with these tissues receive successful treatment.^{40,41}

Second liver cancer (metastatic liver cancer): The majority of the time, liver cancer does not begin there but instead spreads from other organs such the pancreas, colon, stomach, chest, or lungs. This malignancy is referred to as the second liver cancer since it has returned to its initial site. The major location of these tissues determines how they are called and

handled. eg. Lung cancer, not liver cancer, is the term used to describe cancer that begins in the lungs and spreads to the liver. It is additionally handled like lung cancer. **Secondary liver cancer includes:**

Haemangioma: The most common type of malignant tumor of the liver, haemangioma begins in the bloodstream. Numerous hepatic haemangiomas are symptomatic but do not need to be treated. However, some can bleed and require surgery to be removed.⁴²

Hepatic adenoma: Hepatocytes, the primary kind of liver cell, are the origin of hepatic adenoma, a malignant tumor. Most are asymptomatic and don't need to be treated. However, some do actually result in symptoms, like pain, a mass in the belly, or blood loss. Many doctors frequently advise surgery to remove the tumor if at all possible due to the risk that it may rupture, causing major blood loss, and the lower risk of developing liver cancer. Utilizing specific drugs can raise the chance of forming these tissues. If a woman uses birth control pills, she is more likely to have one of these muscles, though it is uncommon. These muscles can also be developed in men who use anabolic drugs.

General nodular hyperplasia: It contains A tumor-like development known as focal nodular hyperplasia (FNH) is brought on by many cell types (hepatocytes, bile duct cells, and connective tissue cells). FNH tissues can generate symptoms even though they are harmful. Without real liver cancer, it can be challenging to identify, and doctors occasionally remove it when the diagnosis is uncertain. Women are more likely than men to have FNH tissues as well as hepatic adenomas.⁴³

4. Sign and symptoms

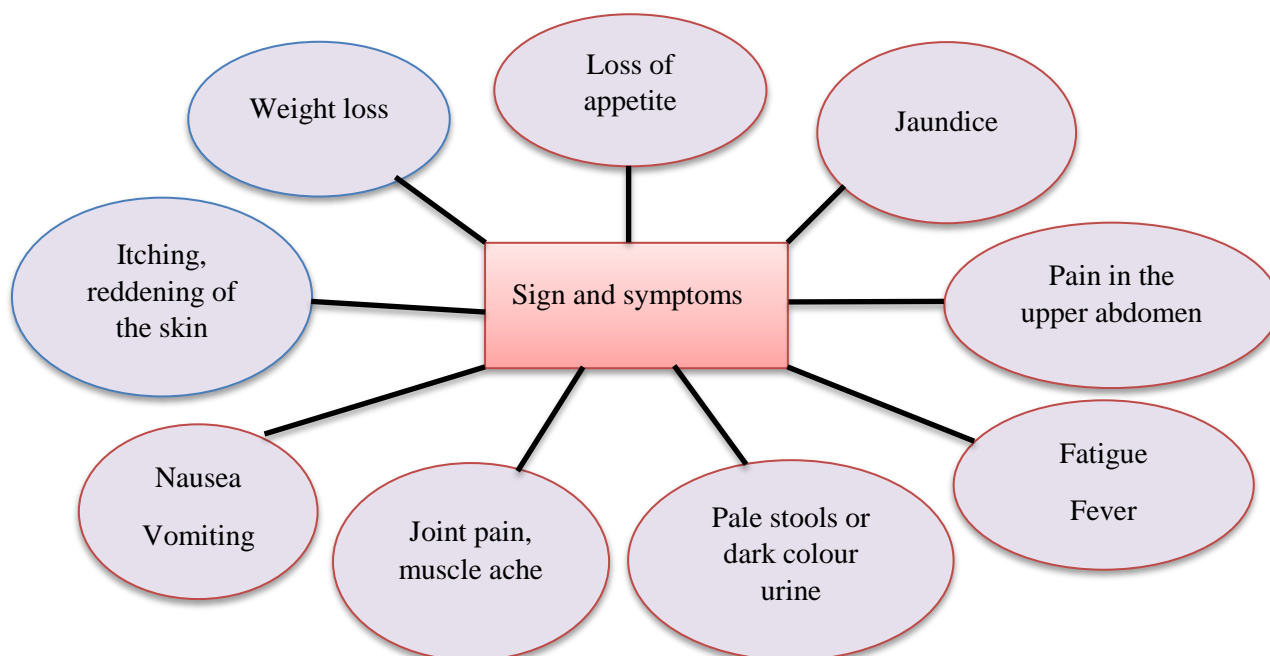


Figure 4: Various sign and symptoms associated with DILI, in some cases allergic symptoms like hives and swollen lymph nodes can occur. In very severe cases, when liver failure occurs, a person may experience confusion or a coma also.

5. Diagnosis

Idiosyncratic DILI, there are no diagnostic tests diagnosis, it is assessed on the basis of temporal association with drug used and abnormal liver functioning tests. The first steps we have to take in the diagnostic evaluation of drug induced liver injury are as follow:

5.1 History of patient: Drug intake, including herbal and dietary supplements, Possible drug-drug interaction, Intake of alcohol, Chronic liver disease i.e., chronic viral hepatitis, NAFLD, Concomitant diseases e.g., Diabetetes, heart failure, sepsis.

5.2 Sign and symptoms: yellow Colour of urine and sclera, nausea, vomiting, abdominal pain, abnormal bleeding, weakness, fatigue, fever, ascites, rashes, icterus, pruritus, right hypochondrium.

5.3 Blood tests: complete blood count (CBC), liver functioning test which include (ALT, ALP, GGT, R value).

5.4 Serological test: acute viral hepatitis A, B, C (anti-HAV IgM, HBsAg, anti-HCV, HCV RNA), autoimmune hepatitis, (ANA anti smooth muscle antibody, IgG level).

5.5 Serological tests if needed according to patient history: Hepatitis E (anti-hepatitis E virus IgM), CMV, EBV, HSV (if patient exhibits atypical lymphocytosis, lymphadenopathy).

5.6 Imagery study: includes ultrasound, CT scan, MRI.MRCP when indicated or pancreato-biliary etiology is supposed, fibro scan in case of fibrosis.

5.7 Other: Budd- Chiari syndrome and Wilson's disease.

ALP-alkaline phosphatase, ALT- alanine aminotransferase, ANA- antinuclear antibody, CMV-cytomegalovirus, CT-computerized tomography, EBV- Epstein-Barr virus, GGT-gamma-glutamyl transferase, HAV- hepatitis A virus, Hbc-hepatitis B core antigen, HBsAg- hepatitis B surface antigen, HCV- hepatitis C virus, HSV- herpes simplex virus, IgG-immunoglobulin G, IgM,-immunoglobulin M, MRCP- magnetic resonance cholangiopancreatography, MRI- magnetic resonance imaging, NAFLD- non-alcoholic fatty liver disease, RNA- ribonucleic acid, ULN- upper limit of normal range, R = (ALT value ÷ ALT ULN) ÷ (ALP value ÷ ALP ULN). Elevated AST may be related with bone or cardiovascular injury as well as disorders like myocardial infarction and rhabdomyolysis. ALT is directly related to the liver. Hepatocellular damage continues to be the most typical manifestation and is linked to the worst consequence.^{44,45}

6. Treatment and Management

When a patient develops DILI, the offending medication must be stopped, along with supportive and symptomatic care. In most situations, the liver injury becomes better after drug discontinuation. It is still debatable whether to use glucocorticoids for immune-mediated reactions and Ursodeoxycholic acid (UDCA) for cholestatic liver injury. The use of antioxidants as a therapy option for severe DILI has also been suggested. Some therapies for DILI include N-acetylcysteine (NAC) for paracetamol overdose, L-carnitine for Valproic acid overdose.⁶

Acetaminophen-induced liver injury: The following 3 medications available for acetaminophen-induced liver injury i.e., N-Acetylcysteine therapy (NAC therapy):

- 140 mg/kg for a 72-hour oral drug loading period followed by 70 mg/kg every 4 to 72 hours.
- A pharmaceutical loading regimen lasting 72 hours consisted of 150 mg/kg over an hour, followed by 50 mg/kg in 4 hours, and a decline of 418.75 mg/kg in 67 hours.
- 21-hour prescription uploads of 150 mg/kg over one hour, 50 mg/kg over the next four hours, and then a reduction of 100 mg/kg over the next sixteen hours.

A NAC controlled study as a continuation of fusion 72 hours in patients with severe liver failure. For DILI patients with a cholestatic pattern of liver injury, Ursodeoxycholic acid (UDCA), 13 to 15 mg/kg, may be beneficial. With the exception of autoimmune DILI, steroids have no specific use in the

management of DILI. Other medications, like antioxidants and silymarin, have long been used to treat other forms of hepatic toxic binding and may be helpful for DILI patients as well. In patients with severe DILI, liver transplantation may be required to avert mortality from severe liver failure.¹⁵

Ingestion of Amanita mushrooms can lead to liver damage by a toxin; it causes hepatocyte necrosis and inhibits RNA polymerase II. The intestine phase comes first in the presentation, and then the hepatic phase. Vomiting, nausea, and discomfort in the abdomen are signs of the intestinal stage. This is followed by a noticeable recovery, but the levels of AST and ALT then increase and jaundice starts to appear. It is crucial to manage any fluid and electrolyte imbalances because the intestinal stage, which can lead to metabolic problems and dehydration, precedes the hepatic phase. This will prevent the re-absorption of a toxin.

Silibinin since silibinin stops amanitin from reaching the hepatocyte; it is widely accepted as a remedy for poisoning by toxins. Within 48 hours of importing mushrooms, it must be administered. Currently, an IV dose of 20 to 50 mg/kg/day is advised, lasting 48 to 96 hours. Penicillin G is also known to eliminate and encourage the elimination of toxins in high doses. For continuous IV administration, the suggested dose is 1,000,000 IU/kg on the first day and 500,000 IU/kg for the following two days. Studies also support co-management with the NAC. Finally, although no specific research has been done on Amanita mushroom poisoning, the Molecular Adsorbent Recirculating System may be thought of as increasing liver function if implemented early. To diagnosis drug-induced hepatitis, patients who present with fever, rash, and eosinophilia should be taken into consideration. Since studies have indicated that biochemical testing is normally performed six months after DILI, corticosteroid treatment should be taken into consideration if DILI is severe. Patients who have a cholestatic image may present with severe pruritus complaints. Emollients, hydroxyzine, diphenhydramine, bile acid resins, and rifampicin are among the medications that can be used to treat these people.

Antitubercular drugs: After the diagnosis of DILI, 3 hepatotoxic drugs, namely isoniazid, rifampicin and pyrazinamide will be discontinued immediately. Depending on the severity of second-line tuberculosis drugs such as streptomycin or amikacin, ciprofloxacin or ofloxacin, may be started until the liver test returns to normal, or the jaundice decreases or the transaminases drop to < 2 × ULN. Another new drug as moxifloxacin can be used instead of first-line drugs. Conventional treatment that includes consecutive treatment, first with rifampicin followed by isoniazid 3-7 days later may be prescribed. If tolerated, pyrazinamide may be started by monitoring liver tests. Otherwise pyrazinamide may be discontinued and both isoniazid and rifampicin may be continued for as long as 9-12 months depending on the underlying disease.⁴⁶

The removal of the problematic medicine is a hallmark of DILI treatment. Premature withdrawal is supposed to stop the progression to ALF; however there isn't much solid proof to back this up. A medicine that is only taken for a few days, often just a couple, can have a lethal result. There isn't a recognized ALF remedy for the undetectable DILI right now. To treat severe pruritus, many doctors use antihistamines such diphenhydramine and hydroxyzine. Additionally, almost 30% of the DILI research participants received Ursodeoxycholic acid, but its efficacy in treating serious and persistent DILI has not been proven.⁴⁷

Table 1: Some medications related with drug induced liver injury and their biochemical presentation

Sno	Biochemical presentation	Medication associated with DILI
1.	Cholestatic type of liver injury (ALP>2×ULN or ALP/ALT<2) with both ALP and ALT >1×ULN	Immunosuppressive agents: N Azathioprine Gynecological agents: Oral contraceptives Neuropsychiatric agents: Carbamazepine, Chlorpromazine, Tricyclic antidepressants Anti-inflammatory agents: Sulindac Antimicrobial agents: Amoxicillin-clavulanate acid, Erythromycin, Trimethoprim-sulfamethoxazole Cardiovascular agents: Clopidogrel, ACE inhibitors Endocrine agents: Anabolic steroids
2.	Hepatocellular type of liver injury (ALT>5×ULN and Bilirubin >2 ×ULN)	Immunosuppressive agents: Allopurinol Neuropsychiatric agents: Bupropion fluoxetine, Methyldopa, Nefazodone, Paroxetine, Risperidone, Sertraline, Trazodone, Valproic acid Cardiovascular agents: Amiodarone, Lisinopril, Quinidine, Statins Endocrine agents: Acarbose, Troglitazone Gastrointestinal agents: Cimetidine, Omeprazole Anti-inflammatory agents: Acetaminophen, Bromfenac, Diclofenac, Ibuprofen, Naproxen Antimicrobial agents: Ciprofloxacin, Isoniazid, Ketoconazole, Nitrofurantoin, Protease inhibitors, Pyrazinamide, Rifampin, Tetracycline, Trimethoprim-sulfamethoxazole Environmental exposures: Amatoxin Other: Halothan
3.	Mixed type of liver injury (ALT>5×ULN or Bilirubin >2×ULN) and (ALP >2×ULN or ALP/ALT<2 with both ALP and ALT>1×ULN	Immunosuppressive agents: Azathioprine Neuropsychiatric agents: Amitriptyline, Phenytoin, Antimicrobial agents: Clindamycin, Protease inhibitors, Reverse transcriptase inhibitors, Sulfonamides Cardiovascular agents: ACE inhibitors, Statins

7. Histopathological features associated with DILI

The term "histopathology" means "the study of tissue in connection to disease." The tissues that were sent for testing and their characteristics as seen under a microscope are described in the histopathology report. A biopsy report or a pathology report are other names for a histopathology report.⁴⁸

Liver biopsy is the procedure which helps to find out the histopathological feature of the disease. An invasive procedure with a minimal risk of consequences is liver biopsy. Liver biopsy should only be performed as a last resort in rare instances of diagnostic uncertainty regarding other causes, provided that the patient will benefit from chronic liver cirrhosis, cirrhosis, piliosis, vascular damage, sinusoidal obstruction syndrome (SOS), cell lipidosis, adenomas, and malignant tissue.

A typical histology feature of DILI is acute hepatitis. Hepatocellular damage, including liver cirrhosis, and portal and parenchymal inflammation are its symptoms. Selectively inflammatory cells include lymphocytes, plasmahistiocytic cells, and neutrophils. In general, confluent necrosis, in the absence of any normal liver cells, may result in severe liver failure; further separation is not conceivable, as seen in the case of halothane hepatitis. Inflammation alone or in combination with liver necrosis to varying degrees is therefore a key hallmark of acute hepatitis in DILI cases, although hepatic necrosis of the liver may be detected in the absence of inflammatory cells as a separate disease organization.

Especially in the hands of skilled practitioners, liver biopsy is regarded as a safe technique. A mortality rate of 19% in the first three months following biopsy is seen in patients with severe liver failure and liver cirrhosis. Systemic-related deaths are generally uncommon, with rates ranging from 0.01 to 0.1%. Intraoperative hemorrhage, which accounts for 0.03 to 0.07 percent of deaths following liver biopsy, is the leading cause. In the most recent study, there were no fatalities, but major (pain-related) complications were found in 7 out of 1,955 cases. These complications were 0.36 percent of the time, and included 5 punctures where bile was intended, 1 pneumothorax, and 1 hemoperitoneum that required surgery as well as a liver biopsy and histological analysis.⁴⁷

8. Risk factors for DILI

The risk factors for DILI include a wide range of elements, such as age, gender, concomitant drug use, co-morbidity, and heredity.

Age and gender, a risk factor for DILI is getting older; for example, the likelihood of isoniazid hepatotoxicity increases with age. Due to the prevalence of paracetamol (74%) and idiosyncratic drug reactions (67%) in women, it is widely believed that women are more susceptible to develop DILI. However, a recent analysis of a Spanish registry revealed no general gender difference. Instead, men over 60 had a significantly higher risk of developing a cholestatic injury, while women under 60 had a significantly higher risk of developing a hepatitis-like injury.

In some cases, **combination therapy** increases the risk of a drug-induced liver problem. For instance, hepatotoxicity is more likely to happen when isoniazid is administered along with rifampicin and pyrazinamide than when it is used alone.

Genes as risk elements DILI are likely a complex genetic disease in which a few genetic variations as well as environmental risk factors are responsible for liver injury.

There has been a multi-step model of the genetic and molecular underpinnings of idiosyncratic DILI proposed. It encompasses both upstream drug-specific pathways that produce reactive metabolites and downstream common pathways that directly and indirectly cause cell stress and death.

Daily intake Although several drugs, such as diclofenac, amoxicillin/clavulanate, and flucloxacillin, have a relationship to dose that can be established, there may be a historic belief that idiosyncratic DILI cannot be predicted based on dose. Bosentan-related idiosyncratic liver damage has also been shown to be dose-dependent. An extended dose of duloxetine was linked to liver damage in a patient who had no indications of hepatotoxicity at a lower dose, and there have been case reviews where dose reduction triggered the onset and disappearance of hepatotoxicity brought on by mianserin. It may not be true that idiosyncratic medication reactions are completely dose-independent. In contrast, Utrecht found that individuals given medication doses greater than 10mg daily experienced idiosyncratic drug reactions more frequently. Patients who received pharmacological doses of 1 gram or more per day were, on the other hand, more prone to experience idiosyncratic drug reactions. Therefore, there is some connection between a drug's daily doses.

Alcohol consumption drinking alcohol there is no evidence to support the claim that drinking more alcohol increases the risk of liver damage from medications other than methotrexate, isoniazid, and halothane. Long-term methotrexate users are more likely to develop fibrosis or cirrhosis if they consume substantial amounts of alcohol. But while methotrexate by itself may not result in severe liver fibrosis, additional risk factors such as diabetes mellitus type, being overweight, and heavy alcohol consumption may increase the likelihood of liver damage. It is well known how alcohol use, both short-term and long-term, affects the risk of acetaminophen hepatotoxicity. Studies linking alcohol to a higher risk of idiosyncratic DILI may have been influenced by patients' poor nutritional status and advanced age. Potential registries failed to discover a meaningful correlation between intake of alcohol and the DILI severity.

Underlying Disease States Whether persistent liver illness will raise the risk of DILI is a matter of debate. There is a misconception that those with cirrhosis and chronic liver disease aren't always at risk for DILI, but those who already have liver disease are more likely to experience complicated courses and negative effects from DILI. Patients with increased baseline aminotransferase levels are more likely to have hepatotoxicity after statins.

Immunologic Mechanisms The pathogenesis of idiosyncratic DILI involves both the innate and acquired immune systems; these may be the most crucial processes in the pathogenesis of DILI. Analyses of DILI are supported by the presence of eosinophilia in peripheral blood and/or the liver of a patient with acute liver injury. The presence of hypersensitivity symptoms such as rash, fever, and eosinophilia is detected in 25% to 30% of patients who are thought to have DILI.

Mitochondrial DNA Mutations Several medications, such as valproate, salicylate, and antiretroviral medicines, damage the liver through mitochondrial toxicity; a recent preliminary study linked mitochondrial DNA alterations to the liver damage brought on by some substances. In the DILI network research, 17 individuals with probable valproate hepatotoxicity were examined for genetic polymorphisms in the mitochondrial DNA polymerase gamma (POLG) gene. The frequency of genetic variations is evaluated between occurrences and historical controls when POLG are sequenced.

^{49,50}

9. Effect of COVID-19 on liver injury

The coronavirus which is also known as coronavirus 19 (COVID-19), has infected millions of individuals globally in a relatively short time, is caused by the novel coronavirus known as acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It quickly became apparent that people who were overweight or diabetic had a poor prognosis for COVID-19, clearly pointing to a connection between liver illness and severe COVID-19. It is not surprising that patients with chronic liver disease (CLD) may be more susceptible to side effects after SARS-CoV-2 infection given that CLD is linked to immune system malfunction and inflammation. According to preliminary COVID-19 data, healthy HIV-positive individuals also demonstrated abnormal liver function tests, raising the possibility that SARS-CoV-2 can cause liver damage. By lowering the liver's combo of proteins involved in natural defences and pathogen-related pathogen identification, liver injury can cause a mild immune deficiency. Immune dysregulation is a feature of both cirrhosis and CLD. CLD paralyzes the immune system's response to homeostatic liver function. Open immune cells and elevated amounts of pro-inflammatory cytokines in the serum are produced when the pattern of cells from damaged liver cells stimulates circulating immune cells (e.g., TNF and IL-6). Importantly, immunological problems associated with the liver can raise the risk of illness. In account of this, it is not unexpected that patients with CLD, particularly those with decreased cirrhosis, are more likely to develop COVID-19 and other diseases that increase the risk of death. It appears to be a lethal combination of cirrhosis and SARS-CoV-2 infection, most likely because of the interaction of biological processes defined by immunological dysregulation. A crucial point is that liver transplantation recovers liver function in people with decreased cirrhosis, lowering the likelihood of COVID-19 death in the general population.

Even in previously healthy individuals, the infection can have a negative impact on liver health although it has not yet been conclusively proven that SARS-CoV-2 can infect hepatocytes, available clinical data show that patients with COVID-19 frequently exhibit abnormal liver function tests, such as aspartate transferase (AST) and alanine transferase (ALT), which may be caused by a variety of factors. It is probable that the immune function from SARS-CoV-2 may play a role in the COVID-19 linked liver Disease since significant liver damage or cholestasis can emerge in extreme cases of a cytokine-induced cytokine, unrelated to COVID-19.⁵¹

Conclusion

Drug induced liver injury remains a significant cause for liver disease. Peoples are less aware about DILI. In most of the cases of DILI, liver can repair itself after withdrawal of suspected drug, but it is not possible in all the cases where the DILI is more severe. So, the liver transplant is recommended by the doctors in that case. In this review of literature, we have discussed the different stages of liver diseases, at which stage it is curable or not. Different causes, pharmacological medications responsible for DILI, pathophysiology, diagnosis, prevention and treatment for liver injury is included in this review. It is important to be aware of and remove the suspected agent as soon as possible to stop the development of chronic liver disease or complete liver failure. There are no specific risk factors for DILI, but existing liver disease and genetic factors may be a priority for some people. Treatment of liver damage caused by drugs and herbs includes immediate drug withdrawal and supportive care aimed at alleviating unwanted symptoms.

Future perspective

DILI will continue to be a significant public health issue in the future due to increased use of medicines and supplements. The greatest contributor to liver disease is still DILI. Despite the fact that it can manifest in many different ways and have a wide range of pharmacological causes, treatment for all situations necessitates stopping the irritant. A recent study found that new molecular biomarkers outperformed conventional biomarkers in terms of sensitivity and specificity. Current DILI studies focus heavily on pre-clinical research, clinical change requires more time for comprehensive analysis to complete. So, in the further study, the involvement of novel molecular biomarkers in the DILI pathway, an assessment of the efficacy of these biomarker indicators in DILI compared to other liver disorders, and a comparison of these biomarker markers on liver damage brought on by the same medication capacity should all be included in future research. In order to significantly enhance DILI diagnosis, treatment, and prediction, the general strategy is to combine new biomarkers with established biomarkers and DILI-related objective programs.

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