Introduction

The formation of esophageal varices depends on an elevation in portal pressure; a hepatic venous pressure gradient **(HVPG)** greater than 10 mmHg is necessary for the development of & bleeding from esophageal varices ***(Thabut et al., 2011)***.The actual recommendation for surveillance in patients with compensated liver disease & small varices at the screening endoscopy is a follow-up examination after 1-2 years ***(Biecker et al., 2009).***The prevalence of esophageal varices **(OV)** in newly diagnosed cirrhotic patients is approximately 60-80% and the 1-year rate of first variceal bleeding is approximately 5% for small esophageal varices & 15% for large esophageal varices ***(Garcia-Tsao et al. ,2010).***

The management of patients with acute variceal bleeding includes not only treatment & control of active bleeding but also the prevention of rebleeding , infections& renal failure ***(Garcia-Pagán et al., 2008)***. The management of acute variceal bleeding with the combination of vasoconstrictors, endoscopic therapy & antibiotics has decreased mortality substantially ***(Gracia-Tsao et al., 2010).*** The current treatment of gastro-esophageal varices has substantially reduced the rate of first & recurrent bleeding

while decreasing the mortality of acute variceal hemorrhage ***(Garcia-Tsao et al., 2010).*** In patients who survive the first episode of esophageal hemorrhage , the risk of recurrent bleeding is as high as 60% with a mortality rate up to 33% ***(Bari et al., 2012).***

Several studies have shown that esophageal variceal ligation **(EVL)** is effective , safe & requires few sessions to obliterate varices and significantly reduces the rate of recurrent bleeding ***(Geraci et al., 2011).*** Varices can be obliterated after 4-5 sessions given over a period of 12-24 week ***(Ouakaa-Kchaou et al., 2011).***

Non selective beta blockers are the most commonly used drugs to prevent variceal bleeding in patients with cirrhosis & esophageal varices ***(Ouakaa-Kchaou et al., 2011).*** Non selective beta blockers are the mainstay of therapy in prevention of first episode of variceal hemorrhage ***(Song et al., 2011).*** Carvidelol has recently been investigated in portal hypertension giving its alpha blocking component & its potential to better diminish portal pressure ***(De Franchis et al.,2010)***.

Model for end stage liver disease (**MELD**) has been a useful tool to predict mortality for patients awaiting liver transplantation. However, the role of the score in predicting complications after liver transplantation has yet to be evaluated ***(Cywinski et al., 2011)***. MELD score was better predictive factor of early mortality after resection for patients with hepatocellular carcinoma **(HCC)** and cirrhotic liver than Child Paugh **(CTP)** score irrespective of etiology of cirrhosis ***(Song et al., 2011)***. Recently, various modifications of the MELD have been introduced and improved accuracy in both, chronic liver failure and acute liver failure ***(Geraci, Arnone et al., 2011)***.

Aim of the Work

To assess the relation between MELD score and grades of esophageal varices (OV) in patients with liver cirrhosis.

Chapter (1)
Cirrhosis

Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases ***(Qua CS, Goh KL et al., 2011).*** The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the most common causes in western countries ***(Innes HA, Hutchinson SJ et al., 2013),*** whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region ***(Liaw YF, Leung N et al., 2008).***

Liver cirrhosis has many other causes, include inherited diseases such as hemochromatosis and Wilson's disease ***(Deutsch M et al., 2013)***, primary biliary cirrhosis, primary sclerosing cholangitis ***(Wu SJ et al., 2011),*** and autoimmune hepatitis ***(Poupon Ret al., 2006).*** Some cases are idiopathic or cryptogenic. In recent decades, NAFLD has become a leading cause of chronic liver disease in Western countries such as the United States, with a prevalence of as high as 30% in the general population ***(Lazo M et al., 2011).*** Thus, NAFLD has attracted extensive attention as an

important cause of chronic liver diseases ***(Tarantino G et al., 2011).***

Although the causes of liver cirrhosis are multifactorial, there are some pathological characteristics that are common to all cases of liver cirrhosis, including degeneration and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissues and regenerative nodules, and loss of liver function ***(El sharkawy AM et al., 2005).*** Fibrosis as a precursor of cirrhosis is a pivotal pathological process in the evolution of all chronic liver diseases to cirrhosis ***(Braet F et al., 2002).***

The pathophysiology of cirrhosis (short overview)

Advanced chronic hepatitis, whatever the etiology, accounts for the development of regenerative nodules surrounded by fibrotic septa that are the histological hallmark of liver cirrhosis ***(Tsochatzis EA et al., 2014)***.These architectural changes are associated with a relevant increase of intra-hepatic resistance to portal blood flow and, as a consequence, an increase of portal pressure ***(Bosch J, Abraldes JG et al., 2010)***. In particular, a portal pressure gradient (the difference between the portal pressure and the inferior cava vein pressure) greater than 5 mmHg defines the

condition of portal hypertension ***(Bosch J, Abraldes JG et al., 2009).***

Portal hypertension is the main driving factor in the natural history of cirrhosis ***(de Franchis R et al ., 2010)***. In the earliest stages of the disease, portal pressure is determined by the increase of liver resistance to portal blood flow caused by histological changes of the liver, like fibrosis and nodules ***(Sethasine S, Jain D et al., 2012).***

Causes

It has many possible causes; sometimes more than one cause is present in the same person. 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 JF, Armstrong GL et al ., 2006)***.

1. Alcoholic liver disease (ALD). Alcoholic cirrhosis develops for 10–20% of individuals who drink heavily for a decade or more. 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.

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 LS et al.,2014. Current medical diagnosis and treatment 2014).*** In the United States, 2/5 of cirrhosis-related deaths are due to alcohol**.**

2. 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 the patient does not have an alcohol history. A biopsy is needed for diagnosis**.** ***(Friedman LS et al., 2014. Current medical diagnosis and treatment 2014).***

3. 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. Host risk factors include human promoter polymorphisms such as TGF-β1 and angiotensin as well as host immune phenotype variations, such as immunosuppressed patients**.** ***(Huang H; et al. 2004).*** Cirrhosis caused by hepatitis C and alcoholic liver disease are the most common reasons for liver transplant. ***(Dan L. Longo .et al., 2011. Harrison's principles of internal medicine).***

4. 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.[7] 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**.**

5. 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.

6. Primary sclerosing cholangitis.(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.

7. 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+ %.

8. Hereditary hemochromatosis. Usually presents with a 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, CQ; Kushner, JPet al., 1993).*** Genetic testing may be used to identify HFE mutations. If these mutations are present, a biopsy may not need to be performed. Treatment is with phlebotomy to lower total body iron levels.

9. Wilson's disease. Autosomal recessive disorder characterized by low serum ceruloplasmin and increased hepatic copper content on liver biopsy, and elevated 24-hour urine copper. May also have Kayser-Fleischer rings in the cornea and altered mental status. This condition affects 1 in 30,000 people.

10. Alpha 1-antitrypsin deficiency , Autosomal recessive disorder of decreased levels of the enzyme alpha 1—antitrypsin (AAT). Patients may also have chronic obstructive pulmonary disease (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.

11. Cardiac cirrhosis. Due to chronic right sided heart failure which leads to liver congestion.
12. Galactosemia
13. Glycogen storage disease type IV
14. Cystic fibrosisHepatotoxic drugs or toxins ***(Dan L. Longo .et al., 2012. Harrison's principles of internal medicine. (18th ed.).***

Signs and symptoms

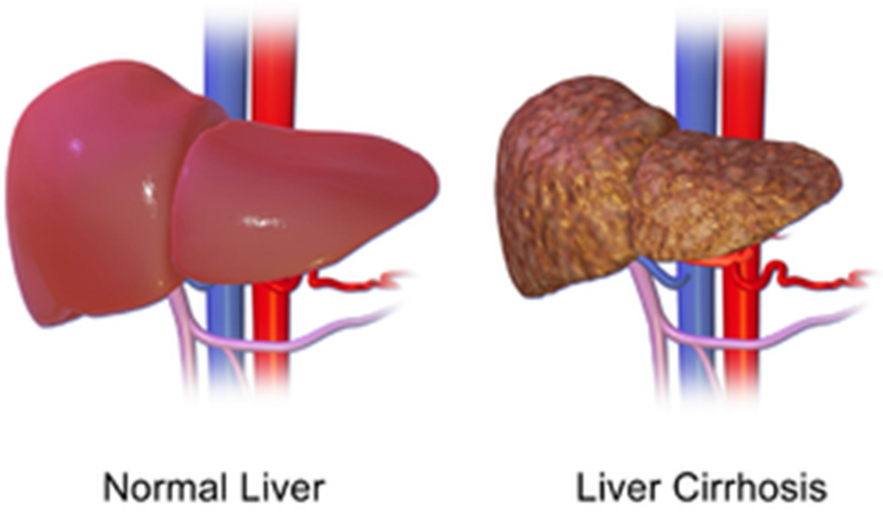

Figure (1): Normal liver & cirrhotic liver.

Cirrhosis has many possible manifestations. These signs and symptoms may be either as a direct result of the failure of liver cells or secondary to the resultant portal hypertension. There are also some manifestations whose causes are nonspecific, but may occur in cirrhosis. Likewise, the absence of any does not rule out the possibility of cirrhosis. ***(Friedman LS et al., 2014. Current medical diagnosis and treatment 2014).***

Cirrhosis of the liver is slow and gradual in its development. It is usually well advanced before its symptoms are noticeable enough to cause alarm. Weakness and loss of weight may be early symptoms.

1- Liver dysfunction

The following features are as a direct consequence of liver cells not functioning.

- Spider angiomata or spider nevi are vascular lesions consisting of a central arteriole surrounded by many smaller vessels (hence the name "spider") and occur due to an increase in estradiol. One study found that spider angiomata occur in about 1/3 of cases. ***(Li CP, Lee FY et al., 1999).***

- Palmar erythema is a reddening of palms at the thenar and hypothenar eminences also as a result of increased estrogen. ***(william, james et al.,2005).***
- Hypogonadism, a decrease in sex hormones manifest as impotence, infertility, loss of sexual drive, and testicular atrophy, can result from primary gonadal injury or suppression of hypothalamic/pituitary function. Hypogonadism is associated with cirrhosis due to alcoholism and hemochromatosis**.** ***(van Thiel, DH; Gavaler et al ., 1981)***
- Liver size can be enlarged, normal, or shrunken in people with cirrhosis.
- Ascites, accumulation of fluid in the peritoneal cavity (space in the abdomen), gives rise to flank dullness (needs about 1500 ml to detect flank dullness). This may be visible as increase in abdominal girth. ***(Dan L. Longo .et al., 2012. Harrison's principles of internal medicine. (18th ed.)***
- Jaundice is yellow discoloration of the skin and mucous membranes (with the eye being especially noticeable) due to increased bilirubin (at least 2–3 mg/dL or 30 μmol/L). Urine may also appear dark. ***(Dan L. Longo et al., 2012. Harrison's principles of internal medicine. (18th ed).***

2- Portal hypertension

- Liver cirrhosis increases resistance to blood flow and higher pressure in the portal venous system, resulting in portal hypertension. Effects of portal hypertension include:
- Splenomegaly (increase in size of the spleen) is found in 35% to 50% of patients.
- Esophageal varices result from collateral portal blood flow through vessels in the stomach and esophagus (a process called portacaval anastomosis). When these blood vessels become enlarged, they are called varices and are more likely to rupture. Variceal rupture often leads to severe bleeding, which can be fatal.
- Caput medusa are dilated periumbilical collateral veins due to portal hypertension. Blood from the portal venous system may be shunted through the periumbilical veins and ultimately to the abdominal wall veins, manifesting as a pattern that may resemble the head of Medusa.
- Cruveilhier-Baumgarten murmur is a venous hum heard in the epigastric region (on examination by stethoscope) due to collateral connections forming