# INTRODUCTION

Oesophageal varices are the most critical porto-systemic shunts that develop secondary to portal hypertension, which is considered a main complication of liver cirrhosis ***(D'Amico et al., 2014).***

The development of esophageal varices in cirrhotic patients can transform the disease from a pre-clinical to a clinical stage ***(Wang et al., 2014).*** Variceal bleeding occurs in 20–40% of cirrhotic patients with esophageal varices and is associated with a high morbidity and mortality ***(D'Amico et al., 2014).*** The mortality associated with each episode of variceal bleeding ranges from 17% to 57% ***(Wang et al., 2014).***

The use of endoscopic prophylactic band ligation and non-selective beta blockers can decrease the risk of esophageal bleeding by 50% ***(Puente et al., 2014).***

So, the current guidelines recommend screening of all liver cirrhosis patients by endoscopy to identify those at risk of bleeding so that they can be administered prophylactic therapy ***(de Franchis and Baveno, 2015).***

Endoscopically, the presence of large varices and/or red spots on the varices indicates a high risk of bleeding ***(de Franchis, 2010).*** The practice guideline from the American College of Gastroenterology (ACG) and the American Association for the Study of Liver Disease (AASLD) for

gastroesophageal varices suggests that all patients with hepatic cirrhosis should be screened for varices at least every other year ***(Garcia-Tsao et al., 2007).***

The prevalence of esophageal varices among cirrhotic patients is variable, ranging from 24% to 80%. Therefore, endoscopic screening of all patients with liver cirrhosis would result in a large number of unnecessary endoscopies and additional burden to endoscopic units ***(Jensen, 2002).*** Repeated endoscopic examinations are unpleasant for the patients and result in a high cost. In addition, patient compliance with the screening program may be reduced ***(Merli et al., 2003).***

For these reasons, several studies have examined how to identify patients with varices using non-invasive or minimally invasive methods to avoid endoscopy in patients with a low risk of varices. These studies include biochemical, clinical and ultrasound parameters, also, transient elastography, computerized tomography (CT) scanning and video capsule endoscopy ***(Giannini et al., 2006 and Robic et al., 2011).***

In this study, we aim to investigate non-invasive predictors of esophageal varices in patients with liver cirrhosis.

# AIM OF THE WORK

The aim of the study was to test the accuracy of using right liver lobe/serum albumin ratio as non-invasive predictor of esophageal varices in cirrhotic patients, for restricting performance of screening endoscopy.

# COMPLICATIONS OF HEPATITIS C VIRUS (HCV)

## Introduction:

Hepatitis C virus (HCV) is an infectious, hepatotropic virus belonging to the Flavivirus family ***(Lingala and Ghany, 2015).*** Hepatitis C appears to be endemic in most parts of the world. The global prevalence is about 3%; however, there is considerable geographical and temporal variation in the incidence and prevalence of infection and of genotypes ***(Armstrong et al., 2006).*** In Europe, the prevalence ranges from 0.5% to 2%, the prevalence may be as high as 5% to 15% in some parts of the world, and different regions have a different risk profile and age demographic ***(Nouroza et al., 2015).*** Egypt had the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy ***(Frank et al., 2000).*** Currently, due to efficacy of the new antiviral drugs, the prevalence of HCV in Egypt is going to decrease ***(Kandeel et al., 2017).***

HCV is transmitted most often through exposure to infected blood. Sexual or vertical transmission is rare. The most common route of transmission, before blood donor testing was instituted in 1992, was through blood transfusions. Currently, the most common route of transmission is intravenous drug use, a result of a new epidemic of illicit heroin and prescription

narcotic abuse has surfaced among the young ***(Suryaprasad et al., 2014).***

Following acute infection, up to 45% of young, healthy patients may develop a vigorous antibody and cell-mediated immune response, which leads to the spontaneous eradication of the virus and lifelong immunity ***(Gerlach et al., 2003).*** However, the majority of infected patients fail to clear the virus. This results in chronic infection and progressive liver damage. Persistent viraemia is accompanied by variable degrees of hepatic inflammation and fibrosis over time. Recent studies suggest that 50% or more of hepatocytes may be infected with hepatitis C virus ***(Pawlotsky, 2004).*** Persistent infection appears to be due to weak CD4+ and CD8+ T-cell responses during acute infection, which fail to control viral replication ***(Pawlotsky, 2004).***

Acute HCV infection is characterized by co-infection with multiple viral subtypes representing highly diverse inter-patient genetic variability ***(Smith et al., 2010).*** When chronic infection is established, HCV may not be cytopathic. Liver damage probably results from locally driven immune responses, which are mainly non-specific. Local inflammation triggers fibrogenesis, in which hepatic stellate cells play a major role. Cirrhosis is facilitated by factors such as chronic alcohol consumption, non-alcoholic steatohepatitis, and coincidental viral infections ***(Pawlotsky, 2004).***

Acute hepatitis C virus (HCV) infection refers to the first six months of HCV infection following presumed HCV exposure ***(Blackard et al., 2008).*** Following exposure to the virus, the majority of patients are asymptomatic ***(Villano et al 1999).*** About 30% of patients have features such as fatigue, arthralgia, or jaundice, associated with a transient rise in serum amino-transferases, particularly ALT whoever, Fulminant hepatic failure is rare. Some patients, particularly younger women, will then spontaneously clear the virus. However, the majority of people will develop chronic infection ***(Alter and Seeff, 2000).*** Black people appear to be least likely to spontaneously clear HCV ***(Pearlman, 2006).***

Chronic hepatitis C infection is generally defined as persistence of HCV RNA in the blood for at least 6 months ***(Younossi et al., 2015).*** Patients are usually asymptomatic but may present with features of chronic liver disease (e.g., jaundice, ascites, signs of hepatic encephalopthy) and sometimes decompensated cirrhosis or hepatocellular carcinoma. Occasionally, patients may present with signs of extrahepatic manifestations (e.g., vasculitis, renal injury, porphyria cutanea tarda) ***(Webster et al., 2015).***

Diagnosis may be made after routine laboratory tests reveal elevated serum aminotransferase activities but some patients may have normal levels ***(Webster et al., 2015).*** Factors that influence the development of chronic liver disease include older age at time of infection and male sex ***(Seeff, 1997).***

In a large, prospective study of patients with advanced hepatitis C-related liver disease, regular coffee consumption was associated with lower rates of disease progression ***(Freedman et al., 2009)***. Caffeinated coffee consumption greater than 2 cups daily is associated with reduced histological activity (inflammation) in chronic HCV ***(Costentin et al., 2011).*** Daily cannabis use is strongly associated with moderate-to-severe fibrosis and steatosis ***(Hézode et al., 2008 and Ishida et al., 2008).***

## Complications of HCV:

### 1. Hepatic complications:

**(1) Liver cirrhosis.**

**(2) Hepatoma:** Hepatoma is typically only seen in those hepatitis C virus (HCV)-infected patients with cirrhosis but can occur in patients without cirrhosis ***(Hu and Tong, 1999).*** The incidence in western nations has increased in the past 2 decades, mainly because of the large pool of people with hepatitis C ***(Colombo, 1999).***

### 2. Extra-hepatic complications: (will be discussed later)

**Liver cirrhosis:**

Cirrhosis is a diffuse pathological process, characterized by fibrosis and conversion of normal liver architecture to structurally abnormal nodules known as regenerative nodules ***(Ratib et al., 2015).*** Approximately 20%-30% of subjects chronically infected with HCV are estimated to develop Liver cirrhosis 15-25 years later ***(Alberti et al., 1999).***

A recent systematic review found that, in HCV-infected patients with compensated Liver Cirrhosis, 2.8%-11.7% develop hepatic decompensation, 1.8%-8.3% develop Hepatoma, and 2.7%-6.7% die or undergo liver transplantation each year ***(Alazawi et al., 2010).***

Scoring systems have been developed to help determine disease severity. The two most commonly used are the Child-Pugh-Turcotte (CPT) ***(Child et al., 1964 and Pugh et al., 1973)*** and, more recently, the Model of End-Stage Liver Disease (MELD) ***(Durand et al., 2005).*** Other scoring systems continue to be evaluated ***(Jepsen et al., 2014).***

- **CPT:** based on the presence of ascites and hepatic encephalopathy, serum bilirubin, albumin, and clotting (prothrombin time and INR) and is divided into Child A, B, and C with increasing disease severity. (table. A).

**Table (1):** CPT classification

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Grade 1-2 | Grade 3-4 |
| Bilirubin micromol/L (mg/dL) | <34.2 (<2) | 34.2-51.3 (2-3) | >51.3 (>3) |
| Albumin g/L (g/dL) | >35 (>3.5) | 28-35 (2.8-3.5) | <28 (<2.8) |
| Prothrombin time<br>Seconds over control<br>INR | <br><4<br><1.7 | <br>4-6<br>1.7-2.3 | <br>>6<br>>2.3 |
| CPT classification:<br>Child A: score 5-6 (well compensated);<br>Child B: score 7-9 (significant functional compromise);<br>Child C: score 10-15 (decompensated) | | | |

- **MELD:** electronically calculated from the serum bilirubin, sodium, creatinine, and clotting (INR and prothrombin time) by a specific computer programme ***(Kim et al., 2008), (Kamath et al., 2001).*** This is the classification system used for the allocation of livers for transplantation in the US.

## Complications of Cirrhosis:

### (1) Portal hypertension:

Portal hypertension (PHT) is defined as aportal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) greater than 5mmHg ***(Wongcharatrawee and Groszmann, 2000).*** Portal hypertension is considered clinically significant (CSPHT) when clinical manifestations of the disease appear or when portal pressure gradient exceeds a threshold value of 10mmHg. In case of cirrhosis, the portal pressure gradient is determined by its equivalent, the hepatic venous pressure gradient (HVPG) ***(Bosch et al., 2008)***. Gastro-intestinal manifestations of portal hypertension:

### 1. Portosystemic collaterals:

Portal hypertension leads to the formation of collaterals that decompress the portal circulation by returning blood to the heart via the systemic venous circulation. The major sites of collaterals are: ***(Vianna et al., 1987).***

(i) Rectum, where the systemic inferior mesenteric vein connects with the portal pudendal vein and results in rectal varices.

(ii) Umbilicus, where the vestigial umbilical vein communicates with the left portal vein and gives rise to prominent collaterals around the umbilicus (caput medusa).

(iii) Retroperitoneum, where collaterals, especially in women, communicate between ovarian vessels and iliac veins.

(iv) Distal esophagus and proximal stomach, where gastroesophageal varices form major collaterals between the portal venous system and the systemic venous system.

Traditionally, the formation of collaterals has been considered a mechanicalconsequence of the increased portal pressure that will result in the opening and dilatation of pre-existing vascular channels at sites of anatomical communications between the portal and systemic circulations ***(Bosch et al., 2008).*** However, studies challenged these concepts by demonstrating that angiogenesis, the formation of new blood vessels, plays a pivotal role in the development and maintenance of splanchnic hyperemia and portosystemic collateralization ***(Fernandez et al., 2004).***

Ten mmHg is the critical hepatic venous pressure gradient (HVPG) above which, varices form. Bleeding oesophageal varices occurs when the HVPG surpasses 12 mm Hg ***(Groszmann et al., 2005).*** Not all patients who have a HVPG greater than 12 mm Hg bleed. Other local factors that increase variceal wall tension are required. The varix ruptures when the tolerated wall tension is exceeded as the variceal wall thins, the varix dilates and the pressure inside it rises. Larger varices at sites of limited soft tissue support, namely the gastro-oesophageal junction, are at greater risk for variceal rupture and

bleeding in patients who have portal hypertension ***(Toubia and Sanyal, 2008).***

## 2. Portal hypertensive gastrointestinal vasculopathies:

**a. Portal hypertensive gastropathy (PHG)** is a very common finding in cirrhosis (prevalence between 11 and 80%). It is more often observed in the fundus and corpus of the stomach ***(de Franchis, 2010).***

PHG correlates with the severity of liver disease. It has three endoscopic patterns: (i) fine red speckling of gastric mucosa; (ii) superficial reddening, especially on the tips of the gastric rugae; and (iii) the presence of a mosaic pattern with red spots (snake-skin appearance) in the gastric fundus or body ***(Primignani et al., 2000).***

**b. Gastric vascular ectasia** is a collection of ectatic vessels that can be seen on endoscopy as red spots without a mosaic like pattern. When the aggregates are confined to the antrum of the stomach, the term gastric antral vascular ectasia (GAVE) is used ***(Jabbariet al., 1984).***

The prevalence of GAVE syndrome in cirrhosis is low and can be endoscopically difficult to differentiate from severe PHG. Gastric biopsy may be required to differentiate them as, histologically, GAVE lesions are completely distinct from PHG ***(Ward et al., 2004).***

**c. Portal hypertensive enteropathy (PHE)** describes small bowel mucosal changes related to PHT. It is believed to be a frequent finding in patients with cirrhosis, perhaps as common as PHG, and may cause occult GI blood loss ***(Misra et al., 1997).***

PHE has been under-diagnosed in the past due to the difficult access to the small bowel. With advanced techniques such as capsule endoscopy and enteroscopy allowed for better diagnosis of PHE. Essentially, four lesions found in the small intestine are attributed to PHT (Red spots, angioectasias, small bowel varices and inflammation-like lesions) ***(Abdelaal et al., 2010).***

**d. Portal hypertensive colopathy (PHC)** refers to mucosal edema, erythema, granularity, friability, and vascular lesions of the colon in PHT ***(Misra et al. 2005).*** Although they are found in up to 70% of patients with PHT and are more common in patients with OV and PHG, they rarely cause bleeding ***(Bresci et al., 2006).***

## (2) Oesophageal Varices:

Oesophageal varices are extremely dilated sub-mucosal veins in the lower third of the esophagus. They are most often a consequence of portal hypertension, commonly due to cirrhosis ***(Obara, 2006).***

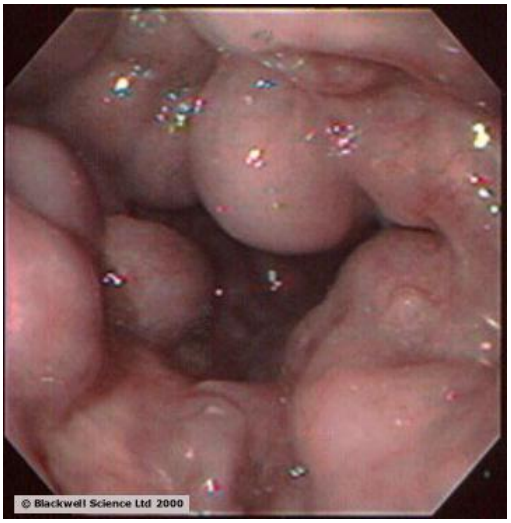


**Figure (1):** Oesophageal varices **(**Gastrohep.com**).**

Oesophageal varices are present in approximately 50% of patients with cirrhosis and their presence correlates with the severity of liver disease ***(Pagliaro et al., 1994).*** It has also been shown that 16% of patients with hepatitis C and bridging fibrosis have esophageal varices ***(Sanyal et al., 2006).***

Patients without varices develop them at a rate of 8% per year ***(Groszmann et al., 2005)*** and Patients with small varices develop large varices at a rate of 8% per year ***(Garcia-Tsao et al., 2007).***

They are dangerous complication of liver cirrhosis, once esophageal varices develop, it tends to bleed, and it is one of the most commonly reported causes of death in patients with cirrhosis, ranging from 17 to 57% ***(Wang et al., 2014).***

Variceal bleeding occurs in 20–40% of cirrhotic patients with esophageal varices and is associated with a high morbidity and mortality ***(D'Amico et al., 2014).*** Failure to control active bleeding is defined as death or need to change treatment defined by one of the following criteria: ***(Thabut et al., 2015 and Ahn et al., 2015).***

1. Fresh haematemesis or nasogastric aspiration of ≥100 mL of fresh blood ≥2 h after the start of a specific drug treatment or therapeutic endoscopy.

2. Development of hypovolaemic shock.

3. 30 g/L drop in haemoglobin (9% drop of haematocrit) within any 24 h period if no transfusion is given. This time frame needs to be further validated.

Endoscopic screening for the presence of esophagogastric varices should be done in all patients after the diagnosis of cirrhosis ***(Lebrec 2005 and de Franchis et al., 2015).***