A STUDY ON NON INVASIVE PREDICTORS OF LARGE ESOPHAGEAL VARICES USING CLINICAL, LABORATORY AND IMAGING PARAMETERS

DISSERTATION SUBMITTED FOR

DM

MEDICAL GASTROENTEROLOGY

(BRANCH IV)

AUGUST – 2009

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

A STUDY ON NON INVASIVE PREDICTORS OF LARGE ESOPHAGEAL VARICES USING CLINICAL, LABORATORY AND IMAGING PARAMETERS

CERTIFICATE

This is to certify that this dissertation entitled "A STUDY ON NON INVASIVE PREDICTORS OF LARGE ESOPHAGEAL VARICES USING CLINICAL, LABORATORY AND IMAGING PARAMETERS" submitted by Dr.S.Arulprakash, to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM., Degree Branch IV (Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

Prof.S.Jeevan Kumar,MD.,DM.,
Professor and HOD,
Department of Digestive Health and Diseases,
Government Peripheral Hospital, Anna Nagar,
Attached to Kilpauk Medical College,
Kilpauk, Chennai-600102

Dr.V.Kanagasabai, MD.,
Dean
Government Kilpauk Medical College,
Kilpauk,
Chennai-600010

ACKNOWLEDGEMENT

At the outset I wish to express my thanks to our Dean Dr.V. Kanagasabai M.D., Government Kilpauk Medical College, Kilpauk, Chennai 600010, for permitting to utilize the clinical materials from this hospital.

I wish to express my sincere thanks and gratitude to my Professor, Dr. S. Jeevan Kumar, MD., DM., Head of the Department, Department of digestive health and diseases & Civil surgeon Medical Officer, Government peripheral hospital, Anna Nagar, attached to Kilpauk Medical College, Chennai, for his meticulous guidance and constant encouragement throughout the study.

I express my extreme gratitude to my Additional Professors, Dr.T.Pugazhendhi, M.D., D.M., and Dr. Usha Srinivas M.D., D.M., for offering me timely advice and help.

I am extremely thankful to Dr. A.R.Venkateswaran, for his consistent support and guidance during his stay with us. I am extremely thankful to our Assistant Professors Dr. R. Balamurali, Dr. S. Chitra, Dr. P. Muthukumarn, and Dr. G. Ramkumar, for their help and eminent guidance throughout the study.

It’s a pleasure to acknowledge the help of staff nurses and endoscopy assistants for their commitments to the work.

I owe special thanks to my postgraduate colleagues Dr. Rathnakar Kini, Dr. Manimaran, Dr. Rajan Babu, Dr. Senthil kumaran, Dr. Shameem Ahmed, Dr. Sasi Anand, Dr. Chezhian, Dr. Subramanian and Dr. Babu Kumar, for their support and encouragement.

I thank all the referring institutions and doctors for their trust and timely referral of the needy patients to our department. I thank all the patients who have ungrudgingly lent themselves to undergo this study without which this study would not have seen the light of the day.

TABLE OF CONTENTS

S. No.	TITLE	PAGE No.
1)	INTRODUCTION	1
2)	LITERATURE REVIEW	4
3)	AIM OF THE STUDY	24
4)	METHODS	25
5)	RESULTS	30
6)	DISCUSSION	39
7)	CONCLUSION	52
8)	BIBLIOGRAPHY	i-vii

INTRODUCTION

Portal hypertension- a major hallmark of cirrhosis is defined as a portal pressure gradient exceeding 5-10 mm Hg. In portal hypertension, portosystemic collaterals decompress the portal circulation and give rise to varices. Development of esophageal varices and gastrointestinal bleeding represents a serious consequence in patients with portal hypertension. At the time of diagnosis of liver cirrhosis, esophageal varices are present in about 40% of patients with compensated disease and in 60% of those with decompensated disease and ascites. [1, 2]

In patients with liver cirrhosis who do not have detectable esophageal varices, the latter appear at a rate of nearly 5% per year. [3–5] Also, the size of varices tends to increase with time. It has been estimated that among those with small esophageal varices, nearly 12% progress to large varices annually.[3]

The annual incidence of first variceal bleeding has been estimated to be around 4% in non-selected patients with cirrhosis of the liver who have not bled previously. [6, 7] It has been shown that the risk of variceal bleeding is related to the size of esophageal varices, [8] with large esophageal varices being at a greater risk; this is possibly due to a higher variceal wall tension

in large esophageal varices. [9] Thus, annual incidence of gastrointestinal bleeding is only 1–2% in patients without varices, 5% in those with small esophageal varices and 15–20% in patients with large esophageal varices. [10]

Mortality rate of an episode of variceal bleeding is around 20–25% within the first week. [11] This figure may even be an underestimation because some patients die of massive variceal bleeding before reaching the hospital. Thus, prevention of such bleeding may be expected to improve the survival of these patients. Long-term administration of beta-adrenergic receptor antagonists has been shown to reduce the incidence of first variceal bleeding in patients with large esophageal varices.[6] However, because this treatment is not free of adverse effects, [11] it should be used only for patients with large esophageal varices. [12, 13] It is currently recommended that patients with liver cirrhosis undergo a screening endoscopy to look for the presence of esophageal varices [14, 15] and, if present, be treated with beta-adrenergic receptor antagonists. These recommendations imply a large workload on endoscopic units and a significant cost burden on patients with liver cirrhosis. As the prevalence of large esophageal varices is only 9–36% in patients with cirrhosis who have not bled, a large number of invasive endoscopic procedures turn out to be negative. Thus, there is a need for non-invasive means to diagnose or predict the presence or absence of large

esophageal varices. Availability of such methods may help limit the number of endoscopic procedures performed for detection of large esophageal varices.

Several studies have evaluated possible non-invasive markers of large esophageal varices in patients with cirrhosis and have found platelet count, splenomegaly, advanced Child status, serum albumin and high portal vein diameter at ultrasonography to be useful for this purpose. [1, 16–24] Such predictive factors may be expected to vary in different populations because of differences in the etiology of liver cirrhosis, severity of liver disease and nutritional status. Data on this aspect in Indian patients with liver cirrhosis, who usually present late, have a poorer nutritional status and have a fair proportion with viral etiology, are limited.

Therefore the study was conducted to evaluate the utility of various clinical, biochemical and ultrasonographic parameters for predicting the presence of large esophageal varices in patients with portal hypertension.

LITERATURE REVIEW

PORTAL HYPERTENSION

Definition: A persistent pressure elevation of >12 mmHg in the portal vein circulation, dilation of the portal vein to >13 mm or an increase in the portal pressure gradient of >7 mmHg (difference between the pressure of the portal vein and that of the inferior vena cava) is termed portal hypertension. The portal vein is 5- 8 cm long with a diameter of 1.2 $\pm$ 0.2 (or 0.97) cm.[29]

Portal hypertension syndrome is caused by increased resistance in the portohepatic circulation and an increase in the splanchnic vein blood flow. The increase in vascular resistance is the decisive factor and, in the majority of cases, is even the sole cause. It can be functional and reversible as well as structural and irreversible. Blood flow correlates directly with vessel diameter to the 4th power; i. e. small radial changes cause large changes to vessel resistance. An increase in the blood flow may favour the occurrence of portal hypertension or enhance its clinical development.

Portal hypertension is classified according to the localization of the flow resistance. Increases in pressure in the portal vascular system are rapidly transferred to the preceding vascular sections, since the portal vein does not possess any venous valves. Depending on whether the localization

lies before, within or beyond the liver, the portal hypertension is broken down into prehepatic, intrahepatic and posthepatic blocks. The intrahepatic form is further subdivided into a presinusoidal, sinusoidal and postsinusoidal rise in resistance.

NON-PARENCHYMATOUS PORTAL HYPERTENSION

1. PREHEPATIC PORTAL HYPERTENSION

2. INTRAHEPATIC PORTAL HYPERTENSION

    A. PRESINUSOIDAL BLOCK

PARENCHYMATOUS PORTAL HYPERTENSION

    B. SINUSOIDAL BLOCK

    C. POSTSINUSOIDAL BLOCK

3. POSTHEPATIC PORTAL HYPERTENSION

ESOPHAGEAL VARICES:

If esophagogastric varices did not form and bleed, portal hypertension would be of virtually no clinical significance. The major blood supply to oesophageal varices is the left gastric vein. The posterior branch usually drains into the azygos system, whereas the anterior branch communicates with varices just below the oesophageal junction and forms a bundle of thin parallel veins that run in the junction area and continue as large tortuous veins in the lower esophagus. There are four layers of veins in the

esophagus. Intraepithelial veins may correlate with the red spots seen on endoscopy and which predict variceal rupture. The superficial venous plexus drains into larger, deep intrinsic veins. Perforating veins connect the deeper veins with the fourth layer which is the adventitial plexus. Typical large varices arise from the main trunks of the deep intrinsic veins and these communicate with gastric varices. The connection between portal and systemic circulation at the gastro-oesophageal junction is extremely complex. Its adaptation to the cephalad and increased flow of portal hypertension is ill-understood. A palisade zone is seen between the gastric zone and the perforating zone. In the palisade zone, flow is bidirectional and this area acts as water shed between the portal and azygos systems. Turbulent flow in perforating veins between the varices and the periesophageal veins at the lower end of the esophagus may explain why rupture is frequent in this region. Recurrence of varices after endoscopic sclerotherapy may be related to the communications between various venous channels or perhaps to enlargement of veins in the superficial venous plexus. Failure of sclerotherapy may also be due to failure to thrombose the perforating veins.

Other manifestations of portal hypertension:

GASTRIC VARICES

These are largely supplied by the short gastric veins and drain into the deep intrinsic veins of the esophagus. They are particularly prominent in patients with extrahepatic portal obstruction.

PORTAL HYPERTENSIVE GASTROPATHY

This is almost always associated with cirrhosis and is seen in the fundus and body of the stomach. Histology shows vascular ectasia in the mucosa. The risk of bleeding is increased, for instance from non-steroidal anti-inflammatory drugs (NSAIDs). These gastric changes may be increased after sclerotherapy. They are relieved only by reducing the portal pressure. Gastric antral vascular ectasia is marked by increased arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. Gastric mucosal perfusion is increased. This must be distinguished from portal hypertensive gastropathy. It is not directly related to portal hypertension, but is influenced by liver dysfunction.

PORTAL HYPERTENSIVE INTESTINAL VASCULOPATHY

Chronic portal hypertension may not only be associated with discrete varices but with a spectrum of intestinal mucosal changes due to abnormalities in the microcirculation.

CONGESTIVE JEJUNOPATHY AND COLONOPATHY

Similar changes are seen in the duodenum and jejunum. Histology shows an increase in size and number of vessels in jejunal villi. The mucosa is edematous, erythematous and friable. Congestive colonopathy is shown by dilated mucosal capillaries with thickened basement membranes but with no evidence of mucosal inflammation.

CLINICAL FEATURES OF PORTAL HYPERTENSION

Cirrhosis is the commonest cause. Past abdominal inflammation, especially neonatal, is important in extra-hepatic portal block. Clotting disease and drugs, such as sex hormones, predispose to portal and hepatic venous thrombosis.

Haematemesis is the commonest presentation. The number and severity of previous haemorrhages, associated confusion or coma and blood transfusion should be noted. Melena, without haematemesis, may result from bleeding varices. The stigmata of cirrhosis include jaundice, vascular spiders and palmar erythema. Anaemia, ascites and precoma should be noted.

<u>Abdominal wall veins:</u>

In intra-hepatic portal hypertension, some blood from the left branch of the portal vein may be deviated via para-umbilical veins to the umbilicus,

where it reaches veins of the caval system. In extra-hepatic portal obstruction, dilated veins may appear in the left flank.

Distribution and direction:

Prominent collateral veins radiating from the umbilicus are termed Caput Medusae. This is rare and usually only one or two veins, frequently epigastric, are seen. The blood flow is away from the umbilicus, whereas in inferior vena caval obstruction the collateral venous channels carry blood upwards to reach the superior vena caval system. Tense ascites may lead to functional obstruction of the inferior vena cava and cause difficulty in interpretation.

Murmurs:

A venous hum may be heard, usually in the region of the xiphoid process or umbilicus. A thrill, detectable by light pressure, may be felt at the site of maximum intensity and is due to blood rushing through a large umbilical or para-umbilical channel to veins in the abdominal wall. A venous hum may also be heard over other large collaterals such as the inferior mesenteric vein. An arterial systolic murmur usually indicates primary liver cancer or alcoholic hepatitis. The association of dilated abdominal wall veins and a loud venous murmur at the umbilicus is termed the Cruveilhier–Baumgarten syndrome. This may be due to congenital

patency of the umbilical vein, but more usually to well-compensated cirrhosis. The para-xiphoid umbilical hum and Caput Medusae indicate portal obstruction beyond the origin of the umbilical veins from the left branch of the portal vein. They therefore indicate intra-hepatic portal hypertension (cirrhosis).

Spleen:

The spleen enlarges progressively. The edge is firm. It is larger in young people and in macronodular rather than micronodular cirrhosis. An enlarged spleen is the single most important diagnostic sign of portal hypertension. If the spleen cannot be felt or is not enlarged on imaging, the diagnosis of portal hypertension is questionable. The peripheral blood shows a pancytopenia associated with an enlarged spleen (secondary 'hypersplenism'). This is related more to reticulo-endothelial hyperplasia than to the portal hypertension and is unaffected by lowering the pressure by a porta-caval shunt.

Liver:

A small liver may be as significant as hepatomegaly, and size should be evaluated by careful percussion. It correlates poorly with the height of portal pressure. Liver consistency, tenderness or nodularity should be

recorded. A soft liver suggests extra-hepatic portal venous obstruction. A firm liver supports cirrhosis.

Ascites:

The portal hypertension raises the capillary filtration pressure, and determines fluid localization to the peritoneal cavity. Ascites in cirrhosis always indicates liver cell failure in addition to portal hypertension.

Rectum:

Anorectal varices are found in 44% of cirrhotic patients, increasing in those who have bled from oesophageal varices. They must be distinguished from simple hemorrhoids which are prolapsed vascular cushions and which do not communicate with the portal system.

DIAGNOSIS OF PORTAL HYPERTENSION

Investigation frequently needs to explore

(1) presence of portal hypertension

(2) etiology

(3) severity

(4) complications

Laboratory parameters:

1. Thrombocytopenia (< 100,000/ mm3) can be taken as evidence of a splenomegaly due to portal hypertension;

2. Decreased hemoglobin values can be seen as a sign of a continuous loss of blood.
3. Testing for occult blood in faeces.
4. Elevated ammonia values hint at an existing shunt circulation.
5. Cholinesterase provides information on the functioning of the liver, facilitating a prognosis.

Tomography of the azygos vein may show enlargement as the collateral flow enters the azygos system. A widened left para-vertebral shadow may be due to lateral displacement of the pleural reflection between the aorta and vertebral column by a dilated hemi azygos vein. Massively dilated para-oesophageal collaterals may be seen on the chest radiograph as a retro-cardiac posterior mediastinal mass.

Barium studies:

Oesophageal varices are seen as filling defects in the regular contour of the esophagus. They are most often in the lower third, but may spread upwards so that the entire esophagus is involved. Widening and finally gross dilatation are helpful signs. Gastric varices pass through the cardia, line the fundus in a worm-like fashion and may be difficult to distinguish from mucosal folds. Occasionally gastric varices are seen as a lobulated mass in the gastric fundus simulating a carcinoma.

Endoscopy

Esophagogastroscopy is considered to be the gold standard diagnostic procedure of choice for the detection of oesophageal or gastric varices. This examination should always be extended to the antrum and the duodenum, since varices can also occur there. Endoscopy allows the detection of oesophageal varices at an early stage of development. It also enables an assessment to be made of the size and preferred localization of the varices as well as imaging the surface of these veins.

The larger the varix the more likely it is to bleed. Colour is extremely important. Varices usually appear white and opaque. Red colour correlates with blood flow through dilated sub-epithelial and communicating veins. Dilated sub-epithelial veins may appear as raised cherry-red spots and red wheal markings (longitudinal dilated veins resembling whip marks). They lie on top of large sub-epithelial vessels. The haemocystic spot is approximately 4 mm in diameter. It represents blood coming from the deeper extrinsic veins of the esophagus straight out towards the lumen through a communicating vein into the more superficial sub-mucosal veins. Red color is usually associated with larger varices. All these colour changes, and particularly the red colour sign, predict variceal bleeding. Intra-observer error may depend on the skill and experience of the endoscopist. On the

whole, agreement is good for size and red signs. Portal hypertensive gastropathy is seen largely in the fundus, but can extend throughout the stomach. It is shown as a mosaic-like pattern with small polygonal areas, surrounded by a whitish-yellow depressed border. Red point lesions and cherry-red spots predict a high risk of bleeding. Black–brown spots are due to intra-mucosal haemorrhage.

Ultrasonography: Ultrasonogram of abdomen provides clue to portal hypertension

Splenomegaly (> 4 ×7 × 11 cm)

- Dilation of the portal vein (> 13 mm)
- Dilation of the splenic vein (> 10 mm)
- Dilation of the ventricular coronary vein (> 6 mm)
- Restricted respiratory modulation of the vascular width of up to 3 mm (increase on inspiration and decrease on expiration) regarding the portal vein and more particularly the splenic vein and the superior mesenteric vein. Decrease in width of the lumen by more than 50% on exhalation - absence of portal hypertension
- Jump in caliber of the portal vein
- Reversal of flow in portal vessels
- Stasis of the gall bladder and gastric walls

- Visible evidence of collaterals
- Recanalization of the umbilical vein
- Cavernous transformation of the portal vein

Endoscopic ultrasound is ideally suited for displaying intramural and perimural oesophageal varices. Endoscopic colour Doppler sonography is another promising procedure, particularly for demonstrating a (still) evident variceal perfusion.

Doppler effect is produced by changes in wavelength due to the reflection of sound on moving particles (e. g. erythrocytes). Consequently, the direction of flow (away from or towards the sound source) as well as the flow rate in arterial and venous vessels can be determined. The flow volume is then calculated by additional sonographic measurement of the vessel diameter. It has been shown that the rate of flow is clearly dependent upon the respiratory activity, so that an increase in blood flow velocity can be determined with maximum expiration as well as postprandially (normal value: 18-30 cm/sec).

In case of a distinct reduction in the flow rate, the flow direction may be reversed (hepatopetal to hepatofugal). Blood flow in the portal venous system is normally hepatopetal as opposed to pulsatile (or only slightly pulsatile) and follows an increased expiration flow rate. Undulating blood

flow when inhaling (hepatopetal) and exhaling (hepatofugal) is evidence of portal hypertension.

Congestion index (CI):

This parameter is the most reliable indicator of portal hypertension. It relates the portal cross-sectional area to the portal blood flow rate. The CI ranks higher than the direct pressure level in the diagnostics of the portal system and the HVPG. These three techniques (in this order) are considered to be the gold standard in early diagnosis of portal hypertension. CI levels of >0.1 are associated with excessive portal pressure with >95% sensitivity and specificity. Sonographic imaging of cavernous transformation in the portal vein usually shows beaded varicose collaterals in the hepatoduodenal ligament.

Arteriography: This technique is costly, time-consuming and high-risk. The injection of contrast medium into the spleen is carried out either percutaneously (sonography-guided) or, preferably, by laparoscopy, this method ensures access to the collaterals if radiological obliteration is planned.

A. Indirect splenoportography via the femoral artery is not only very important, but also low-risk.

B. Hepatic vein phlebography

C. Other procedures that can be applied are indirect mesentericoportography, transjugular or transhepatic splenoportography, umbilical portography and scintigraphic splenoportography.

MEASUREMENT OF PORTAL PRESSURE

Direct measurement:

Direct measurements of portal pressure are invasive investigations based on the surgical, percutaneous transhepatic, or transvenous (transjugular) catheterization of the portal vein. Because of this inconvenience and the associated surgical or hemorrhagic risk, direct measurements of portal pressure are rarely used.

Indirect measurement:

The indirect and safe approach of hepatic vein catheterization, with measurements the WHVP and FHVP, is the preferred technique to estimate portal pressure. The normal HVPG value is between 1-5 mm of Hg. Pressure higher than this implies portal hypertension regardless of clinical evidence. HVPG of more than 10 is predictive of the development of complications. HVPG of more than 12 mm of Hg is threshold pressure for variceal rupture. The main advantages of HVPG are its simplicity, reproducibility and safety.

PATHOPHYSIOLOGY OF VARICEAL HEMORRHAGE

Two theories have been proposed to explain variceal bleeding. The erosion theory suggested that varices bleed when external trauma to their thin and fragile walls is caused by the deglutition of solid food or by gastroesophageal reflux. This theory has been abandoned because of a lack of objective evidence. No relationship between eating and bleeding has been proved, nor is the incidence of reflux and esophagitis greater in patients with bleeding varices than in those without bleeding**.**

On the contrary, the so-called explosion hypothesis suggests that the main cause of bleeding is excessive hydrostatic pressure inside the varices, which is a consequence of increased portal pressure. In support of this hypothesis, many studies have shown that variceal bleeding does not occur before the HVPG reaches a threshold value of 12 mm Hg. In addition, since the introduction of endoscopic techniques to measure variceal pressure, new observations have been made to support the role of increased intravariceal pressure in variceal rupture. Therefore, variceal pressure is higher in patients with previous bleeding than in nonbleeders, and longitudinal studies have shown that variceal pressure is a good prognostic indicator of the risk for bleeding and of the response to pharmacologic therapy. Variceal pressure, size, and wall thickness can be integrated in the concept of wall tension, the

inwardly directed force exerted by the variceal wall to oppose an outwardly directed force that causes further distention. Variceal bleeding occurs when the tension exerted by the thin wall of a varix is beyond a critical value, as determined by the elastic limit of the vessel. At this point, the variceal wall cannot resist further dilatation, and variceal rupture occurs.

According to Frank's modification of Laplace's law, variceal wall tension (WT) can be defined as: $WT = (Pi - Pe) \times r/w$ in which Pi is the intravariceal pressure, Pe the pressure in the esophageal lumen, r the radius of the varix, and w the thickness of its wall.

The natural history of portal hypertension can be described as a function of variceal wall tension. Once wall tension increases to values exceeding the elastic limit of a varix, the patient experiences a first episode of bleeding. After this, the patient remains at a high risk for rebleeding unless wall tension is decreased. Similarly, primary prophylaxis protects the patient from bleeding by preventing or delaying variceal wall tension from reaching the rupture point, which is achieved by decreasing portal pressure and portal–collateral blood flow. An increase in intravascular pressure, together with a high rate of collateral blood flow, causes varices to dilate, and as they dilate, their walls become thinner. At this point, any further

increase in variceal pressure or size or any defect in the variceal wall causes rupture and clinical hemorrhage.

Alcohol intake, post prandial state, physical exercise, and conditions that increase intra-abdominal pressure can increase portal pressure abruptly. In all these circumstances, repeated abrupt increases in portal pressure cause a progressive dilatation of varices and, therefore, increase the risk for variceal bleeding. Circadian variations have been observed in portal pressure—pressure increases during the night and decreases during the afternoon and evening. These physiologic variations in portal pressure may affect the onset of bleeding in patients at risk (those with a high variceal tension in resting conditions); a circadian pattern has been observed in variceal hemorrhage, which is more frequent at midnight, when portal pressure generally is increasing. In patients with cirrhosis, portal pressure is also increased by circumstances that worsen liver failure, such as alcoholic hepatitis, severe infections, and acute or chronic liver failure.

NATURAL HISTORY OF VARICES

Gastroesophageal varices are the most relevant portosystemic collaterals because their rupture results in variceal hemorrhage, the most common lethal complication of cirrhosis. Varices and variceal hemorrhage are the complications of cirrhosis that result most directly from portal

hypertension. Patients with cirrhosis and gastroesophageal varices have an HVPG of at least 10-12 mm Hg. Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease, while only 40% of Child A patients have varices, they are present in 85% of Child C patients. Patients with primary biliary cirrhosis may develop varices and variceal hemorrhage early in the course of the disease even in the absence of established cirrhosis. It has also been shown that 16% of patients with hepatitis C and bridging fibrosis have esophageal varices. Patients without varices develop them at a rate of 5% per year, and the strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an HVPG >10 mmHg. Patients with small varices develop large varices at a rate of 10-15% per year. Decompensated cirrhosis (Child B/C), alcoholic cirrhosis, and presence of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the time of baseline endoscopy are the main factors associated with the progression from small to large varices.

Variceal hemorrhage occurs at a yearly rate of 5%- 15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices.

Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the endoscopic presence of red wale marks. Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients, and despite improvements in therapy over the last decade, it is associated with a mortality of at least 20% at 6 weeks.

Patients with an HVPG >20 mmHg (measured within 24 hours of variceal hemorrhage) have been identified as being at a higher risk for early rebleeding (recurrent bleeding within the first week of admission) or failure to control bleeding (83% vs. 29%) and a higher 1-year mortality (64% vs. 20%) compared to those with lower pressure. Late rebleeding occurs in approximately 60% of untreated patients, mostly within 1-2 years of the index hemorrhage.

Variceal wall tension is probably the main factor that determines variceal rupture. Vessel diameter is one of the determinants of variceal tension. At an equal pressure, a large diameter vessel will rupture while a small diameter vessel will not rupture. Besides vessel diameter, one of the determinants of variceal wall tension is the pressure within the varix, which is directly related to the HVPG. Therefore, a reduction in HVPG should lead to a decrease in variceal wall tension, thereby decreasing the risk of rupture. Indeed, variceal hemorrhage does not occur when the HVPG is reduced to

<12 mmHg. It has also been shown that the risk of rebleeding decreases significantly with reductions in HVPG greater than 20% from baseline. Patients whose HVPG decreases to <12 mmHg or at least 20% from baseline levels ("HVPG responders") not only have a lower probability of developing recurrent variceal hemorrhage, but also have a lower risk of developing ascites, spontaneous bacterial peritonitis and death.

AIMS AND OBJECTIVES

1. To study the incidence of large and small esophageal varices in patients with liver disease.
2. To evaluate various clinical, biochemical and ultrasonographic parameters in predicting the presence of large esophageal varices.
3. To evaluate the sensitivity and specificity of each of the parameters in predicting large esophageal varices.
4. Validating the platelet count / spleen diameter ratio of 909 in predicting large esophageal varices.

METHODS

Patients:

Consecutive newly diagnosed patients with liver disease (cirrhosis / portal hypertension) with or without history of gastrointestinal bleeding between August 2006 and December 2008 at our institution (Department of digestive health and diseases, Government peripheral hospital, Anna nagar, Chennai) which serves as a tertiary referral center were included in this prospective study. Patients were asked to sign an informed consent prior to enrollment in the study.

Inclusion criteria:

- Age: 18 years to 80 years
- Liver disease with portal hypertension

Exclusion criteria:

- Hepatocellular carcinoma detected by ultrasonography and/or elevated alpha-feto protein
- Primary hematologic disorders
- Active gastrointestinal bleeding on admission
- Taking drugs for primary prophylaxis of variceal bleeding
- History of parenteral drug addiction
- History of EST or band ligation, TIPS

- Advanced co-morbidity for endoscopy
- Previous surgical intervention for portal hypertension

Clinical evaluation:

All patients underwent a detailed clinical evaluation at entry. Relevant history, etiology of liver disease (alcohol intake, blood transfusion etc), and physical characteristics including age, gender, symptoms and signs of liver failure (spider angioma, palmar erythema etc.), hepatomegaly, splenomegaly, and abdominal vein collaterals were recorded.

Ascites was graded as none, mild (detectable only on ultrasound), moderate (visible moderate symmetrical abdominal distension) or severe (marked abdominal distension).[25] Hepatic encephalopathy was graded from grade 0 to IV, as per the Conn's grading. [26]

Definition of Terms

1. Compensated cirrhosis — patients without ascites and/or hepatic encephalopathy

2. Splenomegaly — diameter of >100mm by ultrasound

3. Normal platelet count: 150-450 x 10^3/ul

Blood tests:

Hematological and biochemical workup included measurement of hemoglobin, total leukocyte count, platelet count, prothrombin time, and

serum concentrations of bilirubin (total and conjugated), protein, albumin, alanine aminotransferase and aspartate aminotransferase. For each patient, a modified Child-Pugh score was calculated. [27] All patients were tested for HBsAg and antibodies to hepatitis C virus using enzyme immunoassays to determine the cause of liver cirrhosis. Tests for other causes of cirrhosis (serum ceruloplasmin and slit lamp examination for Wilson's disease, tests for autoantibodies for autoimmune liver disease, iron studies for hemochromatosis) were carried out only if there was a suggestive clinical clue. In patients with ascites, ascitic fluid was tapped under aseptic precautions and ascitic fluid albumin and serum-ascites albumin gradients were measured. Patients with SBP were treated accordingly.

Ultrasound Doppler:

All patients underwent ultrasonography after over night fast and the following details were recorded: maximum vertical span of the liver; nodularity of liver surface; spleen size (length of its longest axis); diameter of the portal and splenic veins; presence of portal-systemic collaterals; and presence of ascites.

Endoscopic evaluation:

All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices using video gastroscope

(Pentax) with in 2-3 days of admission. If esophageal varices were present, their size was graded as I-IV, using the Paquet grading system. [28] Furthermore, patients were classified dichotomously either as having large esophageal varices (grade III-IV) or as not having these (no varices or grade I-II). Presence of gastric varices, portal hypertensive gastropathy, duodenopathy and rectal varices were recorded wherever appropriate. Gastric varices were classified according to Sarin classification as isolated gastric or gastroesophageal varices, i.e., gastric varices associated with esophageal varices. The entire clinical, laboratory, ultrasonographic and endoscopic assessments were completed in 4 weeks. Diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings.

STATISTICAL METHODS

Univariate analysis for determining the association of various clinical, laborataroy and ultrasonographic variables with presence of large varices was performed using Student t test for continuous variables and the chi square tests for categorical variables. Differences were considered statistically significant if the two tailed p value was less than 0.05.

All variables that were found to be significant were studied using logistic regression analysis to identify independent predictors for the presence of such varices.

Receiver operating characteristic curves (ROC) analysis was performed on the available data set for the parameter that had the best predictive value of the presence of large esophageal varices. All calculations were made using SPSS software (version 11 for windows; SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics:

One hundred and six patients were included in this study. Age group - median age: 45 years; range 18- 74. 72 were male patients with a male-female ratio of 2.11: 1.

Patient's symptom duration was 10- 240 days with a median of 90 days. Clinically detectable ascites was present in 50 patients and 43 had pedal edema. 53 patients had previous history of GI bleed in the form of hematemesis or malena. 53 patients had jaundice at presentation.

Etiology of liver disease in the study was alcohol (52), followed by HBV (21), Autoimmune hepatitis (5), HCV (2). Severity of liver disease calculated by CTP is as follows, Child A: 27, Child B: 34, Child C: 45.

Baseline demographic and clinical characteristics, including etiology of liver cirrhosis and severity of disease were shown in Table: 1

TABLE: 1 CLINICAL CHARACTERISTICS OF STUDY PATIENTS

S.no	Patient characteristics	No. of Pts	%
1	**Sex**		
	Male	72	67
	Female	34	32

S.no.	Patient characteristics	No. of Pts	%
2	**Etiology**		
	Alcohol	52	49
	Hepatitis B virus	21	19.8
	Hepatitis C virus	2	1.8
	Autoimmune hepatitis	5	4.7
	Cryptogenic	6	5.6
	Others	20	18.8
3	**Child -Pugh class**		
	A	27	25.4
	B	34	32
	C	45	42.4
4	**Clinical findings**		
	Pallor	49	46.2
	Jaundice	53	50
	Pedal edema	43	40.5
	Bleed	53	50
	Ascites		
	None	56	52.8
	Mild	20	18.8
	Moderate	18	16.9
	Severe	12	11.3
	Encephalopathy	10	9.4
	Splenomegaly	42	39.6

TABLE: 2 PORTAL HYPERTENSION RELATED ENDOSCIOPIC FINDINGS

S.No.	ENDOSCIOPIC FINDINGS	n	%
1	NO VARICES	29	27.3%
2	SMALL VARICES	26	24.4%
3	LARGE VARICES	51	48.1%
4	ESOPHAGOGASTRIC VARICES	8	0.07%
5	PORTAL HYPERTENSIVE GASTROPATHY	40	37.7%

Endoscopic findings are shown in table 2. Seventy seven patients had esophageal varices (large varices in 51), 8 had esophagogastric varices. Forty patients had portal hypertensive gastropathy along with esophageal varices. None had isolated gastric varices. Further more of those patients with esophageal varices large varices was found in 30% of CTP class A, 41% of CTP class B and 64% of CTP class C.(table 3)

TABLE: 3 **PRESENCES OF VARICES ACCORDING TO CTP CLASS**

S.No.	CTPCLASS	VARICES	LARGE VARICES	%
1	A=27	17	8	29.6%
2	B=34	27	14	41.1%
3	C=45	33	29	64.4%

TABLE: 4 Relationship of various parameters with presence or absence of large esophageal varices on Univariate analysis

S.no	Variable	Size of the esophageal varices		P- value
		None /small	Large	
1	Sex	35:16	37:18	0.77
2	Median Age	43.3	42.5	0.72
3	Symptom duration	4870 (7-240)	4760 (7-240)	-
4	Pallor	25	24	-
5	Jaundice	24	29	-
6	Pedal edema	21	22	-
7	Bleed	24	29	-
8	Palpable spleen	3	19	-
9	Ascites	14	36	-
10	Etiology			
	Alcohol	28	24	-
	HBV	14	7	-
	HCV	1	1	-
	AIH	3	2	-
	Others	11	15	-
11	Hb	8.8(4.6-12.8)	9.1 (4 -13)	0.43
12	WBC count	8547 (6500-11200)	8198 (4500-9800)	0.18
13	**Platelet count**	**202781(70000-463000)**	**157725(58000-472000)**	**0.02**
14	**Bilirubin**	**2.2 (0.8-7.1)**	**3.1 (0.7-16.1)**	**0.04**
15	SGOT	93.6(25-427)	62.6(21-421)	0.08
16	SGPT	67.8(23-285)	54(12-500)	0.30
17	SAP	184.7 (59-403)	151.4 (56-356)	0.027
18	Prothrombin time			0.838
19	S.Albumin	2.7 (2-3.6)	2.7 (2.4-3.8)	0.478
20	Ascitic Albumin	1.5 (0.6-2.5)	1.6 (1.2-2.9)	0.24
21	SAAG	1.18 (0.6-1.5)	1.1 (0.8-1.6)	0.66
22	**CTP Score**	**9 (5-13)**	**9 (5-13)**	**0.003**
23	Liver Size	11.7 (7-16)	12.1 (7-14)	0.362
24	**Spleen Size**	**11.17 (8.5-18)**	**14.9 (9.2-26)**	**0.0001**
25	**Portal Vein Size**	**11.3 (8-16)**	**13.9 (10-17)**	**0.001**
26	**Splenic Vein Size**	**7.8 (7-11)**	**9.2 (7-11)**	**0.001**
27	Collaterals	8	26	
28	Varices Columns	3(1-4)	3.2(1-4)	0.52
29	Length	8.4 (6-12)	8.1 (6-12)	0.51
30	Gastric Varices	1	7	-

On Univariate analysis Bilirubin, platelet count, CTP score, spleen size, portal vein size and splenic vein size were significantly associated with presence of large varices. Table 4

TABLE: 5 Results of multivariate logistic regression analysis for predictors of presence of large esophageal varices

S.no.	Predictor	P-value
1	Bilirubin	0.08
2	Palpable spleen	**0.0001**
3	Platelet count	**0.001**
4	Spleen size	**0.003**
5	Portal vein size	**0.001**
6	Splenic vein size	**0.001**

Table 5 shows the results of a logistic regression analysis of 106 patients using the predictors found to significant on univariate analysis. On this analysis palpable spleen, platelet count, spleen diameter on USG, portal vein and splenic vein size were found to be statistically significant.

Using the maximum χ 2 value the optimum cut off in this cohort for discriminating patients with large varices from those with small or no varices was determined.

A platelet count cut-off of 1,50,000/mm^3 was chosen with a sensitivity: 72.5% (58-83.7) and specificity of 75% (60.1-83.5).

Positive predictive value: 63.8% (50.5-75.7)

Negative predictive value: 70.5% (55.8-82.7)

Similarly splenomegaly was found to be statistically significant. Spleen size of more than 13 cm cut-off yielded the following

Sensitivity: 88.5% (75.8-95.4)

Specificity: 83% (70.7-91.8)

Positive predictive value: 83.3% (70.2-91.6)

Negative predictive value: 70.5% (75.9-95.2)

Table: 6 Sensitivity and specificity of various parameters in predicting varices

PARAMETERS	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Platelet count <150,000/mm^3	72.5	75	63.8	70.5
Spleen diameter >13 mm	88.5	83	83.3	70.5
Portal vein size >11.5 mm	76.5	80	78	78.6
Splenic vein size >8 mm	70.6	72.6	70.6	72.7
Platelet / spleen diameter ratio 909	98.5	99	97.6	99

The above table shows the sensitivity, specificity positive predictive value and negative predictive value of various parameters in predicting large esophageal varices. The optimum cutoff is mentioned along with the variables.

Receiver operating characteristic curve:

Platelet count

Platelet count is an important factor in predicting the presence or absence of large esophageal varices. ROC curve for the predictor function showed an area under curve of 0.701. {95% CI (0.594-0.808)}. A platelet count of below 1,50,000 had a specificity of 75%.

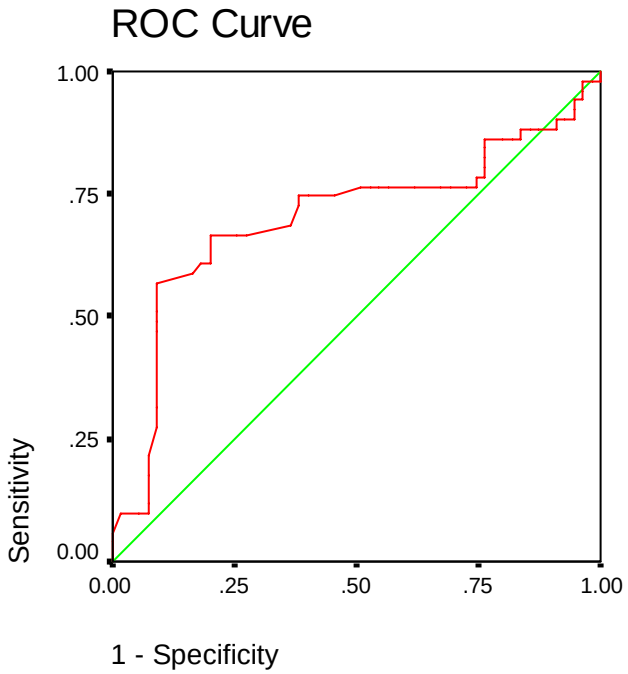


FIG: 7 Platelet count: Area under curve: 0.701[95% CI (0.594-0.808)]

Receiver operating characteristic curve: Spleen size

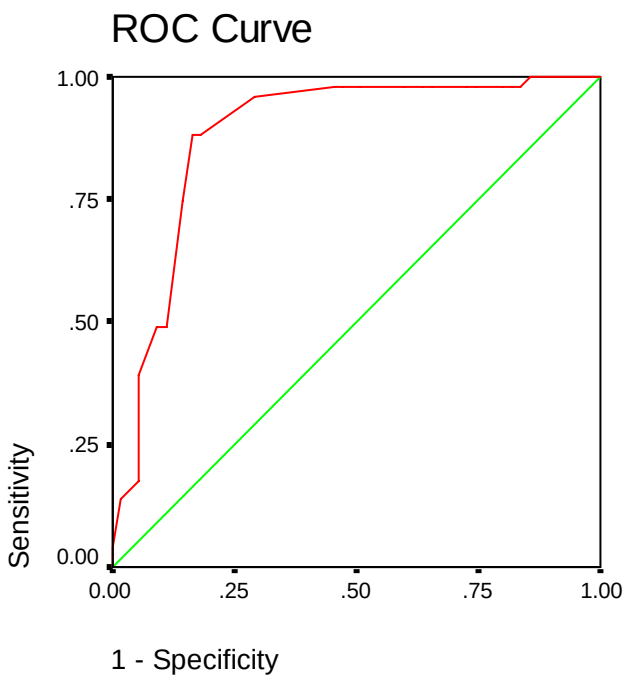


FIG: 8 Spleen size: Area under curve: 0.883 [95% CI (0.813-0.912)]

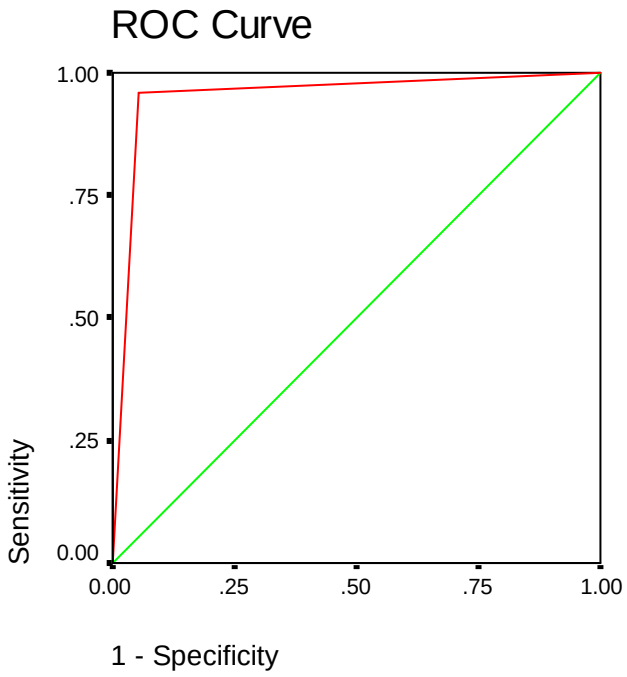


FIG: 9 ROC curve: Platelet/Spleen diameter ratio

Spleen size is an important factor in predictor of presence or absence of large esophageal varices. ROC curve for the predictor function showed an area under curve of 0.883. Spleen size of more than 13 cm had a specificity of 88%.

Platelet /spleen diameter ratio 909

Platelet/Spleen diameter ratio is proven predictor of presence or absence of large esophageal varices. ROC curve for the predictor function showed an area under curve of 0.95. A cut off of 909 yielded a sensitivity and specificity of 98.5% and 99% respectively.

DISCUSSION

The reason for this effort is simple: the number of patients undergoing screening for the presence of OV is likely going to increase in the near future as a result of the growing pool of patients with chronic liver disease. Therefore, there is a particular need for non-invasive predictors of the presence of varices as they might help relieve medical, social, and economic costs.

Most of the studies concerning the non-invasive diagnosis of OV were performed on a particular subgroup of patients while some of the studies lacked uniformity in OV classification or adequate statistical analysis, and only one study analyzed patients with compensated disease. Almost all of the studies were retrospective, although the only prospective study obtained results that were no different from those obtained in retrospective studies. In general, most identified decreased platelet count and splenomegaly as non-invasive predictors of the presence of OV. In this study, only simple, commonly available, reproducible parameters were considered.

These data based on the information obtained from 106 patients with portal hypertension including 51 with large esophageal varices, showed that

six factors had predictive ability for the presence of large esophageal varices on univariate analysis. However, on multivariate analysis, only four of these, namely low platelet count, splenomegaly, portal vein diameter, splenic vein diameter, were found to have independent predictive value. The efficacy of splenomegaly and platelet count arrived by logistic regression analysis was moderate with an area under the ROC curve of 0.883 and 0.701.

Variceal gastrointestinal bleeding is a serious complication of portal hypertension with significant morbidity and mortality. However, this complication occurs primarily in patients with large esophageal varices and is uncommon in those with small varices. Because the occurrence of variceal bleeding can be prevented using pharmacological agents like beta-adrenergic receptor antagonists, it is important to recognize patients who have large esophageal varices and are thus at a higher risk of developing variceal bleeding and likely to benefit from such interventions. It has therefore been recommended that patients with liver cirrhosis should be screened for the presence of large esophageal varices at the time of initial diagnosis and at periodic intervals thereafter throughout life. However, this recommendation imposes a major burden on endoscopy units and significant costs on patients.

In view of this, efforts have been made to identify clinical, laboratory and imaging characteristics that may non-invasively predict the presence or

absence of large esophageal varices with a high degree of accuracy, either reducing or eliminating the need for screening endoscopy. Various parameters found to be important for this purpose in different studies have included splenomegaly, thrombocytopenia, ascites, spider naevi, hepatic encephalopathy, serum albumin concentration, serum bilirubin levels, prothrombin time, Child-Pugh score, etiology of liver disease, portal vein diameter, and derived measures like ratio of platelet count to splenic size.

The four parameters found to have independent predictive ability in this study, namely presence of a enlarged spleen, low platelet count, portal and splenic vein size have been the most consistently identified predictors in previous studies. All the other factors that have previously been shown to have predictive ability in only a few studies were found to lack predictive power in this study. Thus, the results of this study were consistent with those of the previously published data.

According to K. C. Thomopoulos et al. study, esophageal varices were present in 92 patients (50%), and large varices in 33 patients (17.9%).[22] Variables associated with the presence of large esophageal varices on univariate analysis were the presence of ascites and splenomegaly either by clinical examination or by ultrasound ($p<0.01$) and bilirubin ($p=0.01$).

Table 7. Studies Assessing Noninvasive Predictors of Varices or Large Varices

Author	Year	No. Pts	Pts With Varices	CTP Class A/B/C (%)	Predictors	Sensitivity	Specificity	False-Negative Rate	Negative Rate	Validation
Studies Assessing Noninvasive Predictors of Varices										
Fook-Hong et al.[30]	1999	92	53	41/47/12	PLT < 150,000 and ascites	0.75	0.62	0.35	0.40	No
Schepis et al.[1]	2001	143	80	59/41/0	PLT < 100,000 or prothrombin < 70% or PV > 13 mm	0.96	0.44	0.10	0.22	External
Schepis et al., validation	2001	105	57	68/32/0	PLT < 100,000 or prothrombin < 70% or PV > 13 mm	0.89	0.27	0.32	0.18	External
Giannini et al.[23]	2003	145	89	37/36/27	PLT/spleen ratio > 909	1.00	0.93	0.00	0.36	No
Giannini,	2003	145	53	69/31/0	PLT/spleen ratio > 909	1.00	0.77	0.00	0.49	No
Thomopoulos et al.[22]	2003	184	92		PLT < 118,000 or spleen > 135 mm or ascites	0.95	0.37	0.13	0.21	No
Zein et al.[31]	2004	183	47	Nr	PLT < 150,000	0.62	0.90	0.13	0.77	External
Zein, validation	2003	70	26	Nr	PLT < 150,000	0.62	0.86	0.21	0.69	External
Studies Assessing Noninvasive Predictors of Large Varices										
Cottone et al.[32]	1986	213	43	Nr	PV > 13 mm	0.95	0.55	0.02	0.45	No

Chalasani et al.[17]	1999	346	70	22/48/30	PLT < 88,000 and/or splenomegaly	0.90	0.36	0.07	0.30	Internal
Pilette et al.[19]	1999	124	59	50/24/26	PLT < 160,000	0.83	0.58	0.21	0.39	No
Zaman et al.[20]	1999	98	20	33/50/15	PLT < 88,000	0.80	0.59	0.08	0.51	No
Fook-Hong et al.[30]	1999	92	19	41/47/12	PLT < 150,000 and ascites	1.00	0.51	0.00	0.40	No
Madhotra et al.[34]	2002	184	24	43/34/23	PLT < 68,000	0.71	0.73	0.06	0.67	No
Madhotra[21]	2002	184	24	43/34/23	Splenomegaly	0.75	0.57	0.06	0.53	No
Zein et al.[31]	2004	183	19	Nr	PLT < 150,000	0.74	0.82	0.04	0.77	External
Zein, validation	2003	72	9	Nr	PLT < 150,000	0.88	0.76	0.02	0.69	External

Factors independently associated with the presence of large oesophageal varices on multivariate analysis were platelet count, size of spleen and presence of ascites by ultrasound. Using mean values as cut-off points, it is noteworthy that only five out of 39 patients (12.8%) with platelets ≥118($\times 10^9$/l), spleen length ≤135 mm and no ascites had varices. Moreover, all these patients had small sized varices. On the other hand, 15 out of 18 patients (83.3%) with a platelet count <118$\times 10^9$/l, spleen length >135 mm and ascites had varices. Moreover, five out of those 18 patients had large varices (28.3%). They concluded that **thrombocytopenia, splenomegaly and ascites** are independent predictors of large oesophageal varices in cirrhotic patients.

Zaman A et al. identified **platelet count <88,000** was the only parameter identified by univariate/multivariate analysis ($p < 0.05$) as associated with the presence of large esophageal varices or gastric varices. [33]

According to Zaman A et al. study **Platelet count and Child-Pugh class** were independent risk factors for the presence of any varices and the presence of large varices. For the presence of any varices, a **platelet count of 90,000** or less and advanced Child-Pugh class were independent risk factors. For large varices, **a platelet count of 80,000** and advanced Child-Pugh class were independent risk factors associated with varices.

In Chalasani N et al. study, the prevalence of large esophageal varices was 20%.[17] On multivariate analysis, **splenomegaly and low platelet count** was independent predictors of large esophageal varices. Patients with a platelet count of > 88,000/mm3 (median value) and no splenomegaly by physical examination had a risk of large esophageal varices of 7.2%. Those with splenomegaly or platelet count < 88,000/mm3 had a risk of large esophageal varices of 28% ($p < 0.0001$).

Sarwar S et al. in his study of 101 patients concluded that patients with **serum albumin < 2.95 g/dl, platelet count < 88,000 and portal vein diameter > 11 mm** are more likely to have high grade varices. [34] These patients are candidates for surveillance endoscopy.

Prihatini J et al , in his study of 47 patient's, detected varices in 76.6%.[35] Using bivariate analysis, **platelet count** of 82,000/ul (90.9% sensitivity; 41.7% specificity), **portal vein diameter** of 1.15 cm (75% sensitivity; 54.5% specificity) and **splenic size of 10.3 cm** (83.3% sensitivity; 63.6% specificity) were found to be predictive factors for esophageal varices in liver cirrhosis. They concluded that their data showed that platelet count, portal vein diameter and anteroposterior splenic measurement can be used as non invasive parameters to detect esophageal varices in cirrhotic patients.

Amarapurkar et al. found that presence of splenomegaly was associated with presence of esophageal varices but not with large esophageal varices. [36]

In Sharma SK et al. study, of the 101 patients, 46 had large esophageal varices. [37] On univariate analysis, five variables were significantly associated with the presence of large esophageal varices. These included pallor, palpable spleen, platelet count, total leukocyte count and liver span on ultrasound (P = 0.031). On multivariate analysis, two of these parameters, namely **low platelet count** and presence of **palpable spleen**, were found to be independent predictors of the presence of large esophageal varices. A ROC using the predictor function arrived at from this analysis had an area under the curve of 0.760.

Fagundes et al. conducted a study of 111 children with portal hypertension[38] and found esophageal varices in 60% of patients. Only **splenomegaly** showed appropriate sensitivity and negative predictive value (97.7% and 91.7%, respectively). He suggested this as a screening test for esophageal varices among cirrhotic patients.

Platelet count spleen diameter ratio:

In E Giannini et al.'s study of 266 patients, the prevalence rates of OV were 61% and 58% in the first and second groups of patients, respectively. [23]

The platelet count/spleen diameter ratio was the only parameter which was independently associated with the presence of OV in a multivariate analysis. A **platelet count/spleen diameter ratio** cut off value of 909 had 100% negative predictive value for a diagnosis of OV. This result was reproduced in the second group of patients as well as in patients with compensated disease. In a cost-benefit analysis, screening cirrhotic patients according to the "platelet count/spleen diameter ratio" was far more cost effective compared with the "scope all strategy".

Edoardo G. Giannini et al. in his study of 218 cirrhotic patients who underwent screening endoscopy found esophageal varices in 54.1%.[39] The platelet count/spleen diameter ratio had 86.0% (95% CI, 80.7–90.4%) diagnostic accuracy for EV, which was significantly greater as compared with either accuracy of platelet count alone (83.6%, 95% CI 78.0–88.3%, *P* = 0.038) or spleen diameter alone (80.2%, 95% CI 74.3–85.3%, *P* = 0.018). They concluded that the **platelet count/spleen diameter ratio** may be proposed as a safe and reproducible means to improve the management of cirrhotic patients who should undergo screening endoscopy for EV.

According to Zimbwa et al. study, 30 had oesophageal varices at endoscopy and 10 did not. The median platelet count/spleen diameter ratio in patients with varices was 537 (range 371–670) and with no varices 2229

(range 1542–3174). A **platelet count/spleen diameter ratio of < 909** had 100% sensitivity and specificity for the prediction of oesophageal varices in these patients.

Jeon SW et al.'s study of 52 patients, esophageal varices were present in 25 patients (48%).[41] On univariate analysis serum albumin, total bilirubin, prothrombin time, platelet count, spleen size, velocity of portal vein and portal vein diameter were found significant. On multivariate analysis, independent variables were **platelet count, diameter of spleen and platelet count/spleen diameter ratio.** Endoscopic screening for varices is recommended in cirrhotic patients with splenomegaly.

This study also validated of platelet spleen diameter ratio with a cut-off of 909 as per Giannini et al. We found that platelet spleen diameter ratio of 909 was highly predictive of large esophageal varices with a sensitivity and specificity of 98.5% and 99% respectively in this study. The area under ROC curve was 0.95. The platelet count/spleen diameter ratio seems to represent an acceptable surrogate for clinically relevant portal hypertension.

Other parameters:

Tamara Alempijevic et al. in his study of 58 patients, right lobe diameter: albumin and platelet count: spleen diameter ratios were

noninvasive parameters that provided accurate information pertinent to determining the presence of oesophageal varices. [42]

Tarzamni MK et al. In his 85 cirrhotic patients, Portal hypertensive index > 2.08 and spleen size > 15.05 cm were the factors in identifying patients with a low probability of LEV who may not need upper gastrointestinal endoscopy. [43]

Zein[31] and colleagues at the Mayo Clinic report a study of potential noninvasive markers of esophageal varices in a consecutive series of 183 patients with primary sclerosing cholangitis (PSC).[31] The results of the study show that a platelet count of 150,103/dL is associated with an odds ratio of 6.3 (95% CI: 2.6 –15.8) for the presence of varices. This figure corresponds to a sensitivity and specificity of 62% and 90%, respectively, for the detection of esophageal varices, and a negative predictive value of 87%. Corresponding figures for large varices are 74%, 82%, and 96 %, respectively.

These predictive characteristics of the platelet count were validated in a subsequent group of 72 patients with PSC. The authors suggested that a platelet count of < 150,103/dL may be a satisfactory marker for identifying patients with PSC who are likely to benefit from endoscopic screening for esophageal varices. Different cutoff values for the platelet count have

previously been reported to define significant markers for the presence of varices or large varices (Table 7). The lower the proportion of patients in Child-Pugh class A is, the lower the level of the cutoff values tends to be. In six studies that suggested a cutoff value of 100,000/dL, the proportion of patients who were in Child-Pugh class A was 41% in one, 50% in three, and was not reported in two; one of these last two studies was the one by Zein and colleagues, which included more than 50% of patients without cirrhosis. In contrast, in all three studies that suggested a cutoff value of 100,000/dL, the proportion of patients in Child-Pugh class A was 50%. Moreover, each of these three studies aimed at predicting large varices, whereas those that suggested higher cutoff values aimed at predicting varices irrespective of their size. Therefore the different cutoff values for the platelet count in predicting the presence of varices are influenced by the distribution of patients according to the degree of liver dysfunction.

Although the number of studies that have assessed the value of the platelet count in the prediction of varices is substantial, we are still not able to determine a reliable cutoff for application in clinical practice. Low platelet count is associated with the presence of esophageal varices, and, consequently, that it has potential for predicting their presence. However, we still lack adequate information on the true dimension of the association,

probably because of inadvertent spectrum bias in several of the available studies.

In addition to the platelet count, other markers identified are the prothrombin time, albumin concentration, splenic size, and portal vein diameter (on ultrasound). The various predictive rules suggested are associated with sensitivities that range from 0.62 to 1.0 (median, 0.86); values are higher in studies of markers of varices (median, 0.92; range, 0.62–1.0) than in studies of markers of large varices (median, 0.83; range 0.71–1.0).

In this study, prevalence of large varices was 48.11%. Large esophageal varices were more often associated with low platelet count, an enlarged spleen, as observed in other parts of the world. And multivariate analysis also showed the ultrasonographic measurement of spleen, portal vein size and splenic vein size was also associated with large esophageal varices, which are likely to cause a significant bleed. This study indicate that it may be possible to predict the presence of large esophageal varices using simple and non-invasive tools like clinical examination for the presence of a palpable spleen and platelet count with a fairly high degree of accuracy. The high accuracy rates may obviate the need for endoscopy in these patients, restricting the use of this costly and invasive procedure to only those patients

with intermediate scores. Such an approach would reduce both hospital costs and the workload of endoscopy units.

The relationship of these predictors to the presence of large esophageal varices may be easily explained. A palpable spleen as well as large esophageal varices may both be related to presence of a higher portal pressure. Similarly, the low platelet counts in patients with large esophageal varices may reflect a higher rate of splenic sequestration and destruction of these cells consequent to a higher portal pressure.

This study has certain limitations. Our study group represented a select group of patients attending a tertiary care center and included patients with relatively advanced disease. It would be best applied in patients attending large hospitals and may not perform as well in primary care settings. The variable being predicted, that is, the presence of large esophageal varices is not completely objective and is subject to interobserver variation.

CONCLUSION

1. The prevalence of large esophageal varices in our study was 48.1%

2. Our study shows that low platelet count, splenomegaly, portal vein and splenic vein size are independent predictors of the presence of large esophageal varices in patients with cirrhosis of the liver.

3. Use of these parameters may help identify patients with a low probability of large esophageal varices who may not need UGI endoscopy.

4. This may help reduce costs and discomfort for these patients and the burden on endoscopy units.

5. These predictors showed moderate efficacy in predicting the presence of large esophageal varices.

6. The platelet count/spleen diameter ratio seems to represent an acceptable surrogate for portal hypertension. Applying the "platelet count/spleen diameter ratio strategy" for the detection of OV would seem to be more cost effective than the "scope all strategy". Future studies are required to evaluate the reproducibility of the platelet count/spleen diameter ratio for the non-invasive diagnosis of varices.

7. If its efficacy is confirmed, it may permit institution of prophylactic measures like beta-adrenergic antagonists for preventing primary variceal

bleeding in patients with liver cirrhosis, without the need for costly and invasive investigations like gastrointestinal endoscopy.

BIBILIOGRAPHY

1. Schepis F, Camma C, Niceforo D et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? Hepatology 2001; 33 : 333–8.

2. D'Amico G, Luca A. Natural history. Clinical-hemodyanamic correlations. Prediction of the risk of bleeding. Bailliere's Clin. Gastroenterol. 1997; 11 : 243–56.

3. Christensen E, Fauerholdt L, Schlitching P, Juhi E, Poulsen H, Tygstrup N. Aspect of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone.

Gastroenterology1981;81:944–52.

4. Pagliaro L, D'Amico G, Pasta Let al. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ, eds. Portal Hypertension: Pathophysiology and Treatment. Oxford: Blackwell Science, 1992; 72–92.

5. Merli M, Giorgia N, Stefania A et al. Incidence and natural history of small varices in cirrhotic patients. J. Hepatol. 2003; 38: 266–72.

6. Poynard T, Cales P, Pasta L et al. Beta adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589

patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. N. Engl. J. Med. 1991; 324: 1532–8.

7. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995; 22: 332–54.

8. Merkel C, Zoli M, Siringo S et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. Am. J. Gastroenterol. 2000; 95: 2915–20.

9. Nevens F, Bustami R, Scheys I, Lesaffre E, Fevery J. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients. Hepatology 1998; 27: 15–19.

10. D'Amico G, Pagliaro L. The clinical course of portal hypertension in liver. In: Rossi P, ed. Diagnostic Imaging and Imaging Guided Therapy. Berlin: Springer-Verlag, 2000; 15–24.

11. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence based approach. Semin. Liver Dis. 1999; 19: 475–505.

12. Andreani T, Poupon RE, Balkau BJ et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: results of a controlled

trial comparing propranolol, endoscopic sclerotherapy and placebo. Hepatology 1990; 12: 1413–19.

13. Conn HO, Grace ND, Bosch J et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: a multicenter, randomized clinical trial. The Boston-New Haven-Barcelona Portal Hypertension Study Group. Hepatology 1991; 13: 902–12.

14. Grace ND, Groszmann RJ, Garcia-Tsao G et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. Hepatology 1998; 81: 944–52.

15. Jalan R, Haynes PC. UK guidelines on the management of Variceal haemorrhage in cirrhotic patients. Gut 2000; 46 (Suppl. 3–4): III1–15.

16. Amarapurkar DN, Parikh SS, Shankaran K et al. Correlation between spleenomegaly and oesophageal varices in patients with liver cirrhosis. Endoscopy 1994; 26: 563.

17. Chalasani N, Imperiale TF, Ismail A et al. Predictors of large esophageal varices in patients with cirrhosis. Am. J. Gastroenterol. 1999; 94: 3285–91.

18. Ng FH, Wong SY, Loo CK, Lam KM, Lai CW, Cheng CS. Prediction of oesophagogastric varices in patients with liver cirrhosis. J. Gastroenterol. Hepatol. 1999; 14: 785–90.

19. Pilette C, Oberti F, Aube C et al. Non-invasive diagnosis of esophageal varices in chronic liver diseases. J. Hepatol. 1999; 31: 867–73.

20. Zaman A, Becker T, Lapidus J, Benner K. Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch. Intern. Med. 2001; 161: 2564–70.

21. Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophageal

varices in patients with cirrhosis. J. Clin. Gastroenterol. 2002; 34: 81–5.

22. Thomopoulos KC, Labropoulou-Karatza C, Mimidis KP, Katsakoulis EC, Iconomou G, Nikolopoulou VN. Non-invasive predictors of the presence of large oesophageal varices in patients with cirrhosis. Dig. Liver Dis. 2003; 35: 473–8.

23. Giannini E, Botta F, Borro P et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003; 52: 1200–5.

24. Bressler B, Pinto R, El-Ashry D, Heathcote EJ. Which patients with primary biliary cirrhosis or primary sclerosing cholangitis should undergo endoscopic screening for oesophageal varices detection. Gut 2005; 54: 407–10.

25. Arroyo V, Ginès P, Gerbes AL et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996; 23: 164–76.

26. Conn H, Bircher J, eds. Hepatic Encephalopathy Syndrome and Therapies. Bloomington, IL: Medi-Ed Press, 1994; 1–12.

27. Child C, Turcotte J. Surgery and portal hypertension. In: Child CG, ed. The Liver and Portal Hypertension. Philadelphia, PA: Saunders, 1964; 50–1.

28. Paquet KJ. Prophylactic endoscopic sclerosing treatment of esophageal wall in varices: a prospective controlled trial. Endoscopy 1982; 14: 4–5.

29. Kuntz E, Kuntz H.D, Hepatology principle and practice. 2nd edition: Springer Medizin Verlag Heidelberg, 2006.

30. Fook-Hong NG, Siu-Yin W, Ching-Hong L, Kwong -Ming L, Chi-Wing L, Chi-Sing C. Prediction of esophageal varices in patients with liver cirrhosis. J Gastroenterol Hepatol 1999; 14: 785-790.

31. Zein CO, Lindor KD, Angulo P. Prevalence and predictors of esophageal varices in patients with primary sclerosing cholangitis. HEPATOLOGY 2004; 39: 203-209.

32. Cottone M, D'Amico G, Maringhini A, Amuso M, Sciarrino E, Traina M, et al. Predictive value of ultrasonography in the screening of non-ascitic cirrhotic patients with large varices. J Ultrasound Med 1986; 5: 189-192.

33. Zaman A, Hapke R, Flora K, et al. Factors predicting the presence of esophageal varices or gastric varices in patients with advanced liver disease. Am J Gastroenterol 1999;94:3292–6.

34. Sarwar S, Khan AA, Alam A, Butt AK, Shafqat F, Malik K, Ahmad I, Niazi AK. Non-endoscopic prediction of presence of esophageal varices in cirrhosis. J Coll Physicians Surg Pak 2005;15(9):528–31.

35. Prihatini J, Lesmana LA, Manan C, Gani RA. Detection of esophageal varices in liver cirrhosis using non-invasive parameters. Acta Med Indones 2005;37(3):126–31.

36. Amarapurkar DN, Parikh SS, Shankaran K, et al. Correlation between splenomegaly and oesophageal varices in patients with liver cirrhosis. Endoscopy 1994;26:563.

37. Sharma SK, Aggrawal R. prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. Journal of gastroenterology and hepatology 2007;22:1909-1915.

38. Fagundes ED, Ferreira AR, Roquete ML, Penna FJ, Goulart EM, Figueiredo Filho PP, Bittencourt PF, Carvalho SD, Albuquerque W. Clinical and laboratory predictors of esophageal varices in children and adolescents with portal hypertension syndrome. J Pediatr Gastroenterol Nutr. 2008 Feb;46(2):178-83.

39. Edoardo G. Giannini, Atif Zaman, Anna Kreilet al. Platelet Count/Spleen Diameter Ratio for the Noninvasive Diagnosis of Esophageal Varices: Results of a Multicenter, Prospective, Validation Study. Am J Gastroenterol 2006;101, (11).2511 – 2519

41. Jeon SW, Cho CM, Tak WY, Ryeom HK, Kweon YO, Kim SK, Choi YH. The value of Doppler-ultrasonography and laboratory tests as non-invasive predictors of the presence of esophageal varices in patients with chronic liver disease. Korean J Gastroenterol. 2006 Sep;48(3):180-7.

42. Alempijevic T, Bulat V, Djuranovic S, Kovacevic N, Jesic R, Tomic D, Krstic S, Krstic M. Right liver lobe/albumin ratio: contribution to non-invasive assessment of portal hypertension. World J Gastroenterol. 2007 Oct 28;13(40):5331-5.

43. Mohammad K Tarzamni, Mohammad H Somi, Sara Farhang, Morteza Jalilvand. Portal hemodynamics as predictors of high risk esophageal varices in cirrhotic patients. World J Gastroenterol 2008 March 28; 14(12): 1898-1902.

FIG: 1

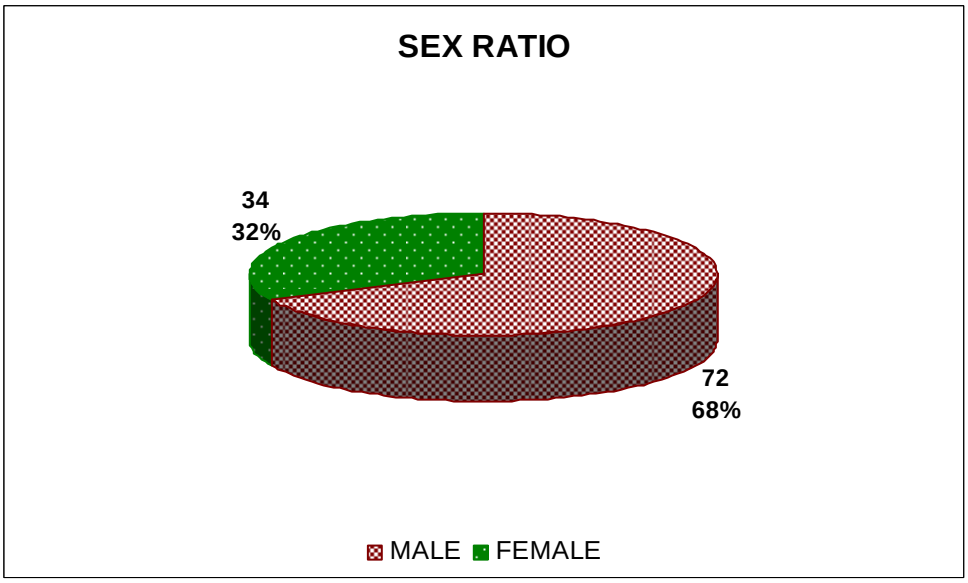

SEX RATIO
34
32%
72
68%
MALE
FEMALE

FIG: 2

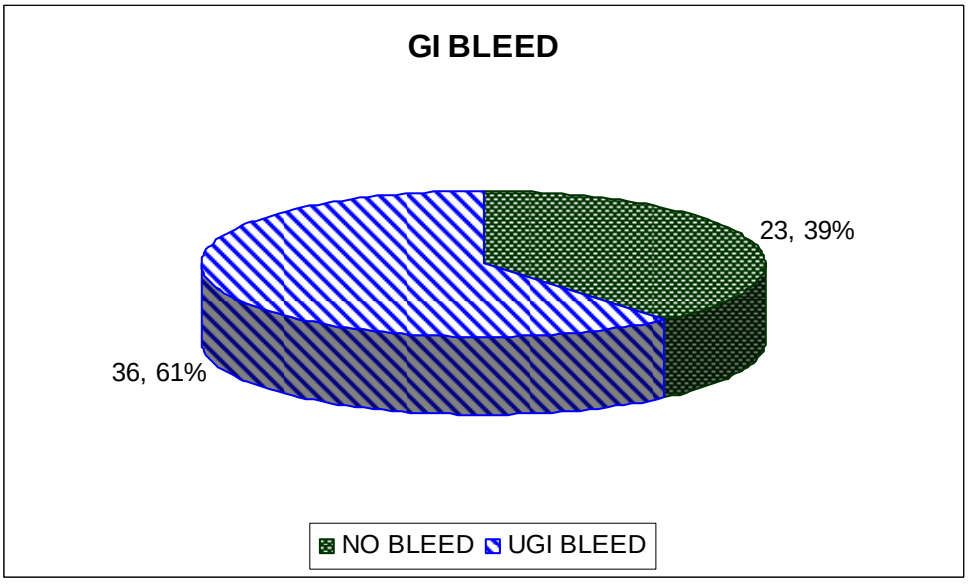

GI BLEED
23, 39%
36, 61%
NO BLEED
UGI BLEED

FIG: 3

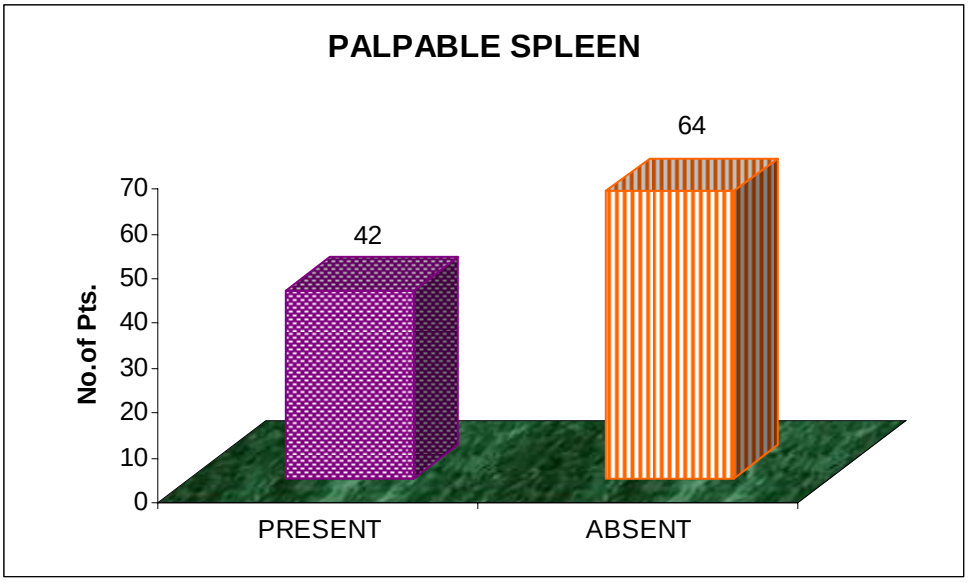

PALPABLE SPLEEN
No.of Pts.
70
60
50
40
30
20
10
0
42
64
PRESENT
ABSENT

FIG: 4

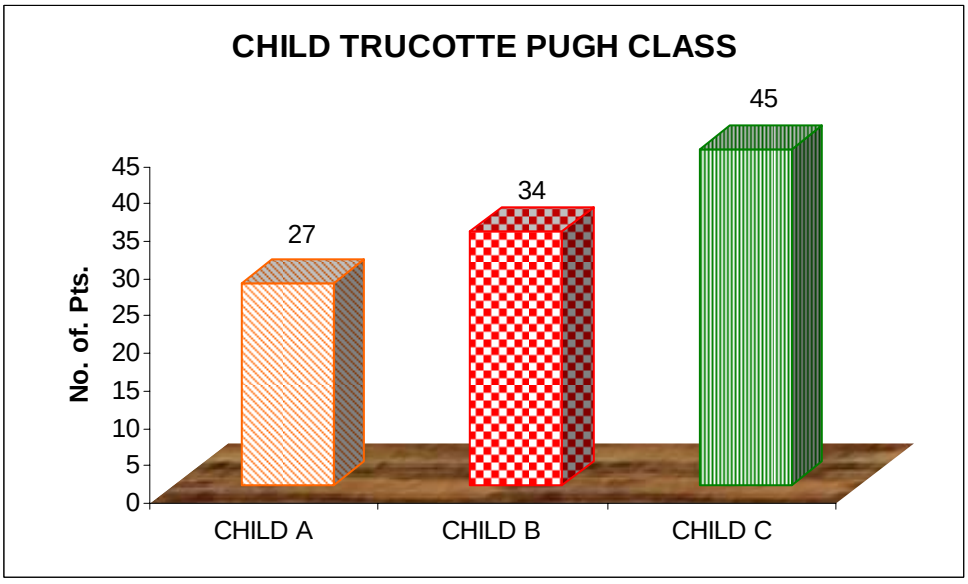

CHILD TRUCOTTE PUGH CLASS
No. of. Pts.
45
40
35
30
25
20
15
10
5
0
27
34
45
CHILD A
CHILD B
CHILD C

FIG: 5

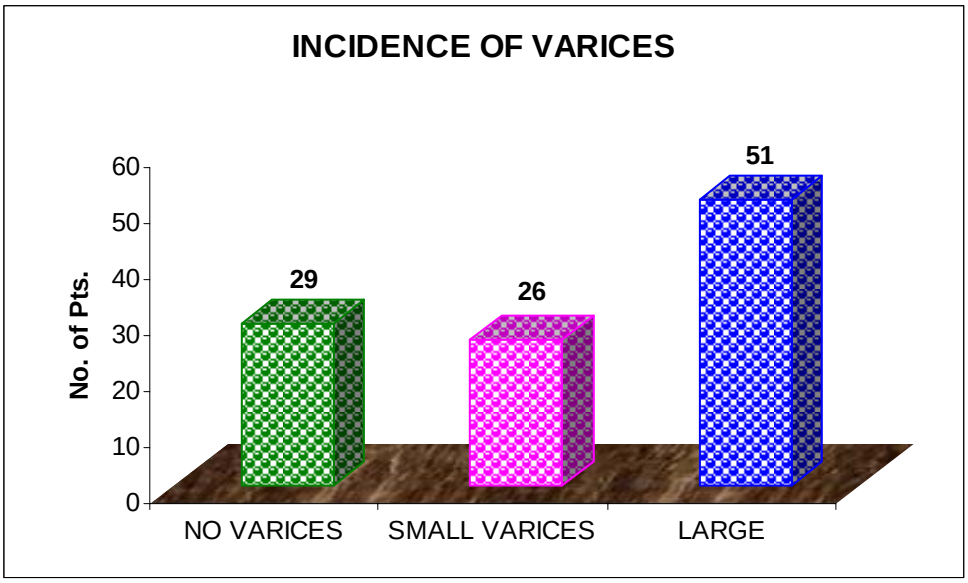
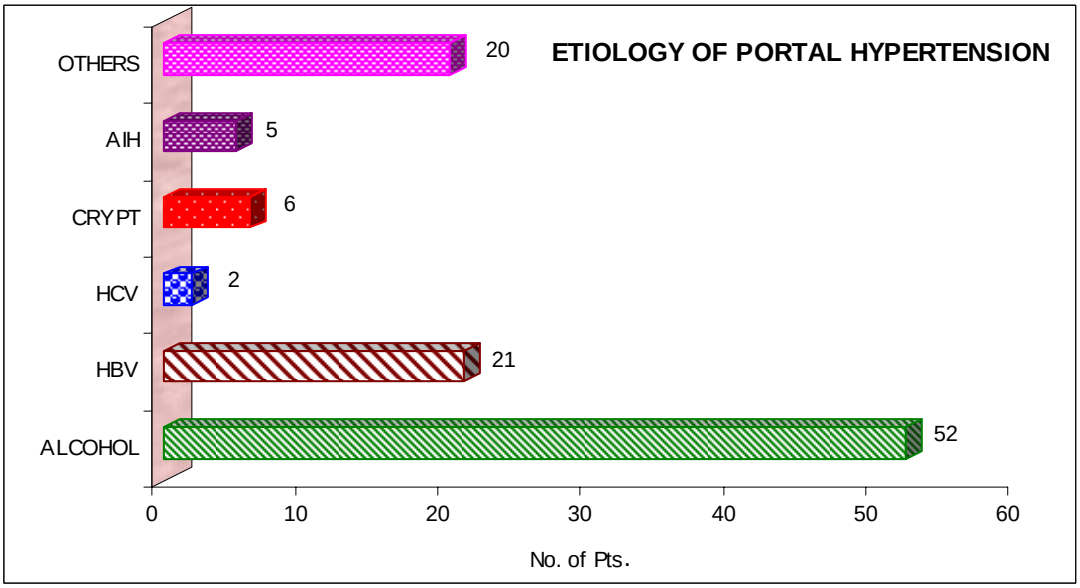

INCIDENCE OF VARICES
No. of Pts.
60
50
40
30
20
10
0
29
26
51
NO VARICES
SMALL VARICES
LARGE

FIG: 6


ETIOLOGY OF PORTAL HYPERTENSION
OTHERS
AIH
CRYPT
HCV
HBV
ALCOHOL
20
5
6
2
21
52
0
10
20
30
40
50
60
No. of Pts.