# INTRODUCTION

Liver cirrhosis (LC) is the final evaluative stage of any chronic liver disease and its outcomes are modulated by the degree and the consequences of portal hypertension (PHT).Unfortunately, clinical investigation of PHT is mainly invasive and implies either hepatic vein catheterization and hepatic vein pressure gradient (HVPG) measurement, or endoscopy for esophageal varices (EV) screening and grading. It was previously demonstrated that a HVPG value higher than 10 mmHg predicts the presence of EV, while a value higher than 12 mmHg is predictive for variceal bleeding. Many efforts have been made to find a noninvasive surrogate marker for PHT or for the presence or grade of EV, but until now, only a few biochemical markers (aspartate aminotransferase [AST] to platelets ratio index) or mixed indexes (platelets count to spleen diameter ratio) have been demonstrated to be partially correlated with the presence of EV ***(Stefanescu et al., 2011)***.

Portal hypertension is the central driver of complications in patients with chronic liver diseases and cirrhosis. The diagnosis of portal hypertension has important prognostic and clinical implications. In particular, screening for varices in patients with portal hypertension can effectively reduce the morbidity and mortality of variceal bleeding ***(Leung et al., 2017).***

Splenomegaly is a common finding in patients with cirrhosis and non-cirrhotic PHT, and is commonly described because of blood congestion, increased portal pressure, augmented resistance to splenic vein outflow, and increased angiogenesis and fibro genesis, These changes of spleen stiffness (SS) can be quantified by transient elastography (TE) ***(Sharma et al., 2013).***

Portal hypertension is one of the complications of chronic liver diseases (CLD). Esophageal varices (EV) are the most relevant Portosystemic collaterals resulting from clinically significant portal hypertension, and the presence of EV correlates with the severity of liver disease. As variceal hemorrhage is the most lethal complication of liver cirrhosis, patients with newly diagnosed cirrhosis in CLD are advised to undergo endoscopic screening for EV. However, endoscopy is an invasive and unpleasant procedure that sometimes requires sedation and carries rare, but serious, complications. Accordingly, several simple, non-invasive and accurate tests have been developed to identify EV. Transient elastography (TE) is a noninvasive tool that measures liver stiffness (LS) correlating to liver fibrosis stage. While TE also shows potential in the prediction of EV, its role is still under debate.

Moreover, the LS-spleen size-to-platelet ratio score (LSPS), which is a combination of three simple examination methods (LS, spleen size and platelet count) has been established to accurately predict EV in patients with

compensated cirrhosis. To date, TE and LSPS have not been performed for the estimation of EV in chronic hepatitis C. The objective of this study was to determine the ability of LSPS in predicting the presence of EV ***(Shibata et al., 2016).***

Several serum and radiological parameters have been put forward for predicting EV, such as serum fibrosis markers, liver stiffness (LS), spleen stiffness (SS), LS-spleen diameter to platelet ratio score. Among them, it has been shown that both liver and spleen stiffness were more accurate in identifying EV and the degree of portal hypertension than other non-invasive parameters. LS have been largely accepted to reflect the degree of fibrosis and the presence of EV in CLD. Several studies have revealed that LS measured by elastography may represent a useful non-invasive tool for predicting EV, notably in combination with other non-invasive parameters. Current European Guidelines (**Baveno Consensus VI 2017)** recommend to avoid screening EGD in patients with LS< 20kPa and platelet count >150, 000. While the role of LS alone in predicting varices is controversial due to unsatisfactory diagnostic accuracy and lack of consistent results, in the last few years, research emphasis has been placed on SS measurement in predicting EV and clinical significant portal hypertension. Portal hypertension leads to spleen congestion and fibrosis, which is sufficient to increase organ stiffness ***(Xiaowen et al., 2016).***

Fibroscan (Transient Elastography- TE) is a type of ultrasound machine that designed for painless, immediate and noninvasive liver and Spleen stiffness measurements ***(Paternostro et al., 2019).***

In the evolution of chronic viral and non-viral hepatitis, liver fibrosis is an important factor associated with prognosis. A precise evaluation of the severity of fibrosis is necessary in these patients for correct staging and, eventually, to take a decision regarding treatment ***(Christoph, 2012).***

Due to the limitations of liver biopsy, non-invasive alternatives including FibroScan (Transient Elastography) have been developed. Transient elastography is an easy and quick clinical non-invasive method to perform and it could be useful to evaluate liver fibrosis & steatosis as to monitor liver disease progression ***(Paternostro et al., 2019).***

Recently, more and more studies have attempted to clarify the utility of SS and LS for EV diagnosis in patients with CLD, but the results have been controversial. Research has shown that SS assessed by elastography was a more effective parameter with high diagnostic accuracy for identifying and grading EV than LS ***(Tseng et al., 2018).***

Splenomegaly is a possible consequence of portal hypertension. Contrary to other ultrasound (US) signs, splenomegaly is a highly sensitive parameter for the diagnosis

of portal hypertension. It is observed by US in 65%–80% of all patients with cirrhosis, and is more frequent in patients with cirrhosis due to viral hepatitis and primary biliary cirrhosis than in patients with alcoholic cirrhosis ***(Berzigotti and Piscaglia, 2012).***

However, splenomegaly is not a specific sign of portal hypertension in patients with cirrhosis, nor can it predict the existence of esophageal varices ***(Sort et al., 2014).*** At the same time, congestion caused by portal hypertension can increase organ viscoelasticity, meaning that increased liver and splenic stiffness is measured by ultrasonographic elastography ***(Dong et al., 2019).***

# AIM OF THE WORK

To assess the predictive value of spleen stiffness measured by fibro scan Compared to Liver stiffness as non-invasive predictors for esophageal varices in patients with chronic liver disease.

# Chapter 1

# PORTAL HYPERTENSION

## Anatomical Background:

### *The Liver Vasculature:*

The liver is a richly perfused organ receiving approximately 25% of the cardiac output. About 75% of hepatic blood flow (rich in nutrients but poorly oxygenated) is supplied by the portal vein. The remainder of the blood supply (oxygen rich) is provided by the hepatic artery. The intrahepatic vasculature is composed of portal venules, hepatic arterioles, lymphatics, hepatic sinusoids, and central venules ***(Mc Cuskey, 2000).***

The hepatic sinusoid, which is the principal site of blood flow regulation, is the narrowest vascular structure within the liver; the highest vascular resistance occurs in the sinusoids ***(Ramadori and Saile, 2004).***

The hepatic sinusoid is the vital site for transvascular exchange between blood and hepatocytes. The sinusoidal surface of the hepatocytes is separated from blood by fenestrated sinusoidal endothelial cells lining the sinusoid, Ku - ppfer cells (liver macrophages) protruding into the lumen of the sinusoid, Pit cells (liver specific natural killer cells) and hepatic stellate cells (HSC) ***(Guyot et al., 2006).***

### *Anatomy of the Portal Venous System:*

The portal vein begins at the junction of the splenic vein (SV) and the superior mesenteric vein (SMV), immediately posterior to the pancreatic neck at about the level of L2.From its origin, it courses superiorly and toward the right passing behind the first part of the duodenum and anterior to the inferior vena cava (IVC). After it enters the liver, the PV divides into right and left branches that re-divide into 4 smaller branches to terminate in the sinusoidal network of the liver ***(Osada et al., 2007).***

The ligamentum teres joins the left branch of the portal vein containing the umbilical vein within it. The left gastric vein (coronary vein) joins the portal vein near its origin (or the splenic vein in 16%). The inferior mesenteric vein draining the left colon and rectum joins the main splenic vein usually in its medial third. The main splenic vein is formed at the splenic hilum by the convergence of the splenic veins (5-15), joined by the short gastric veins ***(Osada et al., 2007).***

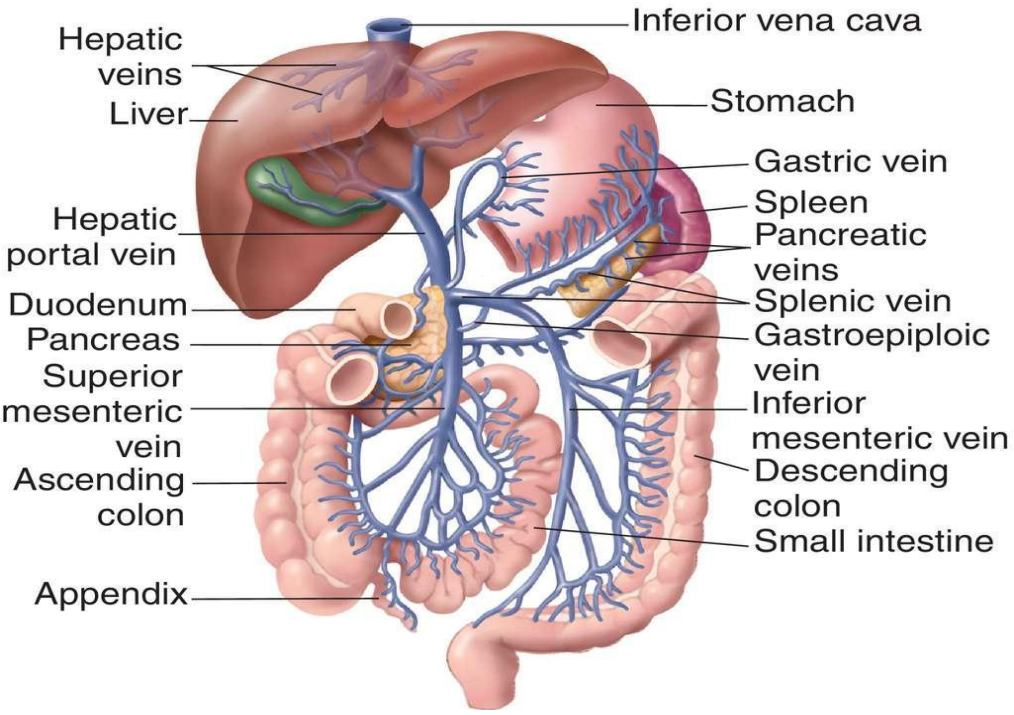


**Figure (1):** Portal circulation ***(Patton and Thibodeau, 2010).***

## ***Portosystemic Collaterals:***

It is necessary that the portal pressure gradient reaches a value of 12 mm Hg for the formation of collateral channels to the vena cava system. Closure of the collaterals can occur gradually when its resistance exceeds that of the Porto-hepatic bed as after porto-caval shunt surgery. Normally 100% of the portal blood flow can be recovered from the hepatic veins, whereas in cirrhosis only 13% is obtained. The remainder enters collateral channels ***(Garcia-Tsao, 2017).***

Portosystemic collaterals could be classified into four main groups ***(Sherlock and Dooley, 2002):***

- **Group I:** At the cardia of the stomach and the anus:

**At the cardia of the stomach:** where the left gastric vein, posterior gastric and short gastric veins of the portal system anastomose with the inter-costal, diaphragmo-oesophageal and azygos minor veins of the caval system. Deviation of blood into these channels leads to varicosities in the submucous layer of the lower end of the esophagus and the fundus of the stomach.

**Oesophageal varices**: the major blood supply of the esophageal varices is the left gastric vein. The posterior branch usually drains in the azygos system, whereas the anterior branch communicates with the varices just below the esophageal junction and forms a bundle of thin parallel veins that run in the junction area and continue in large tortuous veins in the lower esophagus. Typical large varices arise from the main trunks of the deep intrinsic veins and these communicate with gastric varices.

**Gastric varices**: these are largely supplied by the short gastric veins and drain into the deep veins of the esophagus. They are particularly prominent in patients with extra-hepatic portal obstruction.

- **Group II:** In the falciform ligament through the Para umbilical veins, relics of the umbilical circulation of the fetus.
- **Group III:** Where the abdominal organs are in contact with the retroperitoneal tissues or adherent to the abdominal

wall. These collaterals run from the liver to the diaphragm, in the spleno-renal ligament and omentum, lumbar veins and veins developing in scars of previous operations or in small or large bowel stomas.

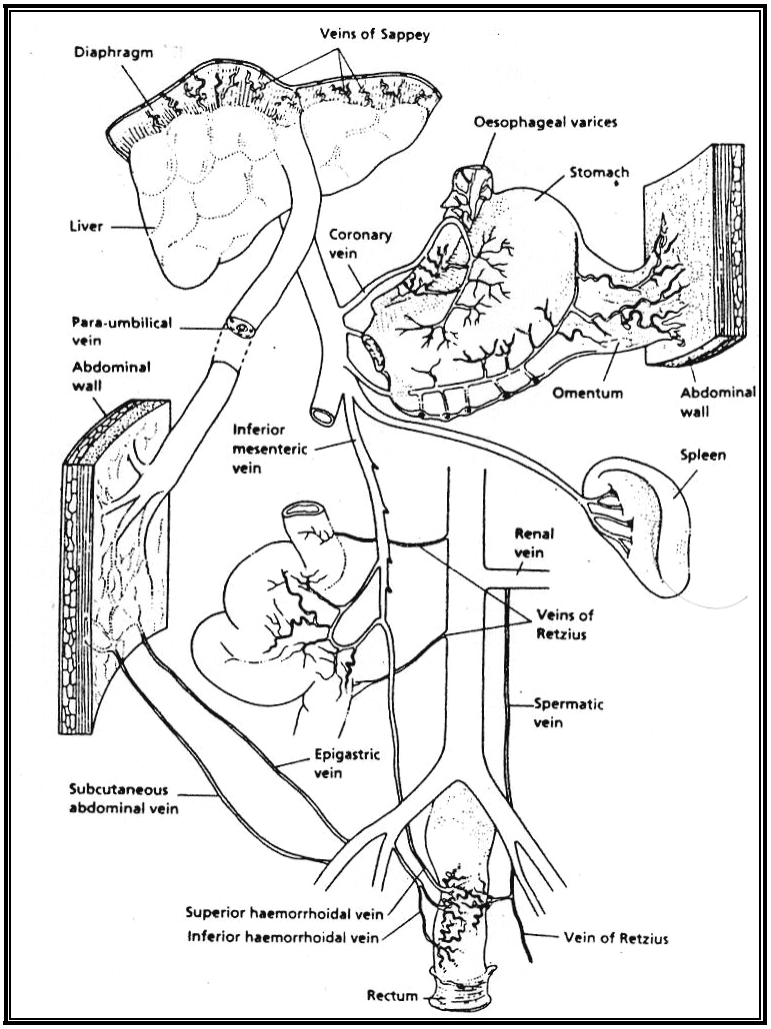


**Figure (2):** Distribution of Portosystemic collaterals ***(Sherlock & Dooley, 2002).***

### *Definition of portal hypertension*

PPG is defined clinically as an increase in the hepatic venous pressure gradient (HVPG).In normal conditions, HVPG ranges between 1 and 5 mmHg, but in portal hypertension, it is more than 5mmHg. However, complications of portal hypertension, e.g. development of esophageal varices, may start when HVPG increases over 10 mmHg, which is known as ‘‘clinically significant portal hypertension’’ (Baveno IV). Clinical decompensation, in form of bleeding, ascites and hepatic encephalopathy, may develop when HVPG increases over a threshold of 10–12 mmHg ***(Ripoll et al., 2007).***

### *Complications of portal hypertension*

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, hepatopulmonary syndrome, hepatic encephalopathy, portal hypertensive gastropathy (PHG), enteropathy and colopathy and disturbances in the metabolism of endo- and xenobiotic (foreign chemical substance) normally metabolized by the liver ***(Berzigotti et al., 2013).***

### *Epidemiology of portal hypertension*

Portal hypertension is almost an inevitable consequence of cirrhosis. About 80 to 90% of totally asymptomatic cirrhotic patients already have an elevated HVPG and endoscopy discloses that 40%of those patients already have esophageal varices. Incidence rate of varices is about 6% per year reaching 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 their size, presence of red color signs, degree of liver failure and HVPG elevation ***(Bosch et al., 2009).***

### *Pathophysiology of portal hypertension*

Portal hypertension is initiated by an increased resistance to portal blood flow and aggravated by an increased Porto-collateral blood flow; Such increased resistance to portal blood flow is most commonly due to CLD (cirrhosis of the liver), which is the most common cause of portal hypertension worldwide, followed by hepatic schistosomiasis ***(García-Pagán et al., 2012).***

Established evidence indicates that cirrhosis is characterized by a progressive intrahepatic vascular remodeling with capillarization of sinusoids, fibro genesis, neo-angiogenesis, and development of intrahepatic shunts, which would lead to increased hepatic resistance leading to increased portal pressure and decreased effective hepatocyte perfusion