INTRODUCTION

Esophageal varices (EV) due to portal hypertension are a major concern in cirrhotic patients because of the risk of bleeding and related high mortality. The prevalence of EV in newly diagnosed cirrhotic patients is approximately 60-80% and the 1-year rate of first variceal bleeding is approximately 5% for small EV and 15% for large EV ***(Bosch et al., 2008).***

According to recent guidelines, they all stated that Esophagogastroduodenoscopy is the gold standard for the diagnosis of esophageal varices, and recommended that all cirrhotic patients should be screened for the presence of EV when liver cirrhosis is diagnosed ***(World Gastroenterology Organization, 2014).***

The mortality from each episode of variceal bleeding is estimated to be 17-57% ***(Jensen, 2002).*** Within the first two years of detection of varices, the incidence of the first attack of bleeding ranges from 20 to 40 % of all cases. This makes the prevention of esophageal variceal bleeding the cornerstone of long-term management of patients with liver cirrhosis ***(D'Amico et al., 2001).***

Endoscopic surveillance is recommended at 1-2 year intervals in patients with small varices and no bleeding so as to evaluate the development or progression of this feature ***(World Gastroenterology Organization, 2014).*** In addition, endoscopic surveillance is recommended at 2-3 year intervals in patients without varices and compensated cirrhosis.

However, subjecting all patients with cirrhosis to screening endoscopy imposes a needless burden of stress and expense on patients and medical facilities. On the other hand, many patients refuse repeated endoscopies because of discomfort and fear of transmission of or contribution to infection as it is associated with disruption of the natural barriers ***(Bosch et al., 2003).*** Moreover, sedation of a cirrhotic patient to perform endoscopy may be hazardous ***(McGuire, 2001).*** Moreover, as the prevalence of high-risk esophageal varices (HEV) at any point in time is approximately 15–25%. Most subjects screened either do not have varices or have varices that do not require prophylactic therapy ***(Garcia-Tsao, et al. 2007)***.

A more affordable approach for screening would be possible if patients at low or high risk of having EV could be identified from easily obtainable clinical variables. As liver fibrosis is related to portal hypertension and EV, an index to detect histological cirrhosis or significant fibrosis would be an effective noninvasive tool to detect the presence of EV and it could reduce the requirement for both liver biopsy and endoscopy in clinical practice ***(Sarangapani et al., 2010).***

Predicting the presence of esophageal varices by noninvasive means would restrict the performance of endoscopy to those patients with a high probability of having varices. Several studies have addressed the issue of identifying patients with varices by non-invasive or minimally invasive

means, with the aim of avoiding endoscopy in those at low risk of having varices. These studies have assessed the possibility of using biochemical markers such as the blood markers of fibrosis or transient elastography, radiological methods like ultrasound parameters and multidetector CT esophagography in establishing this noninvasive diagnosis ***(De Franchis et al., 2008).***

AIM OF THE WORK

The aim of this work is to assess the value of 3 non-invasive indices in predicting the presence of esophageal varices (EV) in patients with hepatitis C-related liver cirrhosis (P2/MS ratio, APRI and PC/SD ratio).

Chapter (I)

PORTAL HYPERTENSION

Portal hypertension (PHT) is a common clinical syndrome which is hemodynamically defined by a pathological increase of the portal pressure in which the pressure gradient between that of the portal vein and that of the inferior vena cava is elevated above its normal values of 1–5 mm Hg. Also, there is formation of porto-systemic collaterals that shunt part of the portal blood into the systemic circulation away from the liver (bypassing it) ***(Garcia-Pagan et al., 2005a).*** All these derangements occur as a result of difficult blood outflow from the portal vascular bed through the liver ***(Bosch et al., 2008).***

Anatomy of portal circulation:

Portal hypertension describes elevated pressure within the portal system, including the portal vein and the tributary veins that drain into it. Veins coming from the stomach, intestine, spleen, and pancreas merge into the portal vein, which then branches into smaller vessels and travels through the liver. If the vessels in the liver are blocked due to liver damage, blood cannot flow properly through the liver. As a result, high pressure in the portal system develops. This increased pressure in the portal vein may lead to the development of large, swollen veins (varices) within the esophagus, stomach, rectum, or umbilical area (belly button).

Varices can rupture and bleed, resulting in potentially life-threatening complications ***(Garcia-Tsao and Lim, 2009).***

When clinical manifestations of PHT are evident or when portal pressure exceeds a threshold value of 10 mmHg, portal hypertension in this case is referred to as clinically significant portal hypertension (CSPH) ***(Bosch et al., 2006).*** While, with values of portal pressure gradient below 10 mmHg but exceeding the normal value of 5 mmhg, portal hypertension is referred to as pre-clinical PHT ***(Bosch et al., 2008).***

The hallmark of PHT is the pathologic increase in the pressure gradient which is the hepatic venous pressure gradient (HVPG) that measures the difference between the portal venous pressure and the inferior vena cava pressure ***(Garcia-Pagan et al., 2005a and b).*** We should use the pressure gradient not the portal pressure itself as a reflection (estimate) of the portal pressure, as the latter may be affected (increased) with any increase in the intra-abdominal pressure as in case of ascites which may increase the portal pressure but not the HVPG as the inferior vena cava pressure will be also increased ***(Sanyal et al., 2008).***

Epidemiology of PHT:

PHT represents one of the leading cause of death and liver transplantation worldwide. Cirrhosis is the leading cause of PHT all over the world as it is responsible for about 90 % of

all cases of PHT. However, other non-cirrhotic causes of PHT can be also identified, each of them contributes to the development of PHT in a variable degree according to its own prevalence and geographical distribution ***(Sarin and Kumar, 2006 and Bosch et al., 2008).*** Schistosomiasis, for example, was considered to be one of the most common non cirrhotic causes of PHT worldwide, especially in developing countries like Egypt ***(Dunn and Kamel, 1981 and Salam et al., 1990).*** However, many schistosomiasis species tend to occur in variable geographic pattern. For example, S. mansoni is mainly found in Africa and Madagascar. It was exported by the slave trade to parts of South America and the Caribbean. While, S. hematobium infection is acquired predominantly throughout Africa, parts of Arabia, Madagascar, Mauritius and the Near east. On the other hand, S. japonicum occurs in Asia, particularly in China, the Philippines and Sulawesi. S. intercalatum occurs only in central as well as West Africa and S. mekongi is found in the Mekong River on the east border of Thailand ***(Kjetland et al., 2012; Stothard et al., 2011).***

Other important causes of non-cirrhotic PHT include portal vein thrombosis (PVT) ***(Wang et al., 2005),*** which is responsible for about 5%-10% of all cases of PHT, and is the leading cause of extrahepatic non cirrhotic PHT in the western countries ***(Bosch et al., 2008),*** nodular regenerative hyperplasia which was considered the main cause of non-cirrhotic PHT in the western world ***(Naber et al., 1991 and Mahamid et al.,***

2005) and idiopathic portal hypertension that causes PHT all over the world but it is particularly common in Asia where it accounted for 15 to 25% of all cases of PHT in India in year 1976 and up to 30% in Japan in year 1982 ***(Datta, 1976 and Okuda et al., 1982).*** However, higher incidence of this disease that may reach up to 40% could be seen in other developing countries ***(Wang et al., 2005).*** Idiopathic PHT is being a rare disease among western population and its incidence is declining in Japan as a result of the improved hygiene and standards of living in these two countries ***(Imai et al., 1993 and Sarin and Kumar 2006).***

Importance of PHT is defined by the frequency and severity of its complications which is consistent with progression of the primary disease towards decompensation. These consecutive complications include porto-systemic collaterals with the development of varices, variceal hemorrhage, ascites, hepato-renal syndrome, porto-systemic encephalopathy, hepato-pulmonary syndrome and congestive splenomegaly. Variceal hemorrhage is the most lethal and the most feared among these complications ***(D'Amico and de Franchis, 2003).***

Gastro-esophageal varices (GEV) represent an important site for porto-systemic anastomosis. Varices are present in about 30-40% of compensated cirrhotic patients at time of diagnosis, i.e. in Child's group (A) patients. However, its prevalence among decompensated cirrhotic patients (as among

Child's C patient group) is increased to about 60-80% ***(D'Amico and Luca, 1997).*** Incidence of new varices development in patients with no varices at first endoscopy ranges from 5-10% annually ***(Merli et al., 2003).***

Once varices developed, they usually continue to increase in size until they eventually rupture and bleed ***(Bosch et al., 2008).*** The overall incidence of variceal bleeding is about 4% per year in patients with small varices while this risk increases to about 15% per year in patients with medium to large sized varices ***(D'Amico and Luca, 1997).*** Once varices start bleeding, spontaneous hemostasis can occur in about 50% of cases with an increased risk of early re-bleeding (over the next 2-5 days). However, this increased risk subsides to the baseline by 6 weeks. Over 70% of survivors of an index bleed will experience recurrent hemorrhage if left untreated and a similar number will die within 1 year. The risk of late re-bleeding (6 weeks later or more) is also present and is linked to the severity of liver failure, ascites, and presence of hepatoma, active alcoholism, and red signs at endoscopy. Each bleeding episode carries a mortality risk of about 20-30% ***(Comar and Sanyal, 2004).***

Sex and age related demographics:

Liver disease demonstrates a sex predilection, with males making up more than 60% of patients with chronic liver disease and cirrhosis ***(Kim et al., 2001)***.

In general, alcoholic liver disease and viral hepatitis are the most common causes for esophageal varices in both sexes. However, veno-occlusive diseases and primary biliary cirrhosis are more common in females; and in females with esophageal varices, alcoholic liver disease, viral hepatitis, veno-occlusive disease, and primary biliary cirrhosis are usually responsible. In males with esophageal varices, alcoholic liver disease and viral hepatitis are usually the cause.

Portal vein thrombosis and secondary biliary cirrhosis are the most common causes of esophageal varices in children. Cirrhosis is the most common cause of esophageal varices in adults.

Classification of PHT:

Portal hypertension is caused by any obstacle that can impede portal blood flow at any level. Therefore, PHT can be classified anatomically (according to the site of this obstacle) into prehepatic, intrahepatic as well as post-hepatic PHT with the intra-hepatic causes of PHT is further subcategorized into pre-sinusoidal, sinusoidal and post-sinusoidal causes ***(Bosch et al., 2008).***

Intrahepatic causes of portal hypertension

Intrahepatic causes of portal hypertension include cirrhosis and hepatic fibrosis or scarring. A wide variety of illnesses are implicated as the cause of portal

hypertension such as, alcohol abuse, Hepatitis B and C infections, Fatty liver (NASH, non-alcoholic steatohepatitis), Wilson's disease, Hemochromatosis, Cystic fibrosis, Primary sclerosing cholangitis, Biliary atresia and Parasitic infections such as schistosomiasis.

Pre-hepatic causes of portal hypertension

Include Portal vein thrombosis or blood clots within the portal vein, splenic vein thrombosis, congenital portal vein atresia or failure of the portal vein to develop, extrinsic compression of the portal vein, arteriovenous fistulae

Post-hepatic causes of portal hypertension

Post-hepatic causes are due to obstruction of blood flow from the liver to the heart and can include Hepatic vein thrombosis (Budd-Chiari syndrome), Inferior Vena cava thrombosis or malformations, Restrictive pericarditis ***(Ponziani et al., 2010; Garcia-Tsao and Lim, 2009).***

Another classification of PHT is a functional one and is based on the results of hepatic vein catheterization (according to the results of wedged hepatic venous pressure (WHVP), free hepatic venous pressure (FHVP) and HVPG). It groups the previously mentioned categories into *pre-sinusoidal, sinusoidal and post-sinusoidal groups.* As regard the pre-sinusoidal group, it includes all the pre-hepatic causes and some of the intra-hepatic, pre-sinusoidal elements. This group shows normal both

WHVP and FHVP on hepatic vein catheterization. On the other hand, the sinusoidal group includes some of the intrahepatic causes (with sinusoidal affection) that shows an elevated WHVP but with normal FHVP. In this case, WHVP gives an excellent correlation with the actual portal pressure. In general, any form of chronic liver disease except chronic cholestatic syndromes can lead to sinusoidal PHT ***(Bosch et al., 2008).*** Lastly, the post-sinusoidal group includes the post-sinusoidal elements of the intrahepatic causes and also the post-hepatic (supra-hepatic) elements. This group shows an elevated HVPG, WHVP and FHVP in case of intra-hepatic post sinusoidal causes while an elevated WHVP and normal HVPG in case of the post-hepatic causes ***(Wongcharatrawee and Groszmann, 2000).***

Some times PHT is described to be an isolated left sided one. This is a rare condition that results in PHT and bleeding from isolated fundic varices. Pancreatic disease and isolated splenic vein thrombosis are the main causes in this condition ***(Köklü et al., 2007).***

Pathophysiology:

As in any other vessel, the pressure within the portal vein is determined by the product of blood flow and the resistance to the flow of this blood, as defined by ***Ohm's law:***

P (pressure) = Q (blood flow) × R (resistance) (Garcia-Pagan et al., 2005b).

Therefore, portal hypertension can result either from:

(a) An increased vascular resistance which can occur at different levels as mentioned before ***(Gupta et al., 1997 and Laleman et al., 2005)***.

(b) The notable rise in portal blood flow. This increased portal blood flow is responsible for maintaining and aggravating PHT later with disease progression ***(Vorobioff et al., 1984).*** In other words, it is a matter of resistance and flow that regulates the portal pressure ***(Wongcharatrawee and Groszmann, 2000).***

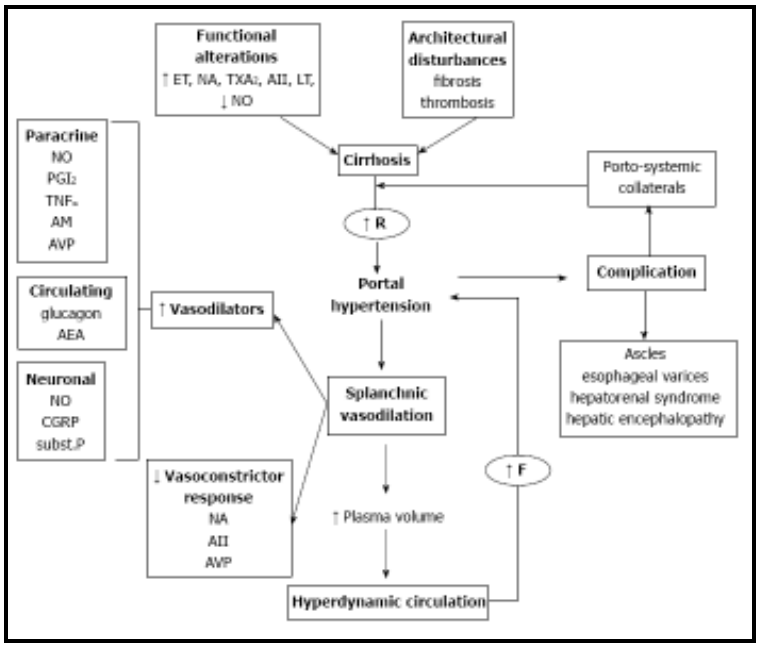

Figure (1): Physiopathology of portal hypertension: in cirrhosis, the initiating factor leading to portal hypertension is an increase in intrahepatic vascular resistance (R), whereas the increase in portal blood flow (F) is a secondary phenomenon that maintains and worsens the increased portal pressure, giving rise to the hyperdynamic circulation syndrome. The different factors implicated in the distinct mechanisms of portal hypertension are shown. AII: angiotensin II; AEA: anandamide; AM: adrenomedullin; CGRP: calcitonine gene related peptide; CO: carbon monoxide; ET: endothelin; H2S: hydrogen sulfide; LT: leukotrienes; NE: norepinephrine; NO: nitric oxide; PGI2: prostacyclin; SP: substance P; TXA2: thromboxane A2. ***(Laleman et al., 2005)***

(A) Increased vascular resistance to the flow of portal blood:

Portal hypertension is initiated by an increased resistance to the portal blood flow. According to the anatomical classification, this can occur at the pre-hepatic (involving the splenic, mesenteric or portal veins), intrahepatic (inside the liver) or at the post-hepatic level (at the level of the outflow tract of blood) ***(Bosch et al., 2008).***

Increased vascular resistance at the pre-hepatic level

Increased resistance to the flow of portal blood at the level of the portal vein before entering the liver gives rise to pre-hepatic PHT. Thus, here, the increased vascular resistance is in the portal vein itself or in its tributaries. PVT represents the classic form and the most common cause of pre-sinusoidal pre-hepatic (infra-hepatic) PHT ***(Bosch et al., 2008).*** Splenic vein thrombosis is another example of the prehepatic PHT, in which the blood flow through the splenic vein may be blocked secondary to either thrombosis or pressure effect by any neighboring mass ***(Weber and Rikkers, 2003).*** Splenic vein occlusion results in venous hypertension in the collateral pathways that carry the splenic blood to the superior mesenteric and portal veins including the short gastric, coronary, and gastro-epiploic veins and the veins located in the upper half of the stomach, producing gastric varices only i.e. "***isolated left sided portal hypertension***". Decompression into the portal venous system may occur through the coronary and epiploic veins and this may result in the development of esophageal varices also. However, splenic vein obstruction may not result in PHT or formation of varices ***(Köklü et al., 2007).***