INTRODUCTION

Liver cirrhosis is a progressive disease that involves inflammation and fibrosis of the liver **(Memik and Dolar., 2005)**. This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupt the biochemical functions of the liver **(Mathews., et al 2006).**

Patients with cirrhosis have a compromised lung function with a reduced transfer factor and ventilation / perfusion abnormalities and arterial hypoxia is seen in 30% - 70% of patient with chronic liver disease, depending on disease severity (**Fallon et al., 2006).**

Certain pulmonary complications are observed frequently in cirrhotic patients, namely; Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) (**Kochar et al., 2011).**

HPS is the commonest pulmonary dysfunction in cirrhotic patients in which the primary pathological process is abnormal pulmonary vasodilation (**Pham et al.,2010).**Dyspnea, platypnea, clubbing, orthodoxia and arterial hypoxemia were the commonest feature of HPS (**Makhlouf et al., 2012)**.

Liver transplantation is an effective treatment for HPS, and prompt recognition of the syndrome and timely referral are important in improving patient outcomes (**Grace and Angus., 2013).**

The other, but far less common pulmonary vascular disorder associated with cirrhosis is POPH. Here, the pulmonary circulatory abnormality is vasoconstriction, and there is fibro obliteration of the vascular bed, the opposite from the changes that occur in HPS. Rarely, patients can have features of both disorders **(Subramanian., et al 2010).**

POPH is a life threatening disease characterized by a marked and sustained elevation of pulmonary vascular resistance, leading to increased pulmonary artery pressure, right ventricular failure, and ultimately death **(Ibrahim., 2010).**

A relationship was established between the severity of liver failure and diffusion tests showing pulmonary complications invasively. Diffusions tests should be performed in addition to the PFT in order to determine pulmonary involvements particularly in patients who are candidates for liver transplantation **(Irem et al., 2008).**

AIM OF THE STUDY

The aim of the study is to evaluate the frequency of hypoxemia and impairment of pulmonary function tests (PFT) in patients with liver cirrhosis and to determine their relation to the severity of liver disease.

Chapter (1)

LIVER CIRRHOSIS

Introduction:

Liver cirrhosis is considered the end stage of a variety of chronic liver diseases **(Schuppan and Afdhal., 2008).**

It results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture, thus it is irreversible in its advanced stages **(Dooley et al., 2011).**

Epidemiology:

In developed countries, cirrhosis is an increasing cause of morbidity and mortality. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide **(Lozano et al., 2012).**

170 000 death per year in Europe **(Blachier et al., 2013)** and 33 539 death per year in the USA **(Hoyert and Xu., 2012).** Moreover, cirrhosis is the main indication for liver transplants in Europe **(Blachier et al., 2013).**

The main causes of liver cirrhosis in developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non alcoholic liver disease.While, infection with hepatitis B virus is the most common cause in sub Saharan Africa and most parts of Asia. **(Blachier et al., 2013).**

The prevalence of cirrhosis is difcult to assess and probably higher than reported, because the initial stages are asymptomatic so the disorder is undiagnosed. Prevalence was estimated about 0·3% in a French screening programme, and the annual incidence was 15.3–132.6 per 100 000 people in studies in the UK and Sweden **(Blachier et al., 2013).**

Pathophysiology:

The pathological hallmark of cirrhosis is the development of scar tissue that replaces normal parenchyma. This scar tissue blocks the portal flow of blood through the organ therefore disturbing normal function. Recent research shows the pivotal role of the stellate cell, a cell type that normally stores vitamin A, in the development of cirrhosis.

Damage to the hepatic parenchyma (due to inflammation) leads to activation of the stellate cell, which increases fibrosis (called myofibroblast) and obstructs blood flow in the circulation **(Hammer et al., 2010).**

In addition, it secretes TGF-β_1, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it secretes TIMP 1 and 2, naturally occurring inhibitors of matrix metalloproteinases, which prevents them from breaking down fibrotic material in the extracellular matrix **(Puche et al., 2013).**

Causes

Cirrhosis has many possible causes; sometimes more than one cause is present in the same patient. Globally, 57% of cirrhosis is attributable to either Hepatitis B (30%) or Hepatitis C (27%). Alcohol consumption is another important cause, accounting for about 20% of the cases **(Perz et al., 2006).**

- **Chronic hepatitis C:**

Infection with the hepatitis C virus causes inflammation of the liver and a variable grade of damage to the organ. Over several decades this inflammation and grade change can lead to cirrhosis. Among patients with chronic hepatitis C 20-30% will develop cirrhosis **(Longo et al., 2012).**

Cirrhosis caused by hepatitis C and alcoholic liver disease are the most common reasons for liver transplant **(Longo et al., 2012).** Hepatitis C can be diagnosed with serologic assays that detect hepatitis C antibody or viral RNA. The enzyme immunoassay, EIA-2, is the most commonly used screening test in the US (**Friedman., 2014).**

- **Chronic hepatitis B:**

The hepatitis B virus causes liver inflammation and injury that over several decades can lead to cirrhosis. Hepatitis D is dependent on the presence of hepatitis B and accelerates cirrhosis in co-infection **(Friedman., 2014).**

Chronic hepatitis B can be diagnosed with detection of HBsAg > 6 months after initial infection. HBeAg and HBV DNA are determined to assess whether patient needs antiviral therapy **(Longo et al., 2012).**

- **Alcoholic liver disease :**

Alcohol seems to injure the liver by blocking the normal metabolism of protein, fats, and carbohydrates. This injury happens through the formation of acetaldehyde from alcohol which itself is reactive, but also leads to the accumulation of products in the liver **(Longo et al., 2012).**

Patients may also have concurrent alcoholic hepatitis with fever, hepatomegaly, jaundice, and anorexia. AST and ALT are both elevated but less than 300 IU/litre with an AST: ALT ratio > 2.0, a value rarely seen in other liver diseases **(Friedman., 2014).** In the United States, 2/5 of cirrhosis related deaths are due to alcohol **(Longo et al., 2012).**

- **Non-alcoholic steatohepatitis (NASH):**

In NASH, fat builds up in the liver and eventually causes scar tissue. This type of hepatitis appears to be associated with obesity (40% of NASH patients) diabetes, protein malnutrition, coronary artery disease, and treatment with corticosteroid medications. This disorder is similar to that of alcoholic liver disease but patient does not have an alcohol history. Biopsy is needed for diagnosis **(Friedman., 2014).**

- **Primary biliary cirrhosis (PBC):**

Damage of the bile ducts leading to secondary liver damage. May be asymptomatic or complain of fatigue, pruritus, and non jaundice skin hyperpigmentation with hepatomegaly. There is prominent alkaline phosphatase elevation as well as elevations in cholesterol and bilirubin. Gold standard diagnosis is antimitochondrial antibodies (positive in 90% of PBC patients). Liver biopsy if done shows bile duct lesions. It is more common in women **(Longo et al., 2012).**

- **Primary sclerosing cholangitis (PSC):**

PSC is a progressive cholestatic disorder presenting with pruritus, steatorrhea, fat soluble vitamin deficiencies, and metabolic bone disease. There is a strong association with inflammatory bowel disease (IBD), especially ulcerative colitis. Diagnosis is best with contrast cholangiography showing diffuse, multifocal strictures and focal dilation of bile ducts, leading to a beaded appearance. Non-specific serum immunoglobulins may also be elevated **(Longo et al., 2012).**

- **Autoimmune hepatitis:**

This disease is caused by the immunologic damage to the liver causing inflammation and eventually scarring and cirrhosis. Findings include elevations in serum globulins, especially gamma globulins. Therapy with prednisone and/or azathioprine is beneficial. Cirrhosis due to autoimmune hepatitis still has 10 year survival of 80% **(Longo et al., 2012).**

- **Hereditary hemochromatosis:**

Usually presents with family history of cirrhosis, skin hyperpigmentation, diabetes mellitus, pseudogout, and/or cardiomyopathy, all due to signs of iron overload. Labs show fasting transferrin saturation of > 60% and ferritin > 300 ng/ml

(Edwards Genetic testing may be used to identify HFE mutations). If these mutations are present, biopsy may not need to be performed. Treatment is with phlebotomy to lower total body iron levels **(Longo et al., 2012).**

- **Wilson's disease:**

Is an autosomal recessive genetic disorder in which copper accumulates in tissues; this manifests as neurological or psychiatric symptoms and liver disease. It is treated with medication that reduces copper absorption or removes the excess copper from the body, but occasionally a liver transplant is required **(Ala et al., 2007).**

- **Alpha 1-antitrypsin deficiency (A1AD):**

Autosomal recessive disorder of decreased levels of the enzyme alpha 1-antitrypsin. Patients may also have COPD, especially if they have a history of tobacco smoking. Serum AAT levels are low and liver biopsy is positive for Periodic acid Schiff Recombinant AAT is used to prevent lung disease due to AAT deficiency **(Longo et al., 2012).**

- **Cardiac cirrhosis:**

Due to chronic right sided heart failure which leads to liver congestion **(Longo et al., 2012).**

- **OTHERS:**
  - **Hepatotoxic drugs or toxins.**
  - **Galactosemia.**
  - **Glycogen storage disease type IV.**
  - **Cystic fibrosis. (Longo et al., 2012).**

Diagnosis:

Most chronic liver disease is notoriously asymptomatic until cirrhosis with clinical decompensation occurs.

Decompensating events include:

- Ascites.
- Sepsis.
- Variceal bleeding.
- Encephalopathy.
- Non obstructive jaundice.

Imaging by ultrasonography, CT, or MRI of an irregular and nodular liver together with impaired liver synthetic function is sufficient for the diagnosis of cirrhosis.

Other findings include:

- Small and shrunken liver.
- Splenomegaly.
- Evidence of portosystemic collaterals.

Differential diagnosis includes:

- Congenital hepatic fibrosis (fibrosis without regenerative nodules).
- Nodular regenerative hyperplasia (nodules but no fibrosis).
- Non-cirrhotic portal hypertension.

A liver biopsy is seldom needed but study of a sample can provide a definitive diagnosis and confirm the aetiology in cases of uncertainty. The transjugular approach yields samples of equal quality to the percutaneous one, is safe, and adds additional prognostic information through measurement of hepatic vein pressure gradient (HVPG). **(Cholongitas et al., 2006).**

In early cirrhosis, however, conventional imaging can lead to false-negative diagnosis so other strategies are needed. Non invasive markers of fibrosis are increasingly used; they are more informative at the extremes of the liver fibrosis range ie, little or no fibrosis, and cirrhosis **(Castera., 2012).**

They include indirect serum markers (simple, widely available indices), direct serum markers that measure biomarkers of fibrosis, and imaging modalities, such as transient elastography **(table1).** These tests should be used and interpreted only once the aetiology is known.

Table (1): Most commonly used non invasive tests for diagnosis of cirrhosis.

Components		Aetiology	Comments
Imaging modalities			
Ultrasonography	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
CT/MRI	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
Fibroscan	Measurement of liver stiffness	All	Exact cutoffs for specific fibrosis stages not established
Acoustic radiation force impulse	Measurement of liver stiffness	All	Validation is still underway
MR elastography	Measurement of liver stiffness	All	Not widely available; further validation needed
Indirect serum non-invasive fibrosis tests			
APRI	AST, platelets	HBV, HCV	
FIB4	Age, ALT, AST, platelets	HBV, HCV, NAFLD	
AST/ALT	ALT, AST All		
Forns index	Age, γGT, cholesterol, platelets	HBV, HCV	
Proprietary serum non-invasive fibrosis tests			
Fibrotest	γGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin	HBV, HCV, NAFLD, ALD	Biopredictive, France
ELF	PIIINP, hyaluronate, TIMP-1	HBV, HCV, NAFLD	Siemens, UK
Hepascore	Age, sex, α2-macroglobulin, hyaluronate, bilirubin, γGT	HCV, NAFLD	Pathwest, Australia
Fibrospect II	Hyaluronate, TIMP-1, α2-macroglobulin	HCV	Prometheus, USA
Fibrometer	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	HBV, HCV, NAFLD, ALD	BioLiveScale, France
Combination strategies			
U/S and Fibroscan	As above	All	Done simultaneously
Fibrotest and Fibroscan	As above	HCV	Done simultaneously; liver biopsy if tests discordant on fibrosis classification
Fibrometer and Fibroscan	As above	HCV	Done simultaneously; results are introduced in a computer algorithm to assess severe fibrosis
APRI and Fibrotest	As above	HCV	Done sequentially; Fibrotest if indeterminate values of APRI

MR=magnetic resonance. APRI=AST-to-platelet ratio index. AST= aspartate aminotransferase. HBV=hepatitis B virus. HCV=hepatitis C virus. FIB4=fibrosis 4 index. ALT=alanine aminotransferase. NAFLD=non-alcoholic fatty liver disease. γGT= γglutamyltranspeptidase. ALD=alcoholic liver disease. PIIINP=N-terminal peptide of type III procollagen. TIMP-1=metallopeptidase inhibitor 1.U/S =Ultrasonography.

(Castera.,2012).

Natural course:

Cirrhosis should no longer be regarded as a terminal disease and the concept of a dynamic process is increasingly accepted. A prognostic clinical subclassification with four distinct stages has been proposed with substantially differing likelihoods of mortality:

- Stage 1 (compensated with no oesophageal varices) has an estimated mortality of 1% per year,
- Stages 2 (compensated with varices),
- Stage 3 (decompensated with ascites), and 4 (decompensated with gastrointestinal bleeding) have annual mortality rates of 3.4%, 20%, and 57%, respectively **(D'Amico et al., 2006).**
- Stage 5 Infections and renal failure, with 67% 1- year mortality **(Fede et al., 2012).**
- Acute decompensating events that lead to organ failure have mortality of 30% **(Moreau et al., 2013).**

Notably, mortality is higher in previously compensated patients than in those with previous decompensation, which suggests greater tolerance of the latter through the effects of the inflammatory response **(Moreau et al., 2013).**

Decompensating events are generally triggered by precipitating factors that include infection, portal vein thrombosis, surgery, and hepatocellular carcinoma.Further prognostication is important, especially for patients in the early asymptomatic phase. The traditional qualitative histological subclassification does not have a stage beyond cirrhosis so cannot be used to refine prognosis further. Semiquantitative histological sub classification based on nodular size and septal width is associated with both HVPG and clinical outcomes **(Kim et al., 2012).**

Subclassification based on quantitative fibrosis assessment with collagen proportionate area in liver tissue is also associated with HVPG and clinical outcomes and is a promising approach **(Manousou et al., 2011).**

Non invasive fibrosis markers, such as Fibroscan, Fibrotest, and ELF, are increasingly being used as prognostic markers **(Vergniol et al., 2011).**The predictive abilities of these methods should ideally be compared with those of semiquantitative or quantitative histological methods to subclassify cirrhosis. For patients with more advanced disease, prognostic scores are widely used to predict survival and the need for transplantation.