INTRODUCTION

Cirrhosis is a serious and irreversible disease. It is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrotic scar tissue as well as regenerative nodules, leading to progressive loss of liver function. It is a major cause of mortality and morbidity worldwide ***(Suhail Ahmed Almani, 2008).***

The MELD score is a short-term (three- to six-month) predictor of survival in patients with end-stage liver disease, but is a weak predictor of survival in patients with compensated liver cirrhosis in the long term ***(Kronenberger et al., 2012).***

In gastroenterology, the Child-Pugh score (also known as the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although originally used to predict mortality during surgery, the Child-Pugh score is now used to determine the prognosis as well as the required strength of treatment, and the necessity for liver transplantation ***(Meng et al., 2013).***

Levels of CRP raise parallelly with the chronic liver disease progression, such as chronic hepatitis and liver cirrhosis, as well as before the progression beginning,

therefore it is a useful prognostic parameter ***(Popovic-Dragonjic et al., 2010).***

The CRP values increases as the stages of liver cirrhosis advance. The highest values of the CRP were found in the Child C class of liver cirrhosis regardless of etiology compared to Child B class and Child A class ***(Burta et al., 2011).***

The association between higher CRP level and short -term mortality suggest that this biomarker has a potential as prognostic predictors in patients with liver cirrhosis ***(Lazzarotto et al., 2013).***

Patients of MELD ≥20 had significantly higher serum level of IL-6 than group of MELD<20 ***(Imad Lahdou et al., 2013).***

One log increment in serum IL-6 was associated with a two-fold increased risk of liver-related mortality ***(Lee et al., 2012).***

The high level of IL-6 in non viral hepatitis was explained that by the fact that IL-6 is mainly metabolized at the hepatic level, so in the presence of hepatic

insufficiency, the elevation of endogenous cytokines is always present ***(Fadwa M. Al-Sharif, 2011).***

The production of acute-phase proteins requires a proinflammatory cytokine as a mediator. Induction of CRP in hepatocytes is principally regulated at the transcriptional level by the cytokine IL-6 ***(Sakhawat H. Rahman et al., 2008).***

Alterations in inflammation-related components, such as TNF-α, IL-6 or adhesion molecules like ICAM-1, have been shown to be of prognostic significance in cirrhotic patients ***(Tacke et al., 2007).***

AIM OF THE WORK

To assess the value of serum levels of C-reactive protein versus interleukin 6 as a marker of the severity of different stages of liver cirrhosis as regard Child-Pugh classification and MELD score.

LIVER CIRRHOSIS

1.1 Definition of Cirrhosis:

The word cirrhosis comes from the Greek word kirrhos, which means orange yellow. Laennec gave cirrhosis its name kirrhos in 1819 in a brief footnote to his treatise De l'auscultation mediate ***(Gunnarsdottir, 2008).***

Cirrhosis is a serious and irreversible disease. It is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrotic scar tissue as well as regenerative nodules, leading to progressive loss of liver function. It is a major cause of mortality and morbidity worldwide ***(Suhail Ahmed Almani, 2008).***

In established cirrhosis the resultant altered functions may remain compensated for variabl lenghths of time but in due course they decompensate and end stage complications occur which become fatal ***(Nayak and Jain, 2011).***

1.2 Epidemiology of Liver Cirrosis:

The exact prevalence of cirrhosis worldwide is unknown. Since compensated cirrhosis often goes undetected for prolonged periods of time, a reasonable estimate is that up

to 1% of populations may have histological cirrhosis ***(Schuppan and Afdhal, 2008).***

This high prevalence of chronic liver diseases in Egypt has led to increasing numbers of Egyptian patients suffering from end stage liver disease, necessitating liver transplantation ***(Hatem Khalf et al., 2005).***

Egypt has the highest prevalence of hepatitis C virus (HCV) infection in the world, averaging 12%-24% in the general population. HCV Genotype 4 is the prevailing genotype in Egypt (90%) ***(Manal A El-Hawary et al., 2007).***

1.3. Pathogenesis and Pathophysiology of Liver Cirrosis:

Ito or stellate cells are the main cellular source of extracellular matrix proteins in the liver. The initiation and maintenance of fibrogenesis in the liver is characterized by two processes. The former is characterized by the activation and transformation of Ito cells to myofibroblasts resulting in increased production of collagen types I and III ***(Kolios et al., 2006).***

In parallel, there seems to be a disturbance of the homeostatic mechanisms involved in extracellular matrix deposition due to reduced expression of the proteolytic

enzymes that degrade the extracellular matrix and increased expression of their inhibitors ***(Kolios et al., 2006).***

Thus, maintaining fibrosis involves decreased production of matrix metalloproteinases (MMPs) and increased production of specific (tissue inhibitors of matrix metalloproteinases (TIMPs) or non specific metalloproteinase inhibitors (alpha1-antitrypsin) Kupffer cells are involved both in processes *via* the production of cytokines and growth factors that induce Ito cell myofibroblastic transformation and also *via* regulation of the production of metalloproteinases and their inhibitors ***(Kolios et al., 2006).***

Kupffer cell-derived transforming growth factor beta one (TGF-β1) has been suggested to drive Ito cell transformation and to induce production of collagen and proteoglycans by these cells ***(Kolios et al., 2006).***

Finally another mechanism that could lead to the phenotypic change of Ito cells is the production of gelatinases by Kupffer cells ***(Kolios et al., 2006).***

1.3.1. Pathophysiology of portal hypertension in cirrhosis:

Portal pressure increases initially as a consequence of an increased resistance to flow mostly due to an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules. In addition to this

structural resistance to blood flow, there is an active intrahepatic vasoconstriction that accounts for 20%-30% of the increased intrahepatic resistance, and that is mostly due to a decrease in the endogenous production of nitric oxide ***(Garcia-Taso et al., 2007).***

Portal hypertension leads to the formation of porto-systemic collaterals**.** However, portal hypertension persists despite the development of these collaterals for 2 reasons: (1) an increase in portal venous inflow that results from splanchnic arteriolar vasodilatation occurring concomitant with the formation of collaterals; and (2) insufficient portal decompression through collaterals as these have a higher resistance than that of the normal liver. Therefore, an increased portal pressure gradient results from both an increase in resistance to portal flow (intrahepatic and collateral) and an increase in portal blood inflow ***(Garcia-Taso et al., 2007).***

1.4. Etiology of Liver Cirrosis:

It is important to know the etiology of cirrhosis, since it can predict complications and direct treatment decisions. It also allows the discussion of preventive measures ***(Schuppan and Afdhal, 2008).***

1.4.1. Most common causes of liver cirrhosis:

- Alcohol (60 to 70 percent).
- Biliary obstruction (5 to 10 percent):
  - Biliary atresia/neonatal hepatitis.
  - Congenital biliary cysts.
  - Cystic fibrosis.
- Primary or secondary biliary cirrhosis.
- Chronic hepatitis B or C (10 percent).
- Hemochromatosis (5 to 10 percent).
- Non alcoholic fatty liver disease (NAFLD) (10 percent).

(Heibelbaugh and Bruderly, 2006)

1.4.2. Less common causes of liver cirrhosis:

- Autoimmune chronic hepatitis types 1, 2, and 3.
- Drugs and toxins:
  - Alpha-methyldopa (Aldomet).
  - Amiodarone (Cordarone).
  - Isoniazid (INH).
  - Methotrexate.
  - Oxyphenisatin (Prulet).
  - Perhexiline.
  - Troglitazone (Rezulin).

  - Vitamin A.
- Genetic metabolic disease:
  - A1-Antitrypsin deficiency.
  - Amino acid disorders (e.g., tyrosinemia).
  - Bile acid disorders.
  - Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases).
  - Lipid disorders (e.g., abetalipoproteinemia).
  - Porphyria.
  - Urea cycle defects (e.g., ornithine carbamoyl-transferase deficiency).
  - Wilson's disease.
- Idiopathic/miscellaneous.
- Granulomatous liver disease (e.g., sarcoidosis).
- Idiopathic portal fibrosis.
- Indian childhood cirrhosis.
- Polycystic liver disease.
- Infection:
  - Brucellosis.
  - Congenital or tertiary syphilis.

- Echinococcosis.
- Schistosomiasis.

- Vascular abnormalities:
  - Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis.
  - Hereditary hemorrhagic telangiecttelangiectasia (Osler-Weber-Rendu disease).
  - Veno-occlusive disease.

(Heibelbaugh and Bruderly, 2006)

1.5.Clinical Presentation of Liver Cirrhosis:

1.5.1. History & clinical examination cirrhotic patients:

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis ***(Heibelbaugh and Bruderly, 2006)***

1.5.2. Common Physical Examination Findings in Patients with Cirrhosis:

- Abdominal wall vascular collaterals (caput medusa).
- Ascites.
- Asterixis.

- Clubbing and hypertrophic osteoarthropathy.
- Constitutional symptoms, including anorexia, fatigue, weakness, and weight loss.
- Cruveilhier-Baumgarten murmur: (a venous hum in patients with portal hypertension).
- Dupuytren's contracture.
- Fetor hepaticus: (a sweet, pungent breath odor).
- Gynecomastia: is the enlargement of the male breast.

(Udell et al., 2012)

- Hepatomegaly.
- Splenomegaly.
- Jaundice.
- Kayser-Fleischer ring (brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease).
- Nail changes:
  - Muehrcke's nails: (paired horizontal white bands Separated by normal color).
  - Terry's nails: (proximal two thirds of nail plate appears white, whereas the distal one third is red)

(Heibelbaugh and Bruderly, 2006)

- Palmar erythema: refers to an intense reddening involving the thenar and hypothenar eminences sparing the center of the palm.The color blanches on pressure and returns rapidly on release ***(Udell et al., 2012).***
- Scleral icterus: can usually be appreciated when the bilirubin level is above 2.5 to 3 mg/dL ***(Udell et al., 2012).***
- Vascular spiders: (spider telangiectasias, spider angiomata) vascular lesions usually found on the trunk, face, and upper extremities.
- Metabolic bone disease and risk of fractures.
- Impaired glucose homeostasis.
- Extrahepatic manifestations of advanced liver disease:
    - Cirrhotic cardiomyopathy.
    - Hepatopulmonary syndromes.
    - Hormonal complications:
        - Testicular atrophy and feminization in men.
        - Hirsutism, amenorrhoea in women.
    - Increased risk of generalized infectious complications.

(Batey, 2008)

1.6. Complications of Liver Cirrosis:

1.6.1. Gastroesophgeal varices:

The most important clinical consequences of portal hypertension are related to the formation of portal-systemic collaterals, including gastroesophageal varices, which are responsible for one of the main complications of portal hypertension, upper gastrointestinal bleeding ***(Gunnarsdóttir, 2008).***

Gastrointestinal bleeding is a dreaded complication of cirrhosis. More than 80% of hemorrhages due to cirrhosis arise from esophageal varices; less common sources include extra-esophageal collateral vessels and diffuse bleeding from the gastric mucosa ***(Sauerbruch et al., 2013).***

Collateral vessels, including those in the esophageal wall, form when the portal pressure is 10 mmHg or higher. As the vessels in the distal third of the esophagus and at the gastro-esophageal junction are covered only by a thin epithelial layer, this is the most common site of bleeding. Variceal bleeding carries a high mortality (20% to 30**%**) ***(Sauerbruch et al., 2013).***

The main cause of variceal bleeding is thought to be excessive hydrostatic pressure inside the varices, which is a consequence of increased portal pressure ***(Gunnarsdóttir, 2008).***

Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease ***(Garcia-Tsao et al., 2007).***

Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the endoscopic presence of red wale marks.Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients ***(Garcia-Tsao et al., 2007).***

Variceal wall tension is probably the main factor that determines variceal rupture. Vessel diameter is one of the determinants of variceal tension. One of the determinants of variceal wall tension is the pressure within the varix, which is directly related to the HVPG. Therefore, a reduction in HVPG should lead to a decrease in variceal wall tension ***(Garcia-Tsao et al., 2007).***

Gastric varices are less prevalent than esophageal varices and are present in 5%-33% of patients with portal hypertension with a reported incidence of bleeding of about 25% in 2 years, with a higher bleeding incidence for fundal varices. Risk factors for gastric variceal hemorrhage include the size of fundal varices and endoscopic presence of variceal red spots (defined as localized reddish mucosal area or spots on the mucosal surface of a varix) ***(Garcia-Tsao et al., 2007).***