A dissertation on

A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL

Submitted in partial fulfilment of requirements for

M.D. DEGREE BRANCH-1

GENERAL MEDICINE

OF

THE TAMILNADU M.G.R.MEDICAL UNIVERSITY

CHENNAI.

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

MAY 2020

CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL**" submitted by **Dr. R. RAMPRASATH** with registration number **201711014**, appearing for M.D Branch-I – General Medicine Degree examination in MAY 2020 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of The Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I, **Dr. R. RAMPRASATH,** solemnly declare that this dissertation entitled "**A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL"** was done by me at Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai between April 2018 to March 2019 under the guidance and supervision of my Chief **Prof. Dr. NALINI KUMARAVEL M.D**. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

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ACKNOWLEDGEMENT

At the outset, I sincerely thank **Prof. Dr. JAYANTHI, M.D.,** Dean, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for having permitted me to use hospital data for the study.

I am grateful to **Prof. Dr. S. RAGUNANTHAN, M.D.,** Director (I/C) and Professor, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3.

I am indebted to **Prof. Dr. NALINI KUMARAVEL M.D.,** Professor of Medicine, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for her valuable guidance.

I would like to thank **Dr. JACINTH PREETHI M.D, Dr. A. PRIYATHARCINI M.D,** Assistant Professors, Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 for their scrutiny.

I would also like to thank all the professors and assistant professors of the department of MGE and biochemistry, radiology for their continuous support and expert guidance.

I express my sincere gratitude to all the patients who participated in the study. Lastly, I thank all my professional colleagues for their support and valuable criticism.

CONTENT

INTRODUCTION

Portal hypertension is a major hallmark of cirrhosis which can be 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. In patients with cirrhosis and portal hypertension, esophageal varices and gastrointestinal bleeding represents a serious complications leading to mortality. 40% of the patients with compensated disease and 60% of the patients with decompensated disease had esophageal varices at diagnosis. [1, 2]

In patients with advanced liver cirrhosis those have no esophageal varices, the increases at a rate of nearly 5% annually. [3–5]. 12% of the patient with cirrhosis gradually increases from small to large esophageal varices at a rate of 12% per year.[3] The size of the varices gradually increases from small to large varices.

In patient with cirrhosis with portal hypertension in non-selected patients the incidence of first variceal bleeding was calculated to be around 4% . [6,7] The size of esophageal varices is directly proportional to risk of variceal rupture and its bleeding. The patients with large esophageal varices being at a higher risk of rupture and bleeding. This would probably due to 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]

Long-term administration of beta-adrenergic receptor antagonists(Propranolol) has been shown to decrease the incidence of first variceal bleeding in patients with large esophageal varices. First episode of variceal bleeding was found to be around 20–25% mortality within the first week. [11] Mortality is mainly due to delayed referral to tertiary care centers and delayed endoscopies. The survival of these patients are improved by appropriate timing endoscopies and referrals. [6]. It should be used only for patients with large esophageal varices because this treatment is not free of adverse effects. [11]. [12, 13]

It is currently advised that patients with liver cirrhosis and portal hypertension to look for the presence of esophageal varices and gastropathy by appropriate scopy techniques.[14, 15] And, if present, treated with oesophagial band ligation and prophylactic beta-adrenergic receptor antagonists(Propranolol). These advise imply a high man power on endoscopic units and to avoid financial issues on patients with liver cirrhosis. A large number of invasive endoscopic procedures turn out to be normal in around 30% of the patients with cirrhosis and portal hypertension. There is no unwanted endoscopic procedures for all patients.

Thus, there is a need for non-invasive methods to predict the presence of large esophageal varices by using biochemical and imaging parameters. Availability of such methods may help to decrease the unwanted endoscopic

procedures performed for detection of large esophageal varices in patients with advanced liver disease.

The non-invasive prediction of large esophageal varices are low platelet count, splenomegaly, advanced Child status ABC, serum albumin and high portal vein diameter at ultrasonography and biochemical parameters in patients with advanced liver disease[1, 16–24]. In different populations, etiology of liver cirrhosis varies and severity of liver disease also changes among different populations. In Indian patients with liver cirrhosis, who usually present late, have a poorer nutritional status who presents early with alcoholic etiology and have a fair proportion with viral etiology, are rare.

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

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 + 0.2 (or 0.97) cm. [29]

Increased resistance in the portohepatic circulation and an increase in the splanchnic vein blood flow causes Portal hypertension syndrome. The increase in vascular resistance is the decisive factor and, in the majority of cases, is even the sole cause. 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

Gastric varices is one of manifestations of portal hypertension and it is supplied by the short gastric veins and deep intrinsic veins of the esophagus. In patients with extrahepatic portal obstruction, these veins are dilated prominently.

PORTAL HYPERTENSIVE GASTROPATHY

Portal hypertensive gastropathy is one of the manifestations of portal hypertension. It is seen in the fundus and body of the stomach. The risk of bleeding is increased, mainly due to gastritis(Peptic ulcer) and also from drugs, non-steroidal anti-inflammatory drugs (NSAIDs). These gastric changes may be raised after endoscopy techniques. It is decreased only by reducing the portal wall tension. Gastric antral vascular ectasia (GAVE) is marked by increased

arteriovenous communications by increasing vascularity between the muscularis mucosa and the veins are prominent. Greater and richest gastric mucosal perfusion is seen. This must be distinguished from portal hypertensive gastropathy. But is influenced by liver dysfunction. Histology shows watermelon stomach.

PORTAL HYPERTENSIVE INTESTINAL VASCULOPATHY

Portal hypertensive intestinal vasculopathy is one of the manifestation of portal hypertension with cirrhosis. Portal hypertensive intestinal vasculopathy is one of the spectrum of mucosal changes in portal hypertension due to abnormal micro circulation.

CONGESTIVE JEJUNOPATHY AND COLONOPATHY

Congestive jejunopathy and colonopathy is one of the manifestations of portal hypertension. Congestive jejunopathy are commonly seen in the duodenum and jejunum. There is an increase in size and number of vessels in jejunal villi. Congestive colonopathy is very rare and it is mainly due to abnormal circulation shown by dilated mucosal capillaries but with no evidence of mucosal and serosal inflammation.

CLINICAL FEATURES OF PORTAL HYPERTENSION

Portal hypertension is mainly caused by cirrhosis. Neonatal sepsis and umblical sepsis is one of the important factors in extra-hepatic portal hypertension. Clotting factor deficiency and drugs, such as oc pills and sex hormones, predispose to extra hepatic portal vein obstruction.

UGI bleed is the first and foremost presentation of cirrhosis. Previous UGI bleed, last blood transfusion, last alcohol binge, previous SBP should be noted. Melena is also one of the manifestations from bleeding varices in cirrhosis. The signs of liver cell failure include alopecia, anaemia, jaundice, testicular atrophy vascular spiders and palmar erythema. Pedal edema, ascites and precoma should be noted.

Abdominal wall veins

Dilated veins may appear in the flanks and back in extra-hepatic portal hypertension. In intra-hepatic portal hypertension, some blood from the portal vein pass through para-umbilical veins to the umbilicus, where it delivers veins of the porto caval system.

Distribution and direction

Caput Medusae means dilated and tortous veins around the umbilicus and flanks. Sometimes the dilated veins also seen in epigastric regions. The blood flow direction is away from the umbilicus,exaggerated flow in portal hypertension. In inferior vena caval obstruction ,the dilated and tortous venous channels carry blood flow towards to reach the superior vena caval system. massive ascites may lead to functional obstruction of the inferior vena cava and causes blood flow towards SVC.

MURMURS

A venous hum of maximum intensity may be heard in the region between xiphoid process and umbilicus. A thrill, shall be felt at the site of maximum intensity and because of blood flowing through the large umbilical veins called as para-umbilical channel to veins around the umbilicus in the abdominal wall. A venous hum can also be heard over other large collaterals (inferior mesenteric vein). Continous murmur heard around the umbilicus and flanks in cirrhosis. The association of dilated abdominal wall veins and a loud venous hum at the umbilicus is known as the Cruveilhier–Baumgarten syndrome. It is due to patency of the umbilical vein, but mostly due to well-compensated cirrhosis. The para-xiphoid umbilical hum and Caput Medusae denote portal obstruction beyond the origin of the umbilical veins.. It indicates intra hepatic portal hypertension (cirrhosis).

Spleen

The spleen progressively enlarges and the edge is firm. It is larger in macronodular cirrhosis. Hypersplenism is the single most significant characteristics sign of cirrhosis with portal hypertension. If the spleen is not present by palpation or is not enlarged on imaging, the diagnosis of portal hypertension is questionable. Hypersplenism,ascites and cirrhosis of the liver is the triad of portal hypertension. This is mostly due to reticulo-endothelial hyperplasia than to the portal hypertension and is unaffected by lowering the pressure by a porta-caval shunt.

Liver

Enlargement of liver should carefully monitored by tidal percussion. It doesn't depend with the height of portal pressure.Hepatomegaly doesnot correlates with height of portal pressure. Liver consistency, tenderness or nodularity should be noted. A soft liver indicates extra-hepatic portal venous obstruction. A firm liver indicates cirrhosis.

Ascites

The portal hypertension causes nitric oxide release causes splanchnic vasodilation and increases the capillary hydrostatic pressure, and influences fluid localization to peritoneal cavity. Ascites in cirrhosis always indicates transudates by sinusoidal portal hypertension secondary to liver cell failure.

Rectum

Among 44% of cirrhotic patients, anorectal varices are found due to portocaval shunt, increasing in those who have bled from oesophageal varices. They sometimes confused with simple hemorrhoids that are prolapsed which is fresh bleeding per rectum and that 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.

In cirrhosis with portal hypertension enlargement of the collateral flow enters the azygos system. In cirrhosis with portal hypertension, the dilated hemi azygous veins may seen as para vertebral shadows. Massively dilated para-oesophageal collaterals may be seen on the chest radiograph as 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 present around cardia and fundus of the stomach it looks like normal mucosal folds and may be difficult to distinguish from mucosal folds, dilated veins may appear in the left flank and around the umbilicus.

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 loc,alization of the varices as well as imaging the surface of these veins.

In cirrhosis with portal hypertension, large esophageal varices are ruptured and bleed viewed by endoscopy as cherry red spot . 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 nearly 2 mm in radius. 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. On the whole, agreement is good for size and red signs. Portal hypertensive gastropathy is one of the manifestations in cirrhosis with portal hypertension mostly seen in fundus, but can extend throughout the stomach. It viewed as water

melon stomach with angry look cherry red spots likely to rupture and bleed. Grade 3 esophageal varices are likely very fragile and bleed to touch causing hematemesis and malena in advanced liver disease.

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 typically suited for showing intramural and perimural oesophageal varices. Endoscopic colour Doppler sonography is another important procedure, particularly for instructing a (still) evident variceal perfusion. Doppler effect is produced due to reflection of sound on moving particles (e. g. erythrocytes) by changing wavelength. The direction of flow (towards or away from the sound source) also the flow rate in arterial and venous vessels can be found. The flow volume is calculated by additional sonographic measurement of vessel diameter. It has been proved that the rate of flow is clearly dependent upon the respiratory activity, so that an rise in blood flow velocity can be found with maximum expiration and also postprandially (normal value: 18-30 cm/sec).

In the event of a distinct decrease in the flow rate, the flow direction may be reversed (hepatopetal to hepatofugal). Blood flow in the portal venous system is usually hepatopetal as opposite to pulsatile (or only slightly pulsatile) and follows a rise in expiration flow rate. Undulating blood flow on exhaling (hepatofugal) and inhaling (hepatopetal) is evident of portal hypertension.

Congestion index (CI)

This parameter is the most trusted indicator of portal hypertension. It connects the portal cross-sectional area to the portal blood flow rate. The direct pressure level in the diagnostics of the portal_system and the HVPG lower than the CI rank. These three techniques (in this order) are trusted_to be the gold standard in early diagnosis of portal hypertension. CI levels of_>0.1 are with

excessive portal pressure with >95% sensitivity and specificity. USG imaging of cavernous transformation in the portal vein usually denotes beaded varicose collaterals in the hepatoduodenal ligament.

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

A. Indirect splenoportography through the femoral artery is low risk and not very important.

B. Hepatic vein phlebography

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

.**MEASUREMENT OF PORTAL PRESSURE**

Direct measurement

Direct measurements of portal pressure are invasive investigations based on the percutaneous transhepatic, surgical, or transvenous (transjugular) catheterization of the portal vein. Because of this discomfort and the hemorrhagic risk or associated surgical risk, direct measurements of portal pressure are not used much.

Indirect measurement

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

PATHOPHYSIOLOGY OF VARICEAL HEMORRHAGE

Two theories has been proposed to demonstrate variceal bleeding. The erosion theory shows that varices bleed during external trauma to their thin and fragile walls that is caused by the gastroesophageal reflux or deglutition of solid food. This theory had been rejected because of a lesser objective evidence. No relation between eating and bleeding had been proved, nor is the development of reflux and esophagitis greater in patients with variceal bleeding than in those without bleeding.

On the other hand, the so-called explosion hypothesis denotes that the main cause of bleeding is increased hydrostatic pressure inside the varices, which is a complication of higher portal pressure. In the evident of this hypothesis, it is shown that the variceal bleeding does not occur before it reaches a threshold value of Hepatic vein pressure gradient 12 mm Hg. Also added that, the introduction of endoscopic techniques to find variceal pressure, new observations had been made

to handle the role of increased intravariceal pressure in variceal rupture. Therefore, variceal pressure is greater in patients with previous bleeding than in nonbleeders, and longitudinal studies have proved that variceal pressure is a good prognostic marker of the risk for bleeding and of the response to pharmacologic treatment. Variceal wall thickness,pressure and size can be combined 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 released by the thin wall of a varix is greater than critical value, as measured by the elastic limit of the vessel. At this point, the variceal wall cannot further variceal rupture and resist dilatation occurs.

According to Frank's modification of Laplace's law, variceal wall tension (WT) can be explained as: $WT = (Pi - Pe) \times r/w$ in which Pi is the value of intravariceal pressure, r the radius of the varix, w the thickness of its wall, Pe the pressure in the esophageal lumen,. The natural history of portal hypertension can be studied as a function of variceal wall tension. Once the wall tension raises to values exceeding the elastic limit of a varix, the patient suffers a first episode of bleeding. After this, the patient remains at a greater risk for rebleeding unless wall tension is decreased. Likely, primary prophylaxis guards the patient from delaying variceal wall tension bleeding by preventing from reaching the rupture point, which is achieved by decreasing portal pressure and portal–collateral blood flow. A rise in intravascular pressure, along with a greater rate of collateral blood flow, causes varices to dilate, and as they dilate, their walls become leaner.

At this instant, any further rise in variceal pressure or size or any lesion in the variceal wall causes rupture,bleeding and clinical hemorrhage.

Alcohol consumption, 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 found approximately in 50% of patients with

cirrhosis. Their presence of large varices directs the advanced liver disease, while only 35% of the patients have varices in child A, they are found in 80% of Child C patients. Patients in the absence of cirrhosis develop varices during routine endoscopic techniques, and the significant non-invasive predictor for development of varices has been used in those with cirrhosis that have no varices during the time of initial endoscopic screening. Patients with mild varices may develop large varices at the rate of 10-15% per year. Alcoholic cirrhosis and decompensated cirrhosis (Child B/C), and appearace of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the instant of baseline endoscopy are the prominent factors associated with the progression from mild to large varices.

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

Other predictors of hemorrhage are the endoscopic presence of red wale marks and decompensated cirrhosis (Child B/C). Although bleeding from esophageal varices stops spontaneously in up to 40% of patients, and despite improvements in treatment over the last few decades, 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 happens in approximately 60% of untreated patients, mostly within 1-2 years of the initial hemorrhage.

Variceal wall tension is the main factor that determines variceal rupture and bleeding. Apart from portal vein diameter one of the factors of variceal wall tension is the portal pressure develops within portal vein which is directly correlated to the HVPG. Therefore, a decrease in HVPG should lead to a decrease in portal vein pressure and there by decreasing variceal tension, thus by reducing the risk of rupture and bleed. In cirrhosis with portal hypertension the patient cannot bleed when HVPG is within normal limit. Patients whose HVPG decreases to <12 mmHg have a lesser chance of developing recurrent variceal bleeding,lesser chance of developing signs of liver cell failure such as alopecia, anaemia, jaundice, pedal edema and hepatic encephalopathy leading to 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. To predict the non-invasive markers of varices for appropriate endoscopic techniques in cirrhosis with portal hypertension.

METHODS

Patients:

Consecutive newly diagnosed patients with liver disease (cirrhosis / portal hypertension) with or without history of gastrointestinal bleeding at our institution (Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, 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 USG
- Primary hematologic disorders
- Current treatment with beta blockers/ nitrate
- 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 signs of liver cell failure such as alopecia, anemia, jaundice, parotid swelling, gynaecomastia, testicular atrophy, palmar erythema, pedal edema, ascites, splenomegaly were recorded.

By ultrasonography of abdomen, mild ascites were noted. Moderate and massive ascites were detected clinically by shifting dullness and fluid thrill. According to West Havens Criteria, encephalopathy were noted

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 Tests such as complete blood counts include hemoglobin,haematocrit ,platelet count and pt/inr were noted to check for bleeding tendencies.

All patients were tested for hepatits B and C are one of the important causes of cirrhosis in developed countries by using ELISA method. Tests for other causes of cirrhosis,Wilson disease diagnosed by urinary copper excretion and serum ceruloplasmin., appropriate tests for autoimmune liver disease, liver biopsy for hemochromatosis) were carried out for diagnosing cirrhosis. 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 ultrasound after overnight fasting the details should be noted are spleen size, portal vein size diameter, spleen vein size diameter, collaterals of the portal system, size of the liver, ascites and other organs such as kidney, pancreas should be noted structurally for the development of complications of portal hypertension in cirrhosis.

Endoscopic evaluation:

All patients with proper history which undergoes cirrhosis should monitor varices by UGI endoscopy techniques avoiding iatrogenic injuries to the normal structures(Pentax). Within 2-3 days of admission. If esophageal varices were present, their sizes was noted and graded, ligated by using endoscopic band ligation or sclerotherapy. In cirrhosis with portal hypertension, gastric varices, portal hypertensive gastropathy, duodenopathy, colonopathy, anorectal varices were noted and treated by proper management to control major bleeding leading to death . Gastric varices were classified according to Sarin classification as isolated gastric or gastroesophageal varices, i.e., gastric varices associated with esophageal varices. Within first month basic investigations and evaluation of esophageal varices by using non-invasive markers for prediction. By using basic laboratory findings and imaging's to arrive for the diagnosis of advanced liver disease.

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 patients were included in this study. Age group - median age: 45 years; range 18- 80. 70 were male patients and 30 are female patients in our study.

Patient's symptom duration was 8- 250 days with a median of 95 days. Clinically detectable ascites was present in 40 patients and 33 had pedal edema, 15 patients had extreme signs of liver cell failure such as alopecia parotid enlargement etc. 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: 25, Child B: 35, Child C: 40.

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	70	70
	Female	30	30

S.no.	Patient characteristics	No. of Pts	%
2	**Etiology**		
	Alcohol	52	52
	Hepatitis B virus	21	21
	Hepatitis C virus	2	2
	Autoimmune hepatitis	5	5
	Others	20	20
3	**Child -Pugh class**		
	A	25	25
	B	35	35
	C	40	40
4	**Clinical findings**		
	Pallor	49	46.2
	Jaundice	53	50
	Pedal edema	43	40.5
	Bleed	53	50
	Ascites		
	None	50	52.8
	Mild	20	18.8
	Moderate	18	16.9
	Massive	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	30	30.0%
2	SMALL VARICES	21	21.0%
3	LARGE VARICES	49	49.0%

Endoscopic findings are shown in table 2. Seventy patients had esophageal varices (large varices in 49). None had isolated gastric varices. Furthermore of those patients with esophageal varices large varices was found in 19% of CTP class A, 39% of CTP class B and 62% of CTP class C. (Table3)

TABLE: 3 PRESENCES OF VARICES ACCORDING TO CTP CLASS

S.No.	CTPCLASS	VARICES	LARGE VARICES	%
1	A=25	14	5	19.0%
2	B=35	27	12	39.0%
3	C=40	33	29	62.0%

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 None /small	Large	P- value
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	9	-
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-**	**14.9 (9.2-26)**	**0.0001**

		18)		
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	-

By using this Univariate analysis Bilirubin, low platelet count, CTP score, spleen size, portal vein diameter and splenic vein diameter 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 100 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 waschosen 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

The above table shows the significant non-invasive 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%.

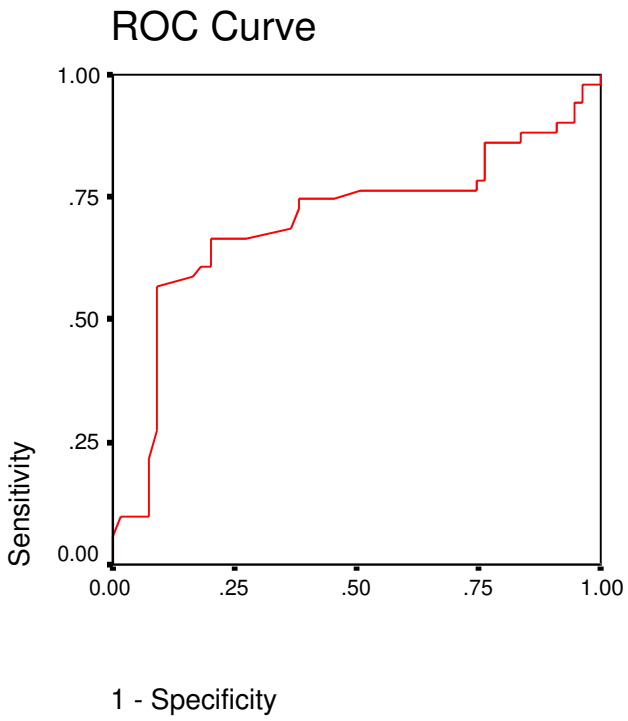

FIG: 7 Platelet count: Area under curve: 0.701[95% CI (0.594-0.808)]

Receiver operating characteristic curve: Spleen size

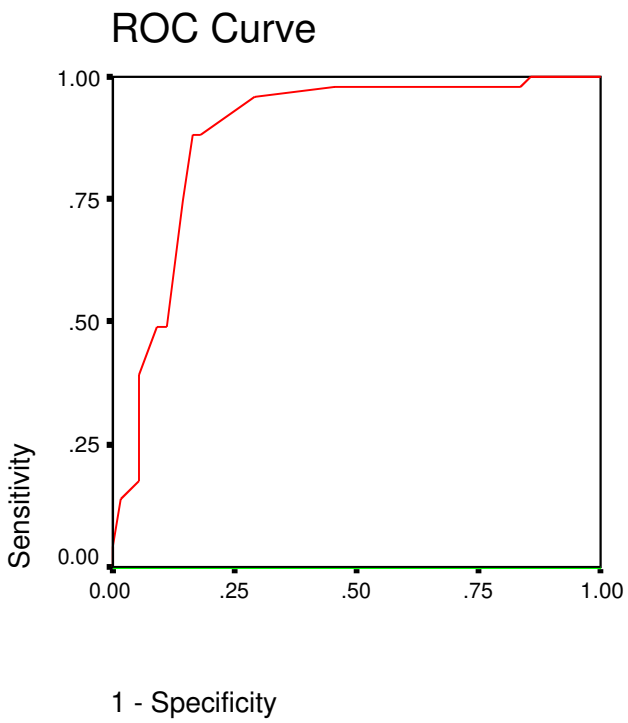

FIG: 8 Spleen size: Area under curve: 0.883 [95% CI (0.813-0.912)]

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%.

DISCUSSION

The reason for this effort is simple, the number of patients with cirrhosis and portal hypertension are likely to increase because of modern lifestyle modifications. The need for non-invasive prediction of large esophageal varices in advanced cirrhosis patients in rural areas may be useful for early referral to tertiary care hospitals.

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 100 patients with portal hypertension including 49 with large esophageal varices, showed that the significant non-invasive predictors of large esophageal varices by using this analysis.

However, on advanced multivariate analysis, 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 patients with portal hypertension increased risk of bleeding should be screened routinely 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 predict the patients who are at risk of portal hypertension in cirrhosis are potential to bleed. 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 found in larger number of patients with low platelet count and splenomegaly in cirrhotic patients.

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	729		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 <118×10^9/l, spleen length >135 mm and ascites had varices. Moreover, five out of those 18 patients had large varices (28.3%). 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, **splenomegaly and low platelet count** was independent predictors esophageal varices in cirrhosis. Patients with a platelet count of > 88,000/mm3 (median value) and absence of splenomegaly by clinical examination had a risk of large esophageal varices. Those with splenomegaly or platelet count < 88,000/mm3 had a risk of large esophageal varices.

Sarwar S et al. in his study of 101 patients concluded that patients with cirrhosis such as non-invasive markers prediction 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 analysis the non-invasve markers predictions were found to be predictive factors for esophageal varices in liver cirrhosis. They concluded that their data showed that low platelet count, portal vein diameter and splenic vein diameter and size of the spleen 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. He suggested this as a screening test for esophageal varices among cirrhotic patients.

Other parameters:

Tamara Alempijevic et al. in his study of 58 patients, right lobe diameter: albumin and low platelet count, platelet count: spleen diameter ratioswere noninvasive parameters that predict the esophageal varices in advanced liver disease. [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.

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 cirrhosis. Various platelet count have been reported to diagnose the varices as significant markers in cirrhosis. 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 49.15%. 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 non-invasive predictors to the presence of large esophageal varices in cirrhotic patients. 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 inter-observer variation.

CONCLUSION

1. The prevalence of large esophageal varices in our study was found to be 49.15%

2. Our study shows that low platelet count, splenomegaly, portal vein and splenic vein size are independent predictors.

3. Use of these parameters help identify patients to perform endoscope for patients only with a high risk of large esophageal varices.

4. These parameters help in avoiding unnecessary endoscopies.

5. This may help reduce costs which will be economical.

6. 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.

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FIG: 1

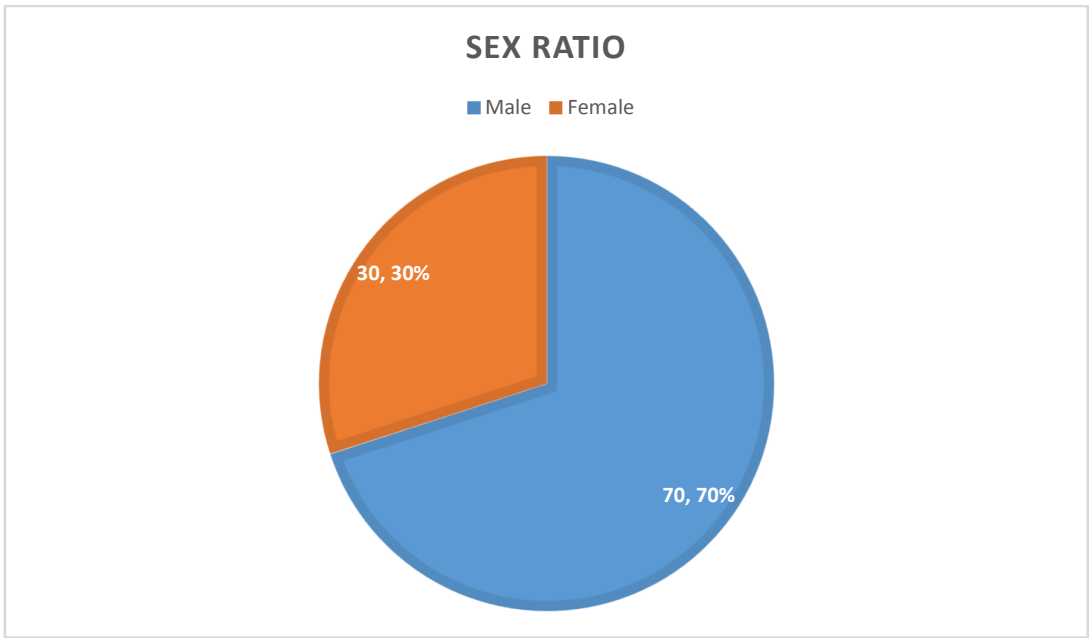

SEX RATIO
Male
Female
30, 30%
70, 70%

FIG: 2

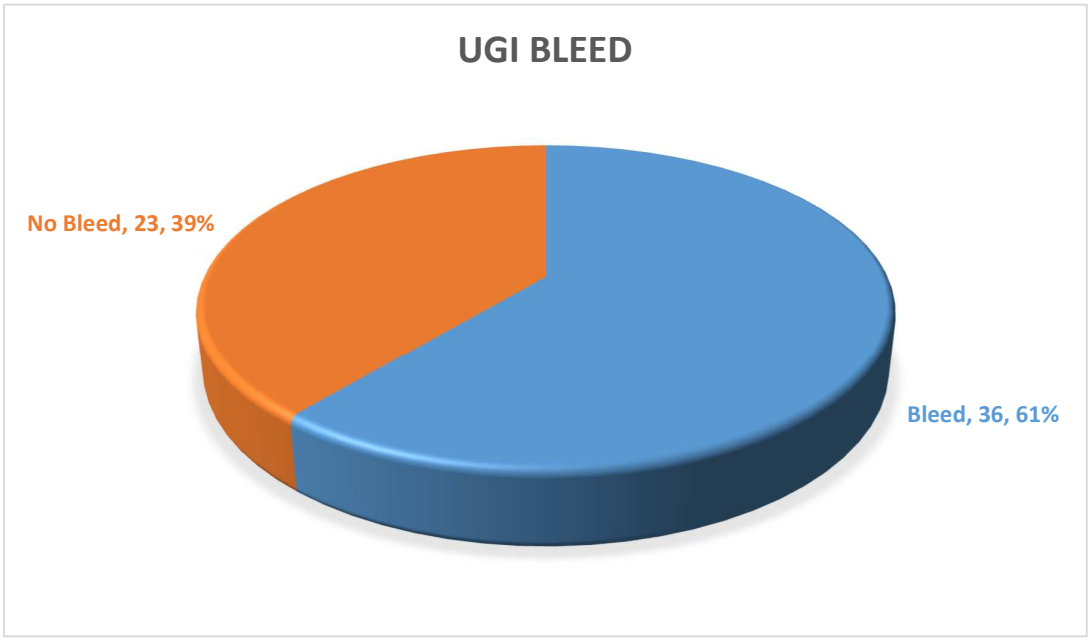

UGI BLEED
No Bleed, 23, 39%
Bleed, 36, 61%

FIG: 3

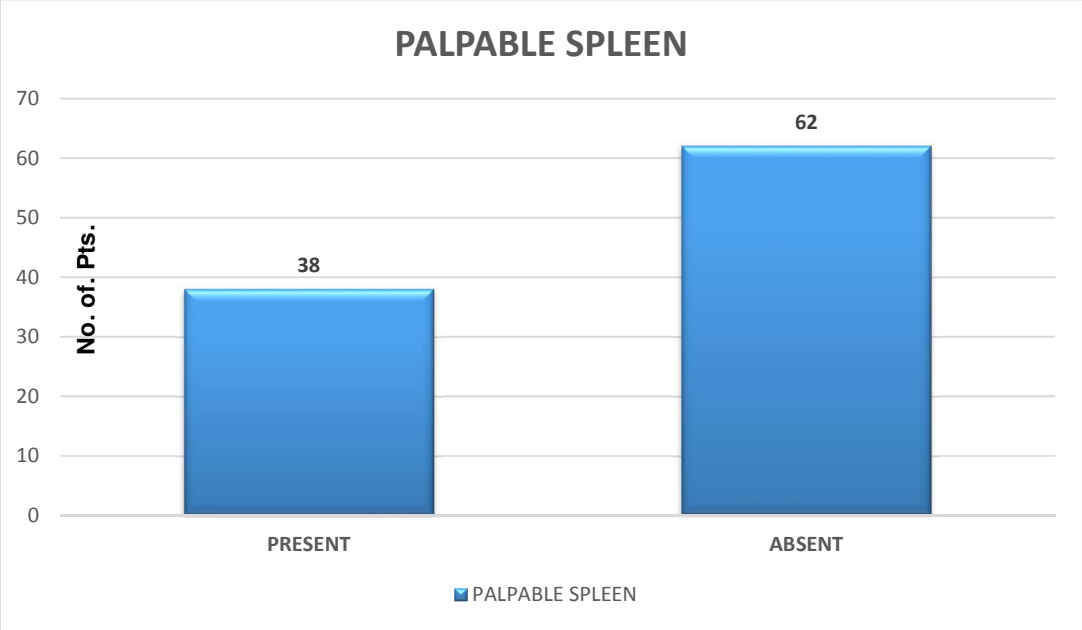

PALPABLE SPLEEN
70
60
50
40
30
20
10
0
No. of. Pts.
38
62
PRESENT
ABSENT
PALPABLE SPLEEN

FIG: 4

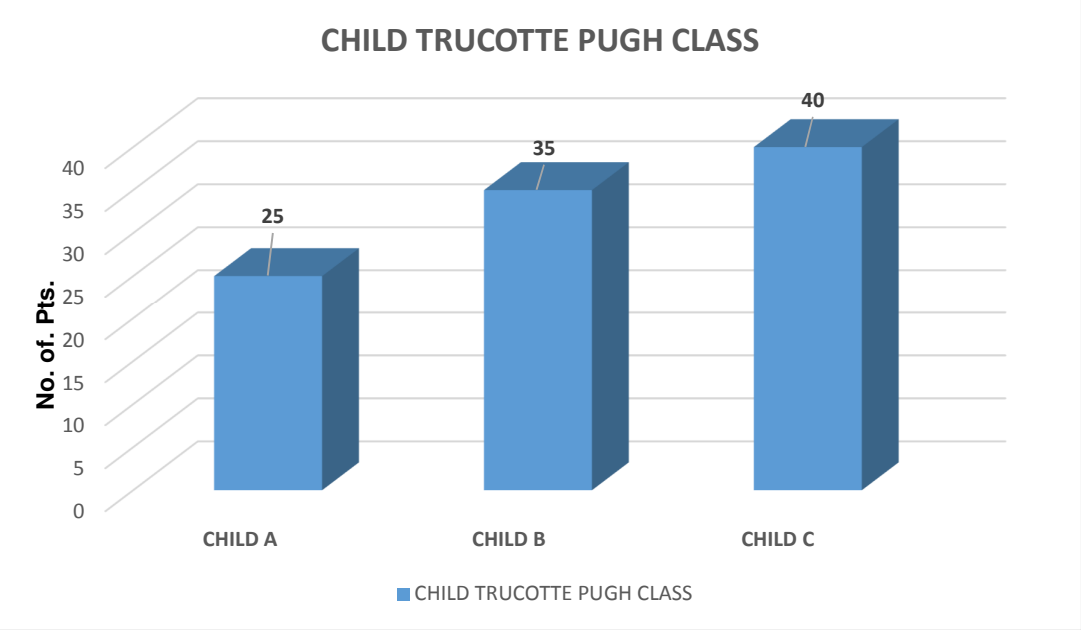

CHILD TRUCOTTE PUGH CLASS
40
35
30
25
20
15
10
5
0
No. of. Pts.
25
35
40
CHILD A
CHILD B
CHILD C
CHILD TRUCOTTE PUGH CLASS

FIG: 5

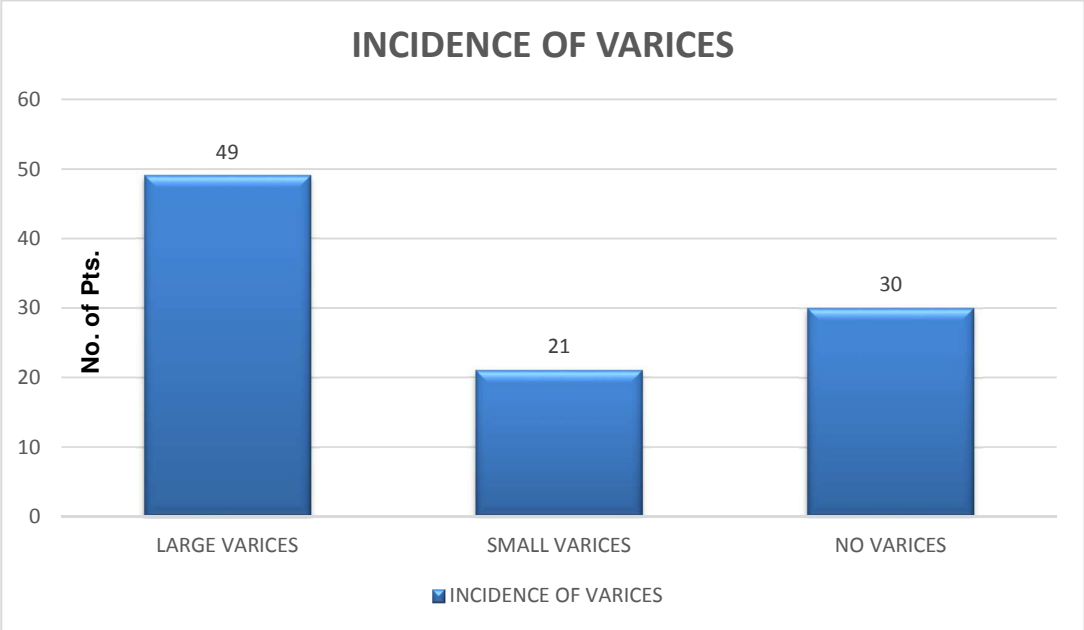
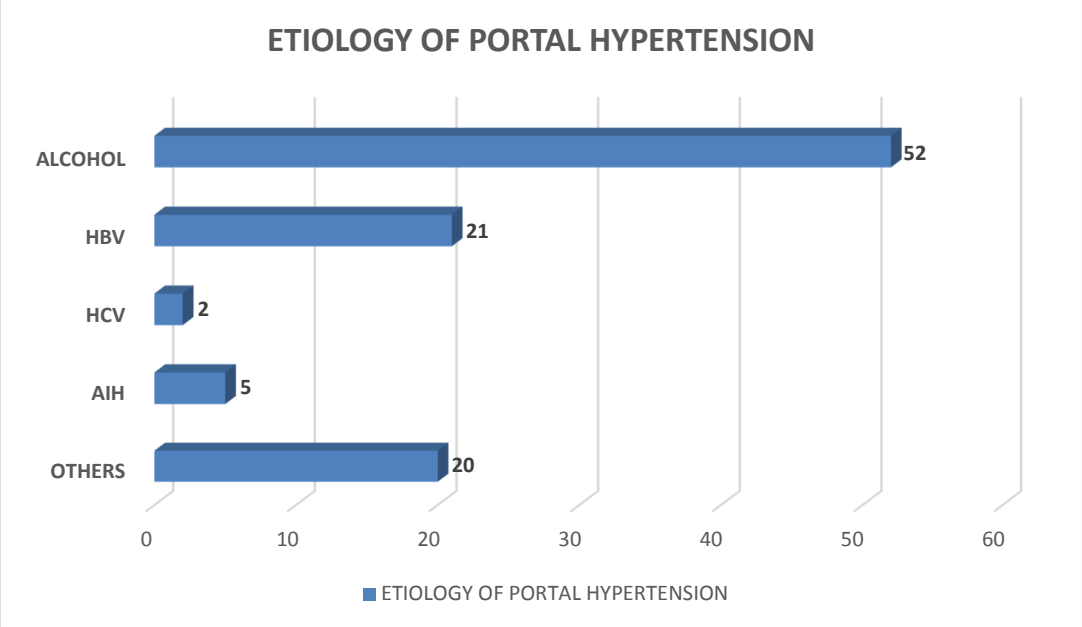

INCIDENCE OF VARICES
60
50
40
30
20
10
0
No. of Pts.
49
21
30
LARGE VARICES
SMALL VARICES
NO VARICES
INCIDENCE OF VARICES

FIG: 6


ETIOLOGY OF PORTAL HYPERTENSION
ALCOHOL
HBV
HCV
AIH
OTHERS
52
21
2
5
20
0
10
20
30
40
50
60
ETIOLOGY OF PORTAL HYPERTENSION

A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL

Name :

Age/Sex :

OP/IP No :

Occupation :

Address :

Contact No. :

SYMPTOMS

-UGI bleed
-Abdominal distension
-Breathlessness
-Swelling of legs
-Abdominal pain
-Easy fatiguability

SIGNS OF LIVER CELL FAILURE

-Jaundice
-Anemia
-Ascites
-Pedal edema
-Alopecia
-Abdominal vein distension
-Gynaecomastia

PAST H/O

-alcoholic
-previous blood transfusion
-H/O tatooing

FAMILY H/O

H/O similar episodes in the family(just as wilson's disease)

EXAMINATION

-Blood Pressure
-Pulse Rate

INVESTIGATION

-Platelet count, Hemoglobin, Total count, RBC, PCV.

-USG abdomen- spleenic size diameter/ascites/ shrunken liver

-Portal vein doppler

-portal vein diameter

-spleenic vein diameter

-spleenic size diameter

-collaterals

INFORMATION SHEET

We are conducting a study on **"A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to identify the non-invasive markers of EVs to reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices. This prospective study was conducted to evaluate non-invasive predictors of large varices(LV)

We are selecting certain cases and if you are found eligible, we may perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail	:	**A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL.**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.

Signature/thumb impression
Patient's Name and Address

Signature of Investigator

Dr.Ram Prasath.R

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு: *மூன்றாம் நிலை பராமரிப்பு மருத்துவமனையில் நாள்பட்ட கல்லீரல் நோய் நோயாளிகளில் பெரிய ஓசோஃபேஜியல் மாறுபாடுகளின் ஆக்கிரமிப்பு அல்லாத முன்கணிப்பு பற்றிய ஆய்வு*

ஆய்வாளர் பெயர் : *ரா.ராம்பிரசாத்*

ஆய்வு நிலையம் : பொது மருத்துவ துறை, சென்னை மருத்துவ கல்லூரி சென்னை

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆயிராய்ச்சியில் பங்கேற்கலாமா அல்லது வேண்டாமா என்று முடிவு செய்ய உதவியாக இருக்கும்.

இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை தயங்காமல் கேட்கலாம்.

இந்த ஆய்வில் உங்களுக்கு தேவையான ரத்த பரிசோதனைகளும்,இதர ஆய்வுகளும் செய்யப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். அதனால் தங்கள் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு ஏற்படாது என்பதையும் தெரிவித்து கொள்கிறோம்

முடிவுகள் அல்லது கருத்துக்கள் வெளியிடும் போது தங்களின் பெயரையோ அல்லது அடையாளத்தாயோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறோம்

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்து கொள்கிறோம்

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு: *மூன்றாம் நிலை பராமரிப்பு மருத்துவமனையில் நாள்பட்ட கல்லீரல் நோய் நோயாளிகளில் பெரிய ஓசோஃபேஜியல் மாறுபாடுகளின் ஆக்கிரமிப்பு அல்லாத முன்கணிப்பு பற்றிய ஆய்வு*

ஆய்வாளர் பெயர் : *ரா.ராம்பிரசாத்*

பங்கு பெறுபவரின் பெயர் :

பங்கு பெருவரின் ஏன் :

பங்கு பெறுபவர் இதனை குறைக்கவும்

- மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. எனது சந்தேகங்களை கேட்கவும் அதற்கான விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது
- நான் இவ்வாய்வில் தன்னிச்சையாக தன் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கு உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்று அறிந்து கொண்டேன்
- இந்த ஆய்வின் சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என்பதை அறிந்து கொண்டேன். நான் ஆய்வில் இருந்து விலகி கொண்டாலும் இது பொருந்தும் என அறிகிறேன்
- இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் பரிசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன்.
- இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்துகொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்: இடம் மற்றும் தேதி

கட்டைவிரல் கை ரேகை

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.R.Ram Prasath
PG in M.D. General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai

Dear Dr.R.Ram Prasath,

The Institutional Ethics Committee has considered your request and approved your study titled **"A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS " - NO.19042018**

The following members of Ethics Committee were present in the meeting held on **03.04.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3 : Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3 : Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch : Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3 : Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC : Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH : Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
9. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3 : Member
10. Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3 : Member
11. Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3: Member
12. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
13. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
14. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

Urkund Analysis Result

Analysed Document: Thesis Final Plagiarism.docx (D58348321)
Submitted: 11/6/2019 9:58:00 AM
Submitted By: rajanramprasath@gmail.com Significance: 16 %

Sources included in the report:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5924853/
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/649564
https://www.medscape.com/viewarticle/564466
https://docplayer.net/9096712-Aasld-practice-guidelines-prevention-and-management-ofgastroesophageal-varices-and-variceal-hemorrhage-in-cirrhosis.html
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3099085/
https://www.researchgate.net/publication/7581749_Non-endoscopic_prediction_of_presence_of_esophageal_varices_in_cirrhosis

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3023101/ Instances where

selected sources appear:

33

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A STUDY OF NON-INVASIVE PREDICTION OF LARGE OESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS IN TERTIARY CARE HOSPITAL"** done by the candidate **Dr. R.RAMPRASATH** with registration Number **201711014** for the award of **M.D.** in the branch of **GENERAL MEDICINE.** I personally verified theurkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 16% of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

Pt. No	Age	Sex	Hb	Platelet count	Spleen size	Portal vein size	Splenic Vein Size	Vein size
1	24	M	8.4	94000	14.0	13.70	11.10	Large
2	45	M	9.6	100400	13.9	14.00	8.20	Large
3	48	F	7.6	205000	10.4	11.40	6.10	Normal
4	67	F	10.6	92000	14.5	13.80	8.20	Large
5	54	M	8.1	200100	11.0	11.00	8.90	Normal
6	23	M	7.8	305600	9.6	9.40	6.20	Normal
7	24	M	7.8	196000	13.1	12.60	7.30	Small
8	54	F	10.6	226400	10.4	11.20	10.10	Normal
9	62	M	11.7	102000	14.2	19.40	8.90	Large
10	52	F	6.8	123000	12.8	13.40	7.10	Small
11	21	M	7.5	96400	13.5	19.20	8.60	Large
12	43	F	8.1	163000	11.7	11.80	8.20	Small
13	53	M	7.8	91500	13.8	14.80	8.00	Large
14	63	F	8.4	95600	13.8	15.90	8.10	Large
15	62	M	7.5	256100	8.4	8.60	6.10	Normal
16	32	M	9.2	141000	11.4	12.80	7.10	Small
17	70	M	8.7	246400	9.0	10.60	10.10	Normal
18	71	M	9.5	90200	14.1	19.40	9.30	Large
19	22	F	10.6	91200	14.4	16.20	11.20	Large
20	52	F	7.6	98100	13.5	13.60	10.10	Large
21	52	M	7.2	111000	12.4	11.60	8.30	Small
22	41	M	9.1	347000	10.2	9.50	7.20	Normal
23	61	M	10.6	178500	13.4	12.50	7.20	Small
24	27	M	8.1	103000	14.9	15.80	9.60	Large
25	74	F	7.5	105000	14.4	14.10	8.10	Large

26	35	F	8.6	96200	14.8	15.60	9.40	Large
27	51	M	6.8	135000	12.8	13.30	7.30	Small
28	33	M	7.2	265800	9.8	11.30	7.90	Normal
29	47	F	9.8	198000	11.1	11.90	7.10	Small
30	22	M	9.1	306500	8.8	10.20	6.20	Normal
31	24	M	7.8	106000	13.7	18.60	9.70	Large
32	48	M	7.4	98100	14.0	13.60	7.20	Large
33	50	M	8.7	110000	14.3	18.60	8.40	Large
34	19	F	7.1	252100	10.8	8.20	8.10	Normal
35	68	M	6.8	184000	12.4	12.20	7.90	Small
36	20	M	9.1	99100	13.9	13.90	10.60	Large
37	60	M	11.8	95100	13.6	16.70	8.10	Large
38	69	M	8.9	325400	9.3	9.80	6.30	Normal
39	39	F	11.5	184600	11.8	11.70	10.00	Small
40	34	M	7.2	298600	8.6	11.20	7.10	Normal
41	54	M	11.2	100500	14.9	19.40	9.40	Large
42	73	M	8.9	96500	13.8	18.40	8.20	Large
43	49	F	10.6	109000	13.6	16.20	7.60	Large
44	26	M	10.2	97600	14.1	13.70	8.10	Large
45	31	M	7.6	308200	10.7	10.10	8.20	Normal
46	25	F	9.8	265700	8.6	9.20	6.10	Normal
47	35	F	7.3	92300	14.7	17.80	8.50	Large
48	48	M	8.9	219800	9.7	11.40	6.20	Normal
49	26	M	9.2	91100	13.8	14.60	10.40	Large
50	36	M	8.2	125000	13.2	13.10	7.10	Small
51	59	M	9.8	98700	14.5	17.60	9.60	Large

52	49	M	12	292700	11.0	8.80	6.10	Normal
53	37	F	10.5	198500	12.4	11.80	7.60	Small
54	47	F	11.6	349800	10.7	11.20	6.30	Normal
55	72	M	10.8	96500	13.6	13.80	11.80	Large
56	67	M	7.2	116000	14.7	19.50	8.60	Large
57	20	M	7	263400	9.4	9.40	7.60	Normal
58	58	M	8.6	108000	13.7	17.30	9.80	Large
59	48	F	6.9	196800	11.6	11.60	8.40	Small
60	38	M	11.6	111500	13.4	11.90	7.00	Small
61	66	M	7.6	98000	14.1	15.80	11.60	Large
62	46	M	8.9	116000	13.7	14.10	9.40	Large
63	25	M	10.2	90400	13.9	16.70	10.90	Large
64	30	M	12	109000	14.4	15.80	8.70	Large
65	46	M	7.2	308200	10.4	8.70	6.20	Normal
66	65	M	12	178800	12.8	12.70	9.40	Small
67	39	F	7.6	96300	14.8	18.60	8.50	Large
68	34	M	9.8	108000	13.7	14.80	8.10	Large
69	24	F	10.6	92600	14.6	13.80	9.60	Large
70	66	M	8.9	219800	10.4	10.20	8.50	Normal
71	49	M	10.7	192300	12.6	13.20	10.50	Small
72	40	M	9.6	105000	13.7	15.30	9.80	Large
73	38	F	8.9	310400	9.2	8.80	6.30	Normal
74	57	M	8.6	98100	14.6	17.30	8.10	Large
75	41	M	7.3	110000	13.9	16.30	9.80	Large
76	29	M	9.6	219800	8.4	11.20	8.50	Normal
77	45	F	7.2	124000	13.7	12.80	7.00	Small

78	19	M	9.6	107000	14.8	19.60	11.20	Large
79	26	M	8.9	332500	9.6	10.60	8.10	Normal
80	25	M	10.7	276200	9.8	8.60	9.60	Normal
81	64	M	10.2	91600	14.3	15.60	8.90	Large
82	42	F	11.4	105000	13.8	16.20	9.90	Large
83	71	M	7.3	325400	9.5	9.70	6.40	Normal
84	35	M	10.4	112300	11.8	11.80	8.50	Small
85	65	F	10.7	94500	14.0	14.70	8.10	Large
86	27	M	7.1	298600	8.4	10.80	8.50	Normal
87	23	M	7.1	168700	13.6	12.60	7.10	Small
88	19	M	7.1	347000	10.5	8.40	8.50	Normal
89	35	M	9.2	104500	13.6	19.20	8.10	Large
90	44	F	7.1	93100	14.7	16.50	11.70	Large
91	56	M	9.2	197200	12.1	13.40	7.30	Small
92	21	M	7.2	289500	10.7	11.40	8.50	Normal
93	69	F	9.5	106000	14.2	15.40	9.40	Large
94	28	M	10.4	306500	9.9	10.00	6.50	Normal
95	44	F	10.2	98500	13.9	17.60	10.20	Large
96	70	M	8.9	109800	13.8	13.90	8.20	Large
97	53	F	10.6	96100	14.1	17.20	8.40	Large
98	64	M	7	162000	13.2	13.40	7.20	Small
99	43	F	9.2	324600	10.9	8.00	6.60	Normal
100	55	M	7.8	106000	13.9	18.50	9.70	Large

AGE	No. of Patients
< 25	18
26 - 45	33
46 - 65	35
> 65	14
TOTAL	100
Mean	44.52
SD	16.279

SEX	No. of Patients
MALE	70
FEMALE	30
TOTAL	100

Hb	No. of Patients
< 7.5	25
7.6 - 9.0	29
9.1 - 10.5	25
> 10.5	21
TOTAL	100
Mean	8.956
SD	1.511

Platelet count	No. of Patients
< 100000	28
100001 - 150000	29
150001 - 300000	20
> 300001	23
TOTAL	100
Mean	167799
SD	84406.458

Spleen size	No. of Patients
< 10.0	17
10.1 - 13.0	27
13.1 - 14.0	33
> 14.0	23
TOTAL	100
Mean	12.486
SD	1.973

Portal vein size	No. of Patients
< 11.0	22
11.1 - 13.0	23
13.1 - 15.0	22
15.1 - 18.0	21
> 18.0	12
TOTAL	100
Mean	13.591
SD	3.193

Splenic Vein Size	No. of Patients
< 7.0	16
7.1 - 8.0	19
8.1 - 9.0	34
9.1 - 10.0	17
> 10.0	14
TOTAL	100
Mean	8.407
SD	1.441

Varices size	No. of Patients
Large	49
Normal	30
Small	21
TOTAL	100

Varices size Vs Age								
Varices size Vs Age	< 25	26 - 45	46 - 65	> 65	TOTAL	Mean	SD	P'value
Large	8	15	17	9	49	46.918	17.008	0.138
Normal	8	10	8	4	30	39.6	16.67	
Small	2	8	10	1	21	45.952	12.726	
TOTAL	18	33	35	14	100			

Varices size Vs Sex			
	Male	Female	TOTAL
Large	33	16	49
Normal	23	7	30
Small	14	7	21
TOTAL	70	30	100
p value	0.634	Not sig	

Varices size Vs Hb					
	< 7.5	7.6 - 9.0	9.1 - 10.5	> 10.5	TOTAL
Large	7	16	14	12	49
Normal	10	10	6	4	30
Small	8	3	5	5	21
TOTAL	25	29	25	21	100
p value	0.219	Not sig			

Varices size Vs Platelet count					
	< 100000	100001 - 150000	150001 - 300000	> 300001	TOTAL
Large	28	21	0	0	49
Normal	0	0	17	13	30
Small	0	8	13	0	21
TOTAL	28	29	30	13	100
p value	< 0.001	Sig			

Varices size Vs Spleen size					
	< 10.0	10.1 - 13.0	13.1 - 14.0	> 14.0	TOTAL
Large	0	0	26	23	49
Normal	17	13	0	0	30
Small	0	14	7	0	21
TOTAL	17	27	33	23	100
p value	< 0.001	Sig			

Varices size Vs Portal vein size						
	< 11.0	11.1 - 13.0	13.1 - 15.0	15.1 - 18.0	> 18.0	TOTAL
Large	0	0	16	21	12	49
Normal	22	8	0	0	0	30
Small	0	15	6	0	0	21
TOTAL	22	23	22	21	12	100
p value	< 0.001	Sig				

Varices size Vs Splenic Vein Size						
	< 7.0	7.1 - 8.0	8.1 - 9.0	9.1 - 10.0	> 10.0	TOTAL
Large	0	3	21	14	11	49
Normal	14	4	9	1	2	30
Small	2	12	4	2	1	21
TOTAL	16	19	34	17	14	100
p value	< 0.001	Sig				