توقعات دوالي المريء في مريض التليف الكبدي الناتج عن فيروس الكبد سي بواسطة حساب قيمة الفيبر 4 في الدم

رسالة مقدمة

تمهيداً للحصول على درجة الماجستير في طلب المناطق الحارة والجهاز الهضمي

من

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INTRODUCTION

Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices (EV) is one of its major complications. The prevalence of esophageal varices in cirrhotic patients ranges between 24% and 69% according to the degree of liver dysfunction ***(De Franchis and Primignani, 2001).*** The incidence of EV development is approximately 5% per year in patients with cirrhosis and the progression from small to large varices occur in 10% to 20% of cases after 1 year ***(De Franchis, 2003).*** In Egypt, it was found that the incidence of varices among portal hypertension patients was 77% ***(Hunter et al., 1998).***

Variceal haemorrhage occurs in 25 to 40% of patients with cirrhosis and varices ***(Grace, 1992),*** the frequency of bleeding from large varices is 30%-53% compared with 5%-18% for small varices ***(De Franchis, 2003).*** Bleeding esophageal varices is the most common cause of upper GI haemorrhage in Egypt as it represented 53.3% of total bleeding cases ***(Esmat et al., 2004).***

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 is the cornerstone of long-term management of patients with liver cirrhosis ***(D'Amico et al., 2001).***

The American Association for the Study of Liver Disease (AASLD) and the Baveno V Consensus Conference on portal hypertension recommended that cirrhotic patients should be screened by esophago-gastro-duodenoscopy (EGD) for the presence of EV when liver cirrhosis is diagnosed ***(Garcia-Tsao et al., 2007; De Franchis, 2010).***

In addition, repeated EGD is recommended at 3 year intervals in patients without varices and compensated cirrhosis and at 2 year intervals in patients with small varices so as to evaluate the development or progression of this feature. Furthermore, if there is evidence of hepatic decompensation, EGD should be repeated annually ***(De Franchis, 2000).***

These recommendations imply a considerable burden on endoscopies and related costs as they require that patients repeatedly undergo an unpleasant invasive procedure, even though the majority of subjects undergoing screening EGD either do not have varices or have varices that do not require prophylactic therapy ***(D'Amico and Morabito, 2004).*** 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).***Therefore, considerable interest in developing models to predict the presence of esophageal varices especially high risk varices by non-endoscopic methods.

It was previously reported that cirrhotic patients with platelet count of <88.000 were five times more likely to have large EV ***(Zaman et al., 1999).*** In addition, splenomegaly was independent predictor of the presence of large EV ***(Chalasani et al., 1999).***

Schepis et al. (2001) found out that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity less than 70%, platelet count less than 100.000 and ultrasonographic portal vein diameter greater than 13 mm are observed. Platelet count/spleen diameter ratio showed the highest accuracy for the non-invasive prediction of the presence of EV in patients with liver cirrhosis ***(Giannini et al., 2003).***

It has also been found that the level of serum-ascites/ albumin concentration gradient (SAAG) is highly correlated with the presence and degree of EV ***(Dittrich et al., 2001).***

Doppler ultrasonography provides a non-invasive access to the portal system and allows for the estimation of both arterial and venous flow ***(Schepis et al., 2001).*** Doppler impedance indices of hepatic and splenic arteries have been described to be elevated in cases of portal hypertension. These indices were higher in patients with varices than in those without ***(Piscaglia et al., 1997).***

Fib 4 is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver. This scare has been studied in liver disease due to hepatitis ***(Martinez et al., 2011).*** When liver biopsy not indicated or not accepted by patient Fib4 which consist of alanine aminotransferase (AIT) level, AST level, platelet count and age appear to be the a strong predicator of decompensated liver cirrhosis. Therefore, Fib4 is also predictor for esophageal avarices in HCV cirrhotic patients ***(Papastergiou et al., 2012).***

AIM OF THE WORK

To evaluate Serum Fibrosis marker FiB**4** as a Predictor for the presence of Esophagogastric Varices in HCV Cirrhotic patients.

Chapter I

PORTAL HYPERTENSION

Portal hypertension is a frequent syndrome – most often caused by chronic liver diseases – which is characterized by an increased portal pressure gradient (PPG; the difference in pressure between the portal vein and the inferior vena cava [IVC], which represents the perfusion pressure of the liver with portal blood). The increased portal pressure leads to other consequences, such as splenomegaly, growth of an extensive network of portal-systemic collaterals that shunt portal blood flow to the systemic circulation by passing the liver and development of a hyperkinetic circulatory state. In normal conditions the PPG ranges between **1** and **5** mmHg. Portal hypertension becomes clinically significant (associated with risk of clinical complications) when the PPG increases to **10** mmHg or above. Values between **5** and **9** mmHg represent subclinical portal hypertension ***(Bosch et al., 2009).***

Anatomy of the Portal Venous System: **Fig. (1)**

The liver has the most complicated circulation of any organ. According to the anatomical peculiarity of the double afferent blood supply of the liver, **75%-80%** of the blood entering the liver is partially deoxygenated venous blood supplied by the portal vein, which collects all the blood that leaves the spleen, stomach, small and large intestine, gallbladder and pancreas. The hepatic artery accounts for the remaining **25%** with well-oxygenated blood ***(Vollmar and***

Menger, 2009).Total hepatic blood flow ranges between **800** and **1200** mL/min, which is equivalent to approximately **100** mL/min per **100** g liver wet weight. Although the liver mass constitutes only **2.5%** of the total body weight, the liver receives nearly **25%** of the cardiac output. The valveless portal vein is a low pressure/low resistance circuit, while the hepatic artery supplies the liver with arterial blood in a high pressure/high resistance system ***(Greenway and Stark, 1971).***

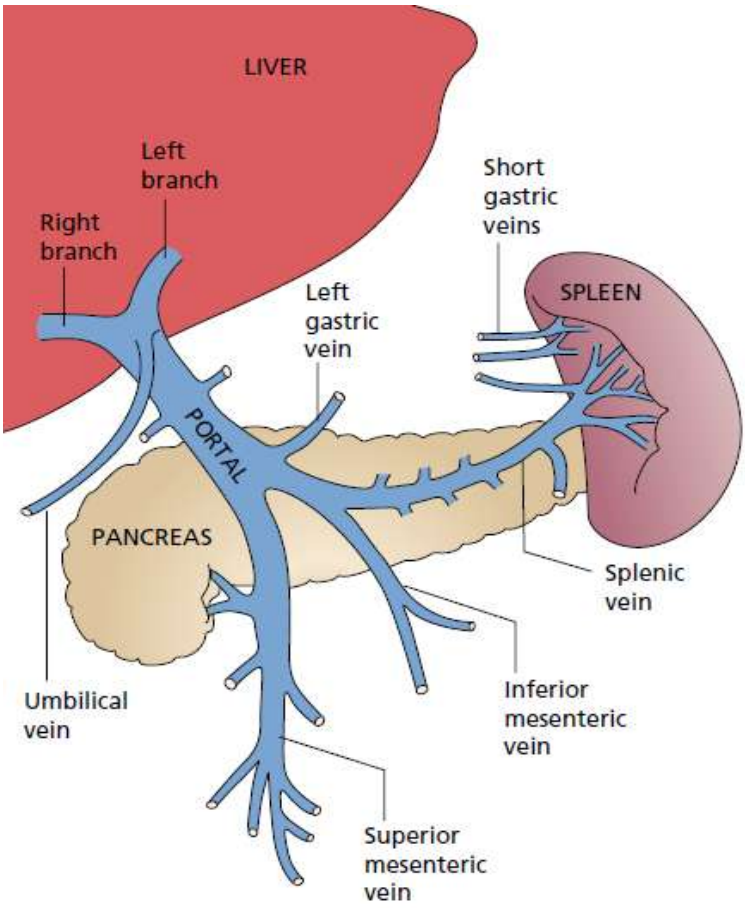

Fig. (1): The anatomy of the portal venous system. The portal vein is posterior to the pancreas ***(Andrew, 2011)***.

The portal vein is formed by the union of the superior mesenteric vein and the splenic vein (splenic veins drain the splanchnic and splenic beds) just posterior to the head of the pancreas at about the level of the second lumbar vertebra ***(Andrew, 2011).***

Numerous small tributaries connect the portal and systemic venous systems, and these can evolve into major collateral channels when portal hypertension supervenes. Formation of such collaterals is triggered when portal pressure rises above the normal level of **5** to **10** mmHg ***(Morris and Wood, 2000).***

The most important of these portal-systemic channels are:

- The left gastric or coronary vein, which connects the esophagocardiac venous plexus with the splenic or portal vein.
- The short gastric and left gastroepiploic veins, which connect the esophageal and gastric plexus with the splenic vein.
- The numerous retroperitoneal portal radicals, which connect to the left renal vein via the left adrenal vein.
- The umbilical and periumbilical veins connecting to the left portal vein.
- The inferior mesenteric vein connecting via the superior haemorrhoidal vein to the middle and inferior haemorrhoidal veins of the systemic circulation, these are often responsible for the formation of large hypertensive haemorrhoids.

(Grace et al., 1998)

In addition to these channels, intrahepatic shunts develop through which a significant proportion of portal venous flow can pass. These routes allow up to **80** per cent of the liver's blood supply to bypass the sinusoidal circulation ***(Morris and Wood, 2000).***

Natural History:

The relevance of portal hypertension derives from the frequency and severity of its complications, which represent the first cause of hospital admission, death and liver transplantation in patients with cirrhosis. These include formation of esophageal or gastric varices, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, portopulmonary hypertension, hepatopulmonary syndrome, hepatic encephalopathy, portal hypertensive gastropathy (PHG), enteropathy and colopathy and disturbances in the metabolism of endo- and xeno-biotics normally metabolized by the liver ***(Berzigotti et al., 2013).***

Portal hypertension is an almost unavoidable consequence of cirrhosis ***(Bosch et al., 2009).*** Between **80** and **90%** of totally asymptomatic patients already have an elevated PPG (measured clinically as an increase in the hepatic venous pressure gradient [HVPG]) and endoscopy discloses that **40%** already have esophageal varices. Among those without varices, this will appear at a rate of **6%** per year (over **10%** in those with a HVPG >**10** mmHg). If untreated, bleeding occurs within

2 years in **10**–**30%** of patients with varices, depending on the size of varices, presence of red color signs, degree of liver failure and of HVPG elevation. Variceal bleeding is associated with a **6**-week mortality of **12**–**20%** and if no effective therapy is provided will recur in two-thirds of the patients within **2** years. Current medical treatment decreases the risk of first and/or recurrent variceal bleeding by approximately **50%**, indicating that better treatments are required ***(Berzigotti et al., 2013).***

Pathophysiology:

Portal hypertension is initiated by an increased resistance to portal blood flow and aggravated by an increased portal-collateral blood flow ***(García-Pagán et al., 2012).*** Such increased resistance to portal blood flow is most commonly due to chronic liver disease (cirrhosis of the liver), which is the most common cause of portal hypertension worldwide, followed by hepatic schistosomiasis. Other causes of portal hypertension account for less than **10%** of cases; among these relatively uncommon causes the more frequent are extrahepatic portal vein occlusion and 'idiopathic' noncirrhotic portal hypertension ***(Berzigotti et al., 2013).*** Hepatic vascular resistance in cirrhosis increases by a dual mechanism; first there is a structural component, related to distortion of liver microcirculation by fibrosis, nodule formation, angiogenesis and vascular occlusion. In addition, there is an increased hepatic vascular tone (dynamic component), owing to the contraction of activated hepatic stellate cells and myofibroblasts around the hepatic sinusoids

and in fibrous septa and of vascular smooth muscle cells in the hepatic vasculature. This dynamic component accounts for approximately **30%** of the increased hepatic resistance in cirrhosis and represents a liver vascular dysfunction, with increased local production of vasoconstrictors (endothelins, angiotensin-II, norepinephrine and thromboxane A**2**) and reduced release of endothelial vasodilators (mainly nitric oxide, but also carbon monoxide) ***(García-Pagán et al., 2012).***

In advanced stages increased splanchnic (portal-collateral) blood flow plays a major role maintaining and aggravating portal hypertension. It is caused by a marked splanchnic arteriolar vasodilation and neoangiogenesis in response to an increased release of vascular endothelial growth factor (VEGF), nitric oxide and other splanchnic vasodilators. Splanchnic vasodilatation is so marked as to determine systemic hypotension, vascular underfilling, stimulation of endogenous vasoactive systems, plasma volume expansion and increased cardiac index (hyperkinetic syndrome), which plays a key role in the pathogenesis of ascites and renal dysfunction in cirrhosis. Formation of portal-systemic collaterals and varices is not only due to increased portal pressure causing opening of pre-existent vessels at sites of communication between the portal and systemic circulation, but is also dependent on angiogenesis ***(Fernández et al., 2009).***

The hypertensive portal vein is decompressed by diverting up to **90%** of the portal flow through portasystemic

collaterals back to the heart, resulting in enlargement of these vessels. These vessels are commonly located at the gastroesophageal junction, where they lie subjacent to the mucosa and present as gastric and esophageal varices. Varices form when the HVPG exceeds **10** mm Hg; they usually do not bleed unless the HVPG exceeds **12** mm Hg (normal HVPG: **1-5** mm Hg) ***(Garcia-Tsao et al., 2007).***

Gastroesophageal varices have **2** main inflows. The first is the left gastric or coronary vein, and the second is the splenic hilum, through the short gastric veins. The gastroesophageal varices are important because of their propensity to bleed. Increased portal pressure contributes to increased varix size and decreased varix wall thickness, thus leading to increased variceal wall tension. Rupture occurs when the wall tension exceeds the elastic limits of the variceal wall. Varices are most superficial at the gastroesophageal junction and have the thinnest wall in that region; thus, variceal hemorrhage invariably occurs in that area ***(Sanyal et al., 2008)***

The following are risk factors for variceal hemorrhage *(Garcia-Tsao et al., 2007):*

- Variceal size - The larger the varix, the higher the risk of rupture and bleeding; however, patients may bleed from small varices too
- The presence of endoscopic red color signs (eg, red wale markings, cherry red spots)

- Child B or C classification, especially the presence of ascites, increases the risk of hemorrhage
- Active alcohol intake in patients with chronic, alcohol-related liver diseases
- Local changes in the distal esophagus (eg, gastroesophageal reflux) – These have been postulated to increase the risk of variceal hemorrhage, but evidence to support this view is weak; studies indicate that gastroesophageal reflux does not initiate or play a role in esophageal hemorrhage ***(Heil et al., 1980)***
- Bacterial infection - A well-documented association exists between variceal hemorrhage and bacterial infections, and this may represent a causal relationship

Note that bacterial infection could also trigger variceal bleeding through a number of mechanisms, including the following:

- The release of endotoxin into the systemic circulation
- Worsening of hemostasis
- Vasoconstriction induced by the contraction of stellate cells

These disturbances provide a rational basis for the treatment of portal hypertension and are being used as therapeutic target ***(García-Pagán et al., 2012).***

Aetiology and classification:

Any disease that may interfere with portal blood flow (at any level between the spleen and the right atrium) may cause portal hypertension. Therefore, causes of portal hypertension can be classified according to their anatomical location in: prehepatic (involving the spleno–portal–mesenteric venous axis), intrahepatic and posthepatic, as summarized in *(table **1**)* ***(Bosch et al., 2009).***

Cirrhosis is the most common cause of portal hypertension in western countries. All other causes included in so-called 'noncirrhotic portal hypertension', account for less than **10%** of the cases. In other geographical areas schistosomiasis (Africa) and portal vein thrombosis (India) are leading causes of portal hypertension ***(Berzigotti et al., 2013).***

The more frequent cause of prehepatic portal hypertension is portal vein thrombosis (PVT). In children this is often secondary to omphalitis, while in adults thrombophilic syndromes, either congenital (such as protein C and S deficiency) or acquired (such as latent myeloproliferative disease) in addition to local factors (such as sepsis, abdominal trauma or surgery) can explain the onset of thrombosis in up to **70%** of cases. In about **30%** these factors are not identified (''idiopathic" PVT).Portal vein thrombosis may present as two distinct clinical scenarios; acute or chronic (portal cavernoma); its diagnosis is based on imaging techniques ***(De Leve et al., 2009).***