Introduction

Portal hypertension is defined by a pathologic increase in portal pressure, in which the pressure gradient between the portal vein and inferior vena cava (the portal pressure gradient) is increased above the upper normal limit of 5 mm Hg. Portal hypertension becomes clinically significant when the Portal pressure gradient increases above the threshold value of 10 mm Hg (e.g., formation of varices) or 12 mm Hg (e.g., variceal bleeding, ascites). Portal pressure gradient values between 6 and 10 mm Hg represents sub clinical Portal hypertension ***(Bosch et al., 2007).***

In the Western world, cirrhosis related to chronic hepatitis C and B and alcoholic cirrhosis are the most common causes for portal hypertension. Non cirrhotic portal hypertension (NCPH) represents a relatively infrequent group of conditions that causes portal hypertension in the absence of cirrhosis. As with cirrhotic portal hypertension, most cases of non cirrhotic portal hypertension are caused by increased portal venous outflow resistance, although, rarely, an increased flow in the portal circulation may be responsible. Ultimately, even in the cases in which there is a chronically increased flow (e.g., in arteriovenous fistulae), intravascular changes evolve, leading to increased resistance ***(Molina and Reddy, 2001).***

Pathphysiologically, the causes for portal hypertension can be categorized into three groups based on whether the block to portal flow is at the portal venous level, in the sinusoidal bed, or at the hepatic veins. Further, pre-sinusoidal resistance to portal flow can occur either at an intra-hepatic site or at the extra hepatic level; similarly, the post sinusoidal hepatic venous outflow blockage could be intra-hepatic or extra-hepatic.

Although development of varices and subsequent bleeding from them are the main manifestations of portal hypertension from all causes, there are unique features related to NCPH that are worthy of mention. The clinical manifestations of pre-sinusoidal portal hypertension characteristically are devoid of ascites and encephalopathy, whereas ascites is a cardinal feature of post-sinusoidal obstruction. The prognosis of portal hypertension caused by pre-sinusoidal conditions is relatively better than that of any cause of portal hypertension ***(Molina and Reddy, 2001).***

The common causes of NCPH include idiopathic portal hypertension (IPH), non-cirrhotic portal fibrosis (NCPF) and extra hepatic portal venous thrombosis (EHPVT). Other causes include schistosomiasis, hepatic venous outflow tract obstruction and congenital hepatic fibrosis. Variceal bleeding in NCPH has lower mortality as compared with cirrhosis because of better liver functions in NCPH ***(Okuda, 2002).***

Budd-Chiari syndrome (BCS) is a rare but potentially life threatening hepatic disorder that results from obstruction of the hepatic venous outflow tract. Obstruction can occur at any level from the hepatic venules to the right atrium ***(Khan, 2005 and Valla, 2009).***

Because BCS is a rare disorder, prospective randomized therapeutic trials to determine the precise effects of routine anticoagulation have been impossible to perform. Specifically, available surveys have not clarified the risk of bleeding. This is of particular relevance to BCS patients who are also at the risk of bleeding from portal hypertension or from complications of percutaneous interventions or surgery ***(Linkins et al., 2003).***

In the current American Associations for the Study of Liver Diseases (AASLD) practice guidelines and recent Baveno V consensus regarding the management of portal vein thrombosis (PVT), anticoagulation has been considered a mainstay therapeutic modality heavily used for PVT, especially in the presence of concomitant prothrombotic disorders. However, the usefulness of long term anticoagulants is often questioned in patients with high-risk varices or a recent history of variceal bleeding caused by extrahepatic PVT. Proponents recommend the use of anticoagulants for its beneficial effects of preventing thrombotic extension and recurrence in patients with prothrombotic disorders and negligible side effects (no fatal anticoagulant-induced bleeding) ***(Amitrano et al., 2003).***

On the contrary, opponents maintain that recurrent thrombotic events are infrequent (3.5–5.5 per 100 patient-

years), and anticoagulants may increase the morbidity of variceal bleeding ***(Thatipelli et al., 2009).***

In chronic PVT, the decision to anticoagulate should be made on an individual case-by-case basis, don't anticoagulate if high risk of bleeding, i.e., variceal bleeding despite optimal medical and endoscopic therapies or if platelet count below 50,000/cmm ***(Parikh et al., 2010).***

Despite the serious nature of complications, no controlled studies have been performed addressing the optimal management of variceal bleeding in patients with PVT Therefore, current guidelines are mainly based on data from studies in patients with portal hypertension caused by liver cirrhosis, in the absence of PVT ***(De Franchis, 2005).***

Although the esophagogastric varices that are liable to bleed and the time of bleeding in portal hypertension cannot be predicted, however there are some clinical and endoscopic signs associated with the high risk of bleeding including size of esophageal varices and presence of cherry red spots. Also, ultrasound findings in portal system could predict both the presence of varices and risk of variceal bleeding ***(Prihatini et al., 2005).***

Aim of the Work

The aim of this work is to evaluate the role of some clinical, endoscopic, laboratory and imaging parameters in the prediction of initial variceal bleeding and rebleeding in patients with non cirrhotic portal hypertension and to identify the frequency of variceal bleeding and rebleeding in these patients.

Chapter one

Anatomy of the Esophagus

The esophagus is a muscular tube, approximately 24 cm in length, extending from the lower end of the pharynx opposite the sixth cervical vertebra to the cardia of the stomach at the level of the eleventh thoracic vertebra ***(Pelot, 1995).*** It has three parts: cervical, thoracic and abdominal parts. The cervical part is about 2 inches in length and lies in the lower part of the neck. The thoracic part lies partly in the superior and partly in the posterior mediastinum. The abdominal part is very short and joins the stomach immediately ***(Snell, 2000).***

Blood Supply:

1- Arterial Supply:

The cervical esophagus receives blood from the superior thyroidal artery as well as the inferior thyroidal artery of thyrocervical trunk, and both sides communicate through a rich collateral network. The thoracic portion of the esophagus is supplied proximally by 2-3 bronchial arteries, and distally by the esophageal arteries arising directly from the aorta ***(Snell, 2000)***. The abdominal portion of the esophagus is supplied by branches arising from celiac axis ***(Pelot, 1995).***

2- Venous Drainage:

The venous drainage of the esophagus begins in a submucosal venous plexus. From this plexus, branches pass through the muscular walls to the surface of the esophagus to form a periesophageal plexus. The venous drainage of the cervical esophagus is usually into the right and left thyroid veins. Venous drainage of the thoracic portion of the esophagus is into the right and left superior intercostal veins, the azygos vein on the right, the hemiazygos vein, an accessory hemiazygos vein on the left, or other variations of the azygos system ***(Pelot, 1995).***

The esophagogastric junction and abdominal portion of the esophagus drain into the right and left gastric veins, which normally form the coronary vein, and into the short gastric veins, which drain into the splenic vein ***(Smith, 2001).***

When portal hypertension exists, or when there is thrombosis of the splenic vein, backflow through the coronary vein and short gastric veins into the lower esophageal branches occurs, causing dilatation and producing varices ***(Pelot, 1995).***

The veins draining the esophagus are classified as intrinsic, extrinsic and venae comitantes of the vagus nerve. The intrinsic veins consist of subepithelial and submucosal plexus running along the length of the esophagus. These veins drain by way of perforating veins into an extrinsic plexus of veins, which drain into the inferior thyroid and brachiocephalic veins in the neck, azygos veins in the thorax, and left gastric vein in the abdominal part of the esophagus ***(Pelot, 1995).***

The intrinsic veins of the gastroesophageal junction are divided into four well-defined zones:

1- <u>Gastric Zone:</u> It is 2-3 cm in length, with its upper border at the gastroesophageal junction and is composed of a radial band of veins in the submucosa and lamina propria ***(Luketic and Sanyal, 2000).***

2- <u>Palisade Zone:</u> This begins at the gastroesophageal junction and extends cranially for 2-3 cm and is a direct extension of the veins of the gastric zone, which run in palisades of longitudinally arrayed veins in the lamina propria. These veins form the primary communication between the portal bed and azygos bed ***(Luketic and Sanyal, 2000).***

3- <u>Perforating Zone:</u> It extends 2-3 cm cranially from the palisade zone. The intrinsic veins drain into the extrinsic veins primarily in this region through valved perforating veins, which normally allow only uni-directional flow ***(Luketic & Sanyal, 2000).*** In portal hypertension, venous dilatation which occurs with increased pressure causes the valves of perforating veins to become incompetent, allowing hepatofugal flow and turbulence in the distal esophagus ***(Farooq and Wong, 2005).***

4- <u>Truncal Zone:</u> This is 8-10 cm in length extending upwards from the perforating zone. The intrinsic veins are composed of 3-4 large venous trunks in the mucosa, which communicate with an irregular polygonal venous plexus in the submucosa ***(Luketic and Sanyal, 2000).***

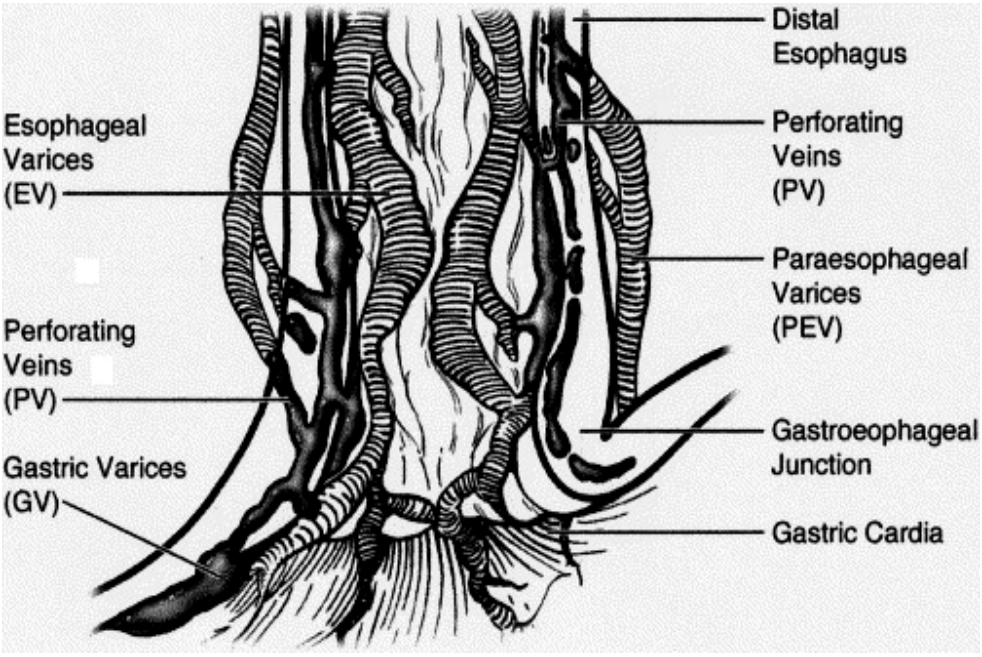

Figure (1): Anatomy of gastroesophageal varices
(Farooq and Wong, 2005).

Anatomy of the Stomach

The stomach is a muscular bag. It consists of fundus, body, pyloric antrum and pylorus ***(Snell, 2000).***

The fundus is the portion of the stomach lying above a horizontal line drawn from the gastroesophageal junction to the greater curvature. The body of the stomach extends from the fundus to the level of the incisura angularis, a constant notch in the lower part of the lesser curvature. The pyloric antrum begins where the body ends and narrows gradually towards the pylorus ***(Eisenberg et al., 1995).***

Blood Supply:

1- Arterial Supply:

The stomach receives blood supply from six primary and six secondary arteries ***(Snell, 2000).*** The primary arteries are: (1) the left gastric artery (branch of the celiac trunk), (2) the right gastric artery (branch of the hepatic artery), (3) right gastroepiploic artery (branch of the gastroduodenal artery), (4) the left gastroepiploic artery (branch of the splenic artery), (5) short gastric arteries (branches of the splenic artery) and (6) gastroduodenal artery. The six secondary arteries are (1) superior pancreaticoduodenal artery, (2) supraduodenal artery, (3) retroduodenal artery, (4) transverse pancreatic artery, (5) dorsal pancreatic artery and (6) left inferior phrenic artery ***(Eisenberg et al., 1995).***

2- Venous Drainage:

The stomach is drained by 5 named veins as well as many other venous tributaries: (1) the left gastric (coronary) vein, (2) the right gastric vein with its pyloric tributaries; both end in the portal vein, (3) right and (4) left gastroepiploic veins and (5) short gastric veins; which drain into the splenic vein ***(Snell, 2000).***

Anatomy of the Portal Venous System

The portal vein is formed by the union of superior mesenteric vein and the splenic vein just posterior to the head of pancreas **(Figure 2)** at about the level of the second lumbar vertebra ***(Hegab and Luketic, 2001).*** It extends slightly to the right of the midline for a distance of 5.5-8 cm before entering the liver at porta hepatis ***(Sherlock and Dooley, 2002)*** and then divides into right and left portal branches, which enter the corresponding lobes of the liver ***(Zwiebel, 2000a).***

The superior mesenteric vein is formed by tributaries from the small intestine, right colon and head of the pancreas and irregularly from the stomach via the right gastroepiploic vein. The splenic veins (5-15 channels) originate at splenic hilum and join near the tail of pancreas with the short gastric vessels to form the main splenic vein, which proceeds in a transverse direction. The left gastroepiploic vein joins the main splenic vein near the spleen. The inferior mesenteric vein, bringing blood from left part of the colon and rectum, usually enters its medial third. Occasionally, however, it enters the junction of superior mesenteric and splenic veins ***(Luketic and Sanyal, 2000).***

Additional contribution to the portal venous blood flow is provided by the left gastric (coronary) vein which drains the lesser gastric curvature and the gastroesophageal junction into the proximal part of portal vein ***(Krige and Beckingham, 2001).***

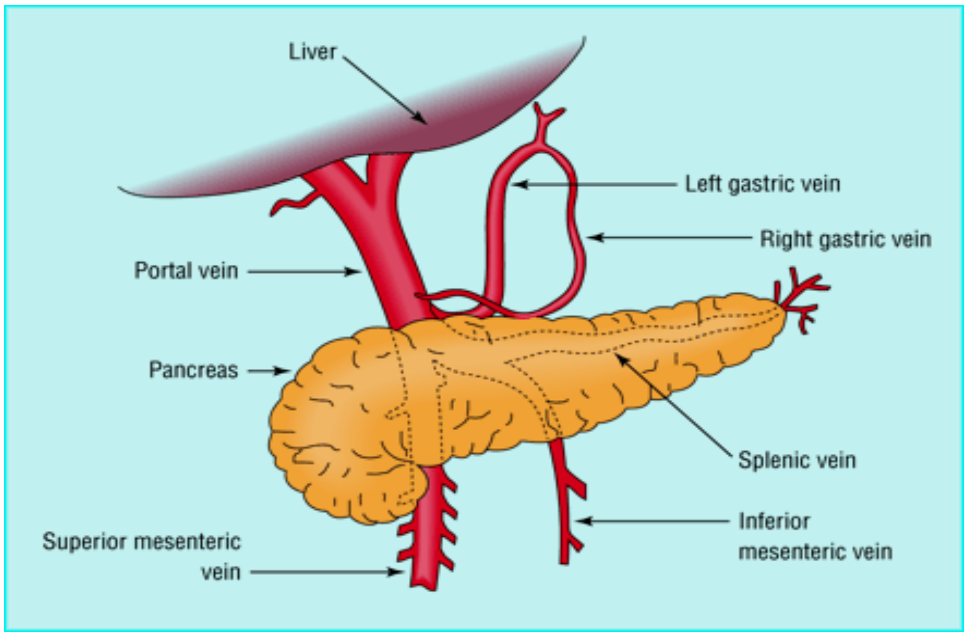

Figure (2): Anatomy of the portal venous system
(Krige and Beckingham, 2001).

The portal venous blood (low pressured, low oxygenated, nutrient-rich blood) mixes with blood coming from the hepatic arteries (high pressured, well-oxygenated blood), either in portal venules or in the sinusoids. The blood is collected from the sinusoids by the hepatic veins which drain into the inferior vena cava ***(Boyer and Henderson, 2000).***

Chapter Two

Portal Hypertension

Introduction:

Portal hypertension (PHT) is a common clinical syndrome defined as the elevation of hepatic venous pressure gradient (HVPG) above 5 mmHg. PHT is caused by combination of two simultaneous occurring hemodynamic processes: 1) increased intrahepatic resistance to passage of blood flow through the liver due to cirrhosis and 2) increased splanchic blood flow secondary duo to vasodilatation within the splanchic vascular bed. PHT can be due to different causes at pre-hepatic, intra-hepatic and post-hepatic sites. Cirrhosis of the liver accounts for approximately 90% of cases of PHT in western countries ***(Al-Busafi et al., 2012).***

Pathophysiology of Portal Hypertension and Esophageal Varices:

A) Intrahepatic circulation:

1. Decrease hepatic vasodilators:

a. Nitric oxide

Decreased vasodilators Nitric oxide (NO) is likely the most potent vasodilator. In cirrhotic livers, NO production/bioavailability is significantly diminished, which contributes to increased intrahepatic vascular resistance ***(Iwakiri and Groszmann, 2006).***

At least two mechanisms explain the decreased NO production. First, the NO synthesizing enzyme endothelial NO synthase (eNOS) is inhibited by negative regulators (such as caveolin-1), which are upregulated during cirrhosis; as a result, NO production decreases ***(Shah et al., 1999).*** Second, oxidative stress is increased in cirrhosis. Liver sinusoidal endothelial cells (LSECs) receive oxidative stress in response to a wide variety of agents, such as bacterial endotoxins, viruses, drugs, and ethanol ***(Lavina et al., 2009).*** During cirrhosis, increased superoxide radicals spontaneously react with NO to form peroxynitrite (ONOO), an endogenous toxicant ***(Radi et al., 2013),*** thereby decreasing NO's bioavailability as a vasodilator ***(Gracia-Sancho et al., 2008).***

b. Carbon Monoxide

Carbon monoxide (CO), a by-product of heme group oxidation by hemeoxygenases (HOs), is considered as an important modulator of intrahepatic vascular resistance ***(Pannen et al., 1998).*** CO activates guanylatecyclase and thereby promotes smooth muscle relaxation, in spite of being less potent than NO. The inhibition of CO production increases portal resistance in normal livers, and HO/CO system is activated in patients with liver cirrhosis Thus, CO may be closely related to the hyperdynamic circulatory state in cirrhosis ***(Tarquini et al., 2009).***