Title: NON ENDOSCOPIC PREDICTORS OF VARICEAL BLEEDING IN PATIENTS WITH LIVER CIRRHOSIS

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MD GENERAL MEDICINE

MMC,APRIL 2012

ROLE OF NON ENDOSCOPIC PREDICTORS OF VARICEAL BLEEDING IN PATIENTS WITH LIVER CIRRHOSIS

ABSTRACT

Background: Esophageal varices develop as a consequence of portal hypertension in patients with chronic liver disease and are present in approximately 50% of patients with cirrhosis of the liver. Mortality rate of an episode of esophageal varical bleeding is approximately 20% at six weeks. Predicting the grade of varices by non-invasive methods at the time of registration is likely to predict the need for prophylactic β blockers or endoscopic variceal ligation in patients with cirrhosis and portal hypertension. Therefore, the present study has been undertaken to determine the appropriateness of the various clinical, biochemical and imaging parameters in predicting the existence and also the grade of esophageal varices in cirrhosis of the liver.

Methods: This was a prospective observational study which included 70 patients with liver cirrhosis who satisfied the inclusion and exclusion criteria.All patients included in the study were subjected to detailed history, clinical examination and blood investigations like liver function tests, complete blood counts including thrombocytopaenia, renal function tests, prothrombin time, Hepatitis B surface antigen, anti-HCV antibody. Ultrasonography of the abdomen and Ascitic fluid analysis including SAAG were done. And the patients were subjected to endoscopy.

Results: Of the seventy cases studied, presence of varices increases as patients progress to decompensated liver disease (Child Pugh grade B & C). Decrease in platelet count below 100000/μL was found to be a predictor of esophageal varices in patients with cirrhosis. Increase in prothrombin time more than 25 seconds is associated with grade 2,3 varices. Value of serum ascitic albumin gradient (SAAG) more than 1.4g/dl is found to be a predictor for presence and large grade of esophageal varices .Portal vein diameter more than 1.3cm is associated with linear increase in grade of varices. Majority of patients with marked hepatic encephalopathy had grade 3 varices. In patients with serum albumin less than 3g/dl most of the patients had grade 3 varices.

Conclusion: A combination of these non invasive parameters in cirrhotic patients like platelet count, portal vein diameter, SAAG, Prothrombin time along with serum albumin, encephalopathy grade, Child pugh score for screening esophageal varices can substantially reduce the cost of health care and discomfort for patients as well as reduce burden on endoscopy units.

Keywords:

- Portal hypertension
- Cirrhosis Liver
- Esophageal varices
- Platelet count
- Prothrombin time

INTRODUCTION

Esophageal varices develop as a consequence of portal hypertension in patients with chronic liver disease and are present in approximately 50% of patients with cirrhosis of the liver. The grade of esophageal varices often correlates with the severity of liver disease. While approximately 85% of individuals with Child Pugh C cirrhosis have varices, they are present in only 45% those with Child-Pugh A cirrhosis.[5]The rate of development of new varices and increase in grades of varices is 8% per year; the former is largely predicted by a hepatic venous pressure gradient (HVPG) exceeding 10 mm Hg[6,7]and the latter by the presence of decompensated cirrhosis, alcohol etiology and red wale signs[11].

Large size varices, the presence of red flag signs, severe liver disease and portal pressure greater than 12 mm Hg[8,9] predict greater risk of bleeding. Mortality rate of an episode of esophageal varical bleeding is approximately 20% at six weeks.[10,11].

Predicting the grade of varices by non-invasive methods at the time of registration is likely to predict the need for prophylactic β blockers or endoscopic variceal ligation in patients with cirrhosis and portal hypertension. Therefore, the present study has been undertaken to

determine the appropriateness of the various clinical, biochemical and imaging parameters in predicting the existence and also the grade of esophageal varices in cirrhosis of the liver.

Its prevalence varies from 20-30% in patients with cirrhosis[8]. After varices have developed, one-third of all patients die of bleeding gastro-esophageal varices[13]. The risk of initial bleeding from varices is 25% to 35% within 2 years, with most first-bleeding episodes occurring within one year after detection of varices[10]. The reported mortality from the first episode of variceal bleeding in western studies ranges from 17% to 57%[15] as compared to 5-10% mortality reported in our population [16].

The Baveno III Consensus Conference on portal hypertension recommended that when liver cirrhosis is diagnosed ,all cirrhotic patients should be screened for the presence of esophageal varices.[14] Repeat endoscopy is recommended at 1–2 years interval in patients with small varices to evaluate the development or progression of varices and 2–3 years interval in patients without varices [19].However, this approach has two major limitations.

Endoscopy is an invasive procedure and secondly the cost effectiveness of endoscopy is also questionable[19] as only 9-36% patients with cirrhosis are found to have varices on screening endoscopy. It may

be more cost-effective when only high risk patients are routinely screened for the presence of varices so as to reduce the procedure cost and increasing burden of endoscopy units. There are factors that predict risk for first variceal hemorrhage[20]. Certain clinical, biochemical and ultrasonographic parameters either singly or in combination have good predictive power for non-invasively assessing the risk of bleeding from varices. However, the factors that predict the presence of varices are not as well defined. Identification of non-invasive predictors of esophageal varices will help us to carry out upper gestrointestinal endoscopy in selected group of patients thus avoiding unnecessary intervention and expenses, at the same time not missing high risk patients with increased chances of bleeding.

AIMS & OBJECTIVES

1. To identify non invasive parameters for prediction of esophageal varices in newly diagnosed patients with cirrhosis, without previous upper gastro intestinal bleed.

2. To assess the Predictive value of Portal vein diameter, Platelet count, SAAG (Serum ascitic albumin gradient),in predicting esophageal varices in cirrhotic patients.

3. To assess the usefulness of prothrombin time in predicting esophageal varices in patients with cirrhosis.

4. To develop parameters for identifying candidates for upper gastro intestinal endoscopic screening.

REVIEW OF LITERATURE

CIRRHOSIS

Definition

Cirrhosis is the end-stage manifestation of every chronic progressive liver disease. It is a diffuse process characterized by loss of hepatic parenchyma, formation of fibrous septa and structurally abnormal regenerative nodules, resulting in the distortion of the normal architecture and of gross vascular anatomy and microcirculation (21,22).

Epidemiology

Liver cirrhosis is a leading cause of death worldwide. It is the end result of a long-lasting process, usually clinically silent and unnoticed by the patient and the physician for years. In the past, up to 30–40% of cases have been discovered at autopsy (23). Due to the widespread use of imaging techniques, such as ultrasound and computed tomography it may be assumed that currently most cirrhotic livers are discovered earlier.

Etiology

Causes of liver cirrhosis

Infectious

Virus hepatitis B, C, D, Schistosomiasis

Autoimmune

Autoimmune hepatitis,Primary biliary cirrhosis, Autoimmune cholangitis, Overlap syndromes.

Metabolic-toxic

Ethanol, Nonalcoholic fatty liver disease (insulin resistance; metabolic syndrome),Indian childhood cirrhosis.

Drug-induced

CCl4, arsenic, methotrexate, isoniazid, amiodarone, a-methyldopa.

Genetic–hereditary

Hereditary hemochromatosis, Wilson's disease,a1-antitrypsin-deficiency, Porphyria cutanea tarda, Glycogen storage diseases, Galactosemia, Tyrosinemia, Urea cycle disturbances, Abetalipoproteinemia, Cystic fibrosis.

Biliary

Secondary biliary cirrhosis (gallstones, strictures),Primary sclerosing cholangitis, Ischemic cholangiopathy, Ductopenia, bile duct atresia, Alagille's syndrome.

Vascular

Chronic right heart failure ,Constrictive pericarditis, Budd-Chiari syndrome, Sinusoidal obstruction syndrome (venoocclusive disease),Hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease).

Cryptogenic

Pathogenesis

The following pathophysiological mechanisms are important in the development of liver cirrhosis

- Hepatocyte death with loss of hepatic parenchyma
- Fibrosis
- Changes in cell growth (hyperplasia, regeneration) and
- Vascular and circulatory alterations.

Cell Death

Chronic loss of hepatocytes is regarded as the primary stimulus and perpetuating factor in the development of liver cirrhosis. In order for cirrhosis to develop, liver cell loss must be sustained and long-lasting.

Liver injury may be mediated by immune mechanisms (for example cytotoxic lymphocytes attacking virally infected hepatocytes), inflammatory reactions (mediated by neutrophils and macrophages) or toxic factors (for example via oxidative stress and calcium-mediated cytotoxicity).

Fibrosis and Circulatory Disturbances

Fibrosis plays a crucial role in nodular transformation of the liver. However, it represents just one facet of liver cirrhosis and must not be equated with cirrhosis [24].Isolated fibrosis, even if extensive, does not necessarily result in cirrhosis. Cirrhosis is more than just widespread liver fibrosis. Further pathogenetic factors, such as liver cell loss and circulatory disturbances, must supervene in order for cirrhosis to develop. The development of liver cirrhosis is accompanied by a marked increase in collagen content and by deposition of extracellular matrix, both produced mainly by stellate cells, which are activated and transformed into myofibroblasts. Progressive disease is characterized by increasing fibrosis with fibrous tissue surrounding islands of hepatic parenchyma, thus leading to the formation of pseudolobuli. Fibrous septa may form bridges between portal tracts (portal-portal septa) and between portal tracts and central veins (portal-central septa). These remodeling processes are accompanied by hemodynamic alterations. Vascular channels within

the fibrous septa lead to the establishment of intrahepatic vascular shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver, which are significant for the development of the sequelae of liver cirrhosis.

Disturbances in Hepatocyte Growth and Proliferation

The proliferation of hepatocytes in a cirrhotic liver is viewed as a reactive regenerative process after cell loss. Regeneration, however, is incomplete, since complete restoration of normal hepatic architecture does not occur and the parenchymal defects are replenished by surrogate tissue. Generally, with advancing cirrhosis and increasing Child-Pugh stage the proliferation of hepatocytes decreases. Nodular transformation in cirrhosis of biliary origin is not pronounced until the late stages of the disease. In alcoholic cirrhosis, hepatocyte proliferation is inhibited which possibly contributes to the micronodular aspect of alcoholic cirrhosis.

Pathology

A simple, reproducible and comprehensible, macroscopical description of cirrhosis is its classification according to the size of nodules, specifically

- Micronodular
- Macronodular, and

- Mixed forms.

Macroscopical Findings

Micronodular Cirrhosis

A liver cirrhosis in which nearly all nodules measure less than 3mm in size. Typical causes for micronodular cirrhotic transformation are chronic alcohol abuse, bile duct obstruction, chronic venous outflow tract obstruction, hereditary hemochromatosis, Indian childhood cirrhosis.

Macronodular Cirrhosis

Macronodular cirrhosis is characterized by nodules greater than 3 mm in size. Liver cirrhosis due to chronic viral hepatitis and autoimmune hepatitis is macronodular. Typical end-stage macronodular cirrhosis is small and hard (“shrunken liver”).

Mixed Forms

If the number of micronodules roughly equals that of macronodules, a mixed form of cirrhosis is said to be present. During the course of the disease micronodular cirrhosis may give way to the macronodular form. Viral superinfections, autoimmune processes and circulatory disturbances account for this transformation. Transformation of macrondular to micronodular cirrhosis does not occur.

DIAGNOSIS

Clinical Manifestations

Physical findings in patients with liver cirrhosis

Ascites : Portal hypertension, Hypoalbuminemia

Hepatomegaly**:** Facultative; small liver in posthepatitic cirrhosis

Splenomegaly : Portal hypertension

Skin Changes

Glazing lips and tongue	:	papillary atrophy
Oral rhagades	:	Zinc deficiency
Spider angiomas	:	Central arteriole with radiating vessels due to increased estrogen
"Banknote" skin	:	Skin atrophy due to zinc deficiency
Palmar erythema	:	↑ estrogen
Dupuytren's disease	:	Palmar fibromatosis; occurs predominantly in alcoholics
Jaundice	:	Advanced hepatocellular failure
Purpura	:	Vascular fragility, thrombocytopenia
Scratch signs	:	Pruritus
Xanthelasma	:	Chronic biliary/cholestatic diseases
Caput medusa	:	portal hypertension

Nail Changes

White nails: Predominantly thumb and index finger

Clubbed fingers/hour glass nails : In hepatopulmonary syndrome

Endocrine Changes

Feminization in men, Abdominal baldness, ↓ Terminal hair in men, Testicular atrophy.

Gynecomastia : Increased ratio of estrogen to free androgen due to decreased testosterone production, and increased peripheral conversion of testosterone to estradiol.

Amenorrhea

Foetor hepaticus : Intestinal methylmercaptans

Muscle atrophy : Cytokines; malnutrition

Parotid gland swelling**:** Malnutrition; predominantly in alcoholics.

Laboratory Findings

Aminotransferases : Viral cirrhosis: ALT > AST

Alcoholic cirrhosis: AST > ALT

Parameters of Cholestasis: Biliary cirrhosis: ↑ALP and gGT

Bilirubin: Serum level rises in advanced stage of cirrhosis

Choline esterase: Parameter of hepatocyte synthetic capacity. Serum level decreases in advanced stage of cirrhosis.

Prothrombin time: Parameter of hepatocyte synthetic capacity. Prolonged in advanced stage of cirrhosis

Albumin: Parameter of hepatocyte synthetic capacity. Serum level decreases in advanced stage of cirrhosis

g-globulins Serum levels are increased with a broad based g-band on serum electrophoresis in 80% of patients with cirrhosis. g-globulins make up for 20–35% of all proteins.

*1)*Autoimmune hepatitis: g-globulins increased in all patients. g-globulins > 50% of total protein.

*2)*Primary biliary cirrhosis: ↑IgM

*3)*Alcoholic cirrhosis: ↑IgA

*4)*Viral cirrhosis: ↑IgG

Blood count : Mild normo- to macrocytic anemia. Leukopenia, thrombocytopenia (hypersplenism)

Ammonia: Serum levels increased in advanced stage of cirrhosis. Levels do not correlate with signs and symptoms of hepatic encephalopathy

Branched-chainamino acids: Serum levels decreased in advanced stage of cirrhosis

Aromatic aminoacids: Serum levels increased in advanced stage of cirrhosis**.**

Imaging Techniques

Imaging techniques play a leading role in the diagnosis of early stages of cirrhosis and in detecting focal (neoplastic) alterations in cirrhotic livers. Sonography, CT-scanning and magnetic resonance imaging are the prime imaging modalities in the diagnosis of cirrhosis.

Course and Prognosis

The natural history of cirrhosis is characterized by a "compensated phase", defined by the absence of complications, such as ascites, variceal bleeding, encephalopathy and by preserved synthetic and excretory functions(albumin $\geq$ 3.5 g/dL, INR $\leq$ 1.5, total bilirubin $\leq$ 1.5 mg/dL), followed by a rapidly progressive phase marked by increasing portal pressure and declining liver function, resulting in the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy and/ or jaundice. The development of any of these complications defines the transition from a compensated to a "decompensated phase". Transition from a compensated to a decompensated stage occurs at a rate of 5–7% per year. During a 10 year follow up of compensated viral cirrhosis, HCC develops in 21–32% of cases, followed by ascites (19.5–23%), jaundice (17%), upper gastrointestinal bleeding (4.5–6%), and encephalopathy (1–2%) [25, 25, 26]. Survival of patients with compensated cirrhosis is significantly longer than that of decompensated patients with median

survival times of 12 years and 2 years, respectively. The mortality risk increases as the stage and the number of complication episodes increases [27,28].

Child-Pugh Classification of Cirrhosis

Factor	Units	1	2	3
Serum bilirubin	mol/L mg/dL	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30-35 3.0-3.5	<30 <3.0
Prothrombin time	seconds prolonged INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

Scoring occurs by adding the points for the various parameters.

5–6 points: Child A (well compensated disease)

7–9 points: Child B (significant loss of hepatic function)

10–15 points: Child C (decompensated disease)

PORTAL HYPERTENSION

Portal hypertension is defined as the elevation of the hepatic venous pressure gradient (HVPG) to >5 mmHg. Portal hypertension is caused by a combination of two simultaneously occurring hemodynamic processes: (1) increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis and regenerative nodules, and (2) increased splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed. Portal hypertension is directly responsible for the two major complications of cirrhosis: variceal hemorrhage and ascites. Varices are dilated, often tortuous veins. They occur most often in the distal esophagus and in the gastric fundus in patients with portal hypertension. Duodenal and rectal varices rarely occur and are of minor clinical importance.

Epidemiology

Two thirds of all patients with liver cirrhosis with increasing portal hypertension develop esophageal varices and a portal hypertensive gastropathy . At the time of diagnosis of cirrhosis 60% of patients with decompensated and 30% of those with compensated cirrhosis already have varices. Approximately 10–15% of patients with esophageal varices concomitantly also have gastric fundal varices

The causes of portal hypertension are usually subcategorized as prehepatic, intrahepatic, and posthepatic.

Classification of Portal Hypertension

Prehepatic

Portal vein thrombosis

Splenic vein thrombosis

Massive splenomegaly (Banti's syndrome)

Hepatic

Presinusoidal

Schistosomiasis

Congenital hepatic fibrosis

Sinusoidal

Cirrhosis—many causes

Alcoholic hepatitis

Postsinusoidal

Hepatic sinusoidal obstruction (venoocclusive syndrome)

Posthepatic

Budd-Chiari syndrome

Inferior vena caval webs

Cardiac causes

Restrictive cardiomyopathy

Constrictive pericarditis

Severe congestive heart failure

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Anatomy, Etiology and Pathophysiology

The veins of the esophageal wall consist of a subepithelial and a submucous plexus. Both plexus communicate through perforating veins. In the distal, precardiac esophagus the veins are mainly subepithelial. Esophageal varices are fed by the gastric coronary veins and the short gastric veins.

The variceal pressure depends on the pressure gradient between the portal vein and the right atrium and varies with respiration. The mean variceal pressure is 20–25 cm H2O. The most important pathogenetic factor in the development and increase in size of gastroesophageal varices is portal hypertension. The hepatic venous pressure gradient (HVPG), determined by the difference between wedged and free hepatic venous pressure, is a good estimate of portal pressure. Varices start developing with HVPG values ≥10–12 mmHg [29].With increasing HVPG values both the transmural variceal pressure and the variceal wall tension rise, and the risk of bleeding increases [30].

Rarely esophagogastric varices may also develop in the absence of portal hypertension. Thus, for example, obstruction of the superior vena cava at the level of junction with the azygos vein, by increasing the outflow resistance of the azygos vein may lead to the development of isolated varices in the proximal esophagus (“downhill-varices”).

Mediastinal tumors, bronchial and esophageal cancer, goiter, fibrous adhesions or inadvertent ligation of vessels during thyroid resection may cause “downhill-varices”. Isolated fundal varices are usually due to an isolated block in the splenic vein.

Diagnosis

The diagnosis of subepithelial varices is made endoscopically. The dilated vessels protrude to a variable degree into the lumen, and their size and the appearance of the vessel wall may be assessed endoscopically. Both have prognostic significance. These aspects of the varices forms the basis for classifying them into different grades . The size of the varix must be graded.

Grade 1 (F1): the varices can be depressed by the endoscope.

Grade 2 (F2): the varices cannot be depressed by the endoscope.

Grade 3 (F3): the varices are confluent around the circumference of the oesophagus.

Laboratory findings, such as thrombocytopenia (<90,000/mL), splenomegaly, platelet count/spleen diameter ratio ,diameter of portal vein (≥13 mm), lowered serum albumin and FibroTest have been proposed as noninvasive predictors of the presence of esophageal varices [30,31]. These parameters, however, especially when esophageal varices

are still small, are unreliable and do not substitute for endoscopy. In subjects with liver cirrhosis the risk of having varices increases with decreasing platelet counts,increasing bilirubin concentration in serum, and rising INR.The probability of having medium or large varices at platelet counts >150,000/mm3 has been reported to be negligible.

Course and Prognosis

In patients with cirrhosis, esophageal varices develop at a rate of approximately 5–12% per year. If on initial endoscopy small (<5 mm) varices are present, the rate of progression to large varices is approximately 10–15% per year [33, 34].Varices may rupture and bleed. Approximately one third to one half of all patients with esophageal varices bleed at least once during their lifetime. Up to 25% of patients with newly diagnosed and untreated esophageal varices will bleed within the first 2 years after diagnosis.

The risk of hemorrhage primarily depends on variceal size. It is 7% within 2 years in patients with small varices (diameter < 5 mm) and rises to 30% in those with large varices (diameter > 5 mm). Acute variceal bleeding always is a life threatening event and the risk of dying from the first variceal hemorrhage is approximately 20% [35,36].Without treatment, recurrent bleeding is the rule which in up to 20% of cases may occur as a fulminant hemorrhage from fundal varices. Rebleeding occurs

within the first 6 weeks in 30% of cases and within 1 year after the first bleed in 70% of patients. The earlier the recurrence, the higher the mortality risk.

The MELD score (≥18) is a good predictor of short-term (6 weeks to 3 months) mortality among cirrhotic patients at first episode of bleeding from esopahgeal varices [37]. Measurement of the HVPG obtained within 48 h of admission also may predict efficacy of treatment and short-term prognosis. However, it is not universally available and simple clinical variables, such as systolic blood pressure, Child-Pugh score and etiology of cirrhosis may be used instead as accurate predictors of short-term prognosis. Due to early and combined use of pharmacological and endoscopic therapies, and short-term antibiotic prophylaxis, in-hospital mortality of patients with cirrhosis and variceal bleeding decreased continuously over the past two decades [38].

Predictors of Variceal Bleeding

Since variceal bleeding is associated with a high mortality risk, it is important to define predictors and to assess the risk of bleeding in order to establish effective prophylactic measures. The risk of variceal hemorrhage depends on the severity of liver disease (MELD score; Child-Pugh score) and rises with decreasing liver function. The size of varices,

variceal pressure and the appearance of the surface of the vessel wall are important predictors of variceal bleeding.

Large vessels with high wall tension are more likely to bleed than small ones [38,39,40]. The wall tension correlates directly with transmural pressure and the diameter of a vessel and indirectly with wall thickness. It increases with rising portal pressure, increasing vessel size and decreasing wall thickness. Thus, not surprisingly, a large vessel with a thin wall will exhibit a higher wall tension than a small vessel with a thick wall and will therefore be more likely to rupture.

The surface appearance of the vessel wall may yield important information regarding impending hemorrhage. Diffuse redness of the vessel, red color signs, such as “cherry red spots” and “red wale marks” (correspond to microtelangiectasia of the varix) and hemocystic spots looking like blood blisters (>4 mm; saccular aneurysm projections), are all thought to indicate a high risk for bleeding . A “white nipple sign” on a varix represents a platelet-fibrin plug and indicates previous bleeding but is not predictive of rebleeding [41].Every third patient with variceal hemorrhage, however, does not present these endoscopic signs.

Thus, hemodynamic parameters are preferable in predicting the risk of variceal bleeding. The level of HVPG is a reliable and independent indicator for esophageal variceal bleeding. The normal value

of HVPG is 5 mmHg. Portal hypertension starts at a HVPG >5 mmHg, but values of >10–12 mmHg are clinically significant. With a HVPG <10–12 mmHg, varices do not develop, and preexisting varices do not bleed. Once HVPG increases to >12–16 mmHg, the risk of bleeding is high, but the degree of portal pressure elevation over 12 mmHg does not correlate directly with bleeding.

Independent risk factors for esophageal variceal hemorrhage:

1)Variceal characteristics

- Size
- Wall tension
- Intravariceal pressure
- Red colour signs

2)Liver function (Child-Pugh-score; MELD score)

3)Continuing alcohol abuse

Prognostic significance of endoscopic and functional criteria for variceal bleeding:

Endoscopic criteria	**Bleeding risk(%)**
1)Red wale markings	
Absent	19
Mild	33
Moderate	39
Severe	80
2)Variceal size	
Small < 3 mm	18
Medium 3–5 mm	29
Large > 5 mm	49

Endoscopic criteria	Bleeding risk(%)
3)Cherry-red-spots	
Absent	23
Mild	32
Moderate	40
Severe	55
4)Liver function (Child-Pugh-Score)	
Child A	17
Child B	31
Child C	39

Portal vein diameter

It had been reported that portal vein diameter was an independent predictor for the presence of varices (42). However, few data are available about the relationship between portal vein diameter and LEV. Studies showed that portal vein diameter was the second most important predictor for LEV in patients with a spleen width of ≤44.5 mm. However, it did not play an important role in predicting LEV in patients with spleen width of > 44.5 mm.

Prothrombin time

Prothrombin time is considered a marker of hepatocellular dysfunction. As portal hypertension is a consequence, in part, of the generalized vasodilation and the hyperdynamic splanchnic and systemic circulatory state, the degree of hepatic function likely affects the

development of portal hypertension via humoral factors and, therefore, the development of varices. Moreover, the degree of liver fibrosis is related to liver function and fibrosis can directly affect portal hypertension. It has been reported that serum fibrosis markers can detect LEV with a high accuracy, though several studies showed prothrombin time was associated with LEV on univariate analysis (43).

SAAG and its association

The development of the serum ascites-to-albumin gradient (SAAG) has replaced the description of exudative or transudative fluid. When the gradient between the serum albumin level and the ascitic fluid albumin level is >1.1g/dL, the cause of the ascites is most likely due to portal hypertension; this is usually in the setting of cirrhosis. When the gradient is <1.1 g/dL, infectious or malignant causes of ascites should be considered. When levels of ascitic fluid proteins are very low, patients are at increased risk for developing SBP.

SAAG appears to retain its predictive value despite diuretics, infusion of albumin, therapeutic paracentesis or infection in the ascitic fluid. The finding of high SAAG denotes high chances of presence of esophageal varices in patients due to cirrhosis.

Prophylaxis and Therapy

The management of patients with esophageal varices aims at three goals:

- Prevention of first variceal hemorrhage (primary bleeding prophylaxis)
- Treatment of acute variceal hemorrhage, and
- Prevention of recurrent variceal hemorrhage (secondary bleeding prophylaxis)

The outcome of the patients critically depends on the success of these measures. There is an increased array of therapeutic options including pharmacological, endoscopic, mechanically compressing (balloon tamponade), radiologic-invasive (TIPSS) and surgical techniques which may be applied according to the clinical situation[44, 45].

Currently β-adrenergic blocking agents, nitrates, vasoconstrictors (e.g. terlipressin) and growth hormone inhibitors, such as somatostatin and octreotide are important. Endoscopic techniques encompass sclerotherapy and band ligation, surgical procedures include the creation of various portal-systemic shunts or the staple-gun transection of the esophagus as a salvage procedure for active variceal bleeding after failure of acute endoscopic therapy.

“Preprimary” Prophylaxis

“Preprimary” prophylaxis refers to the prevention of the development of esophagogastric varices in patients with liver cirrhosis. The best way to achieve this goal is to successfully treat the underlying disease that leads to cirrhotic transformation. Beta-blockers are ineffective in preventing the development of varices in patients with cirrhosis [46]. For cirrhotic patients without varices, screening endoscopy every 3 years, or sooner if liver function deteriorates, is recommended.

Primary Bleeding Prophylaxis

Because every episode of variceal hemorrhage is associated with a high mortality rate, patients with cirrhosis and varices should be treated before the first bleeding occurs. Primary prophylaxis refers to the prevention of the first variceal hemorrhage and relies on measures like

- Lowering portal venous pressure, and
- Obliterating varices

The first goal can be achieved by pharmacotherapy, the latter by endoscopic techniques.

Pharmacotherapy. Nonselective b-blockers reduce portal-venous pressure by reducing cardiac output and splanchnic blood flow. In

addition, splanchnic vasoconstriction is enhanced by an uninhibited activation of α-receptors. Nonselective β- adrenergic antagonists are the mainstay of pharmacologic prevention of a first esophageal variceal hemorrhage [47]. The individual dose of β-blockers must be determined for each patient individually by adjusting the dose weekly with the goal of reducing heart rate by 25% from the baseline value falling below a rate of 55/min or a systolic blood pressure of 90 mmHg (adjust to the maximal tolerated dose).

Treatment with β-blockers is lifelong. Only patients in whom β-blockers lead to a durable decrease of HVPG < 12 mmHg or > 20% from baseline benefit from treatment. Falls in HVPG > 20% are associated with lower mortality [48]. In addition, reduction of HVPG also correlates with a reduced risk of spontaneous bacterial peritonitis or bacteremia . The β-blocker of choice is propranolol, 80–160 mg p.o. daily in 3–4 divided doses; alternatively nadolol 20–240 mg p.o. daily can be used. Nadolol is less lipophilic than propranolol and does not cross the blood–brain barrier. It is better tolerated and leads to less drug withdrawal (4%) due to side effects compared with propranolol (up to 30%).The use of b-blockers also seems warranted in patients, with fundal varices as fundal and esophageal varices usually occur together.

Depending on Child-Pugh class, the number of patients needed to treat in order to prevent one bleeding episode is 5–14. The primary prophylactic effect of β-blockers seems to be more pronounced in patients with large varices and a high Child-Pugh score, which means that in order to achieve the same effect, fewer patients need to be treated. Primary prophylaxis with propranolol is cost-effective, even if compared with no therapy [49].Thus, despite their effectiveness in some patients, HVPG does not fall < 12 mmHg or ≥20% from baseline in up to two thirds of patients treated with β-blockers despite adequate β-blockade.

Possibly Doppler patterns of splanchnic hemodynamics can serve as a non-invasive clue for the a prior identification of good and poor responders to β-blockers. Cirrhotic patients who responded poorly to nadolol, in contrast to good responders, showed a pronounced arterial splanchnic vasodilatation at a baseline echo-color-Doppler study. Therefore, in up to two thirds of patients treated with β-blockers and in 15–25% with contraindications to β-blocker therapy or those who cannot tolerate the required doses because of untoward side effects, the question as to an alternative pharmacologic primary prophylaxis arises.

Long-acting oral nitrates, isosorbide mono- or dinitrate, because of their vasolidating effect lower both the systemic, splanchnic and portal pressure. Combined with β-blockers, the drop in pressure is slightly more

pronounced than with sole β-blocker therapy. Monotherapy with nitrates may impair renal function and worsen a pre-existing ascites. There are even worries that nitrates may increase the mortality rate. Therefore, nitrates should not be used as monotherapy in the prophylaxis of esophageal variceal bleeding. Carvedilol and the long-acting somatostatin analogue octreotide also reduce HVPG but both substances are not used in the long-term prevention of esophageal hemorrhage.

Endoscopic Techniques. Endsocopic multiband ligation (EVL) of esophageal varices is safe and effective. It reduces the rate of first bleeding to 30–40% and the hemorrhage related mortality to 30% within 2 years. Patients with compensated Child-Pugh class A cirrhosis benefit most from ligation. Most authors agree that in patients with high-risk esophageal varices, EVL is more effective than propranolol for the primary prevention of variceal bleeding [50]. However, there are also data showing that in patients in whom propranolol lowers HVPG effectively (<12 mmHg or a decrease of >20%), its efficacy is comparable to ligation .

If quality of life is considered, then EVL is similarly cost-effective as β-blockade .EVL is usually performed once every 2 weeks until varices are eradicated. Recent data show that EVL yields good results even if performed at bi-monthly intervals. Postbanding ulcers occur

regularly and usually are asymptomatic. Proton pump inhibitors may reduce their size. Endoscopic obliteration of varices is followed by lifelong treatment with β blockers. Endoscopic injection sclerotherapy is inferior to EVL and should not be performed in primary prophylaxis of esophageal varices.

Therapy of Acute Variceal Hemorrhage

Patients with acute variceal bleeding are managed in an intensive care unit. The first goal always is to secure vital functions. In somnolent patients, especially before performing the initial diagnostic endoscopy, endotracheal intubation is strongly advised. Erythromycin infusion (250 mg) prior to endoscopy may improve stomach cleansing and quality of endoscopic examination in these patients. Prior to all hemostatic measures, stabilization of cardiocirculatory function is mandatory aiming at a systolic blood pressure of approximately 100mmHg and a haemoglobin value not more than 10 g/dL. Higher blood pressure and Hb values lead to an increase in portal pressure with a higher risk of recurrent bleeding.

Pharmacotherapy

In suspected acute variceal bleeding vasoactive drugs should be started as soon as the diagnosis is made, even before diagnostic endoscopy. Vasoactive drug therapy should be maintained for 2–5 days.

Vasopressin lowers portal pressure by inducing contraction especially of the smooth muscle of splanchnic arterioles. However, vasopressin also causes systemic vasoconstriction which may lead to serious side effects, such as malignant cardiac arrhythmias, myocardial infarction, intestinal ischemia, cerebrovascular ischemia and local tissue necrosis.

Terlipressin, a synthetic analog of vasopressin, Compared to the short acting vasopressin, the action of terlipressin is prolonged to 3–4 h and, most importantly, it does not show the dreaded side effects of vasopressin Possibly the most important action of terlipressin is its beneficial effect on renal function in patients with the hepatorenal syndrome.

Somatostatin has an effect comparable to terlipressin. It reduces splanchnic blood flow, has only few side effects (hyperglycemia) and is well tolerated.**Octreotide,**a long acting analog of somatostatin, has similar efficacy.

Patients with marked hepatic coagulopathy may benefit from fresh frozen plasma.

Bacterial infections in cirrhotic patients are associated with failure to control bleeding and represent an independent risk factor for recurrent

hemorrhage [52]. Antibiotic prophylaxis is an integral part of therapy for patients presenting with variceal bleeding and should be instituted from admission.

Fluoroquinolones (ofloxacin, ciprofoxacin, levofloxacin, norfloxacin) or beta-lactams (amoxicillin-clavulanate, cephalosporins) are effective and reduce the risk of bacterial infections by about 30% and mortality risk by about 9% .Intravenous ceftriaxone (1 g qd) seems to be more effective than oral norfloxacin (400 mg bid) in the prophylaxis of bacterial infections in patients with advanced cirrhosis and hemorrhage .

Endoscopic Techniques. Endoscopic therapy has a success rate of 90%. It is the treatment of choice in patients with acute variceal hemorrhage and should be performed immediately after initial diagnostic endoscopy. Sclerotherapy and urgent band ligation are the endoscopic techniques available to stop acute variceal hemorrhage. Variceal band ligation is superior to sclerotherapy.

Balloon Tamponade. If endoscopic emergency treatment is not readily available, if the bleeding is too rapid to permit endoscopy, or if medical and endoscopic therapy fails to control bleeding (for example, because of insufficient visualization for band ligation), balloon tamponade may achieve a satisfactory compression of the esophagogastric bleeding site in 80–90% of cases. The application of

balloon tamponade serves to gain time until definite hemostasis can be achieved. Because pressure ulcers may develop rapidly, tubes must be deblocked not later than 12 h after placement and then every 4–6 h for a period of 10 min. Complete large volume paracentesis lowers intravariceal pressure and improves respiratory function by lowering the diaphragm.

TIPSS and Surgical Shunts:

If acute variceal bleeding is refractory to all of the above measures, surgical or nonsurgical shunting of portal blood to the systemic circulation is indicated as a salvage procedure. Both methods achieve acute hemostatic success rates of 90–100%.

Prevention of Recurrent Variceal Hemorrhage

Without adequate secondary prophylaxis approximately two thirds of patients rebleed within 6 weeks after the first variceal hemorrhage. Prevention of recurrent variceal hemorrhage is mandatory and is performed by combining band ligation with nonselective b-adrenergic blocking agents. The additional administration of β -blockers in patients in whom esophageal varices have been obliterated by banding further reduces mortality rate from 18% to 7% . The results of combining β-

blockers (propranolol or nadolol) with long-acting nitrates (isosorbide mononitrate) in secondary prophylaxis are controversial.

Shunt procedures should only be viewed as reserve techniques in secondary prophylaxis. Their excellent effect on portal hypertension and on lowering the rate of rebleeding is counterbalanced by the high encephalopathy rate. Surgical shunts should only be considered in recurrent bleeding in Child-Pugh class A patients.

MATERIALS AND METHODS

Study Design: Prospective Observational Study.

Study Population:

Patients admitted with complaints suggestive of liver cirrhosis in Medical Ward, GGH, Chennai, were taken into Study.

Inclusion Criteria:

Patients with cirrhosis of liver without any past history of upper (or) lower gastrointestinal bleed who were diagnosed based on history, physical findings, biochemical parameters, sonography and endoscopic methods.

Exclusion criteria;

1) Patients with history of upper or lower gastro intestinal bleed.

2) Patients on previous/current treatment with drugs for portal hypertension.

3) Patients who had undergone procedures for esophageal varices like banding , sclerotherapy injection (or) shunts.

4) Patients with esophageal varices due to extra hepatic cause.

Ethical Clearance: Obtained.

Informed Consent: Obtained from all patients.

Methodology

A total of 70 patients with liver cirrhosis were identified during the period of February 2011 to December 2011, according to the above criteria and were included in the study. All patients included in the study were subjected to detailed history, clinical examination and blood investigations.

History includes presence of jaundice, abdominal distension, pedal edema,oliguria, haemetemesis, malena, features suggestive of coagulopathy like gum bleed or hematuria included. Clinical examination of the study population was focussed on the presence of jaundice, ,clubbing,dupuytrens contracture, loss of secondary sexual charecters, anemia, gynaecomastia, parotid enlargement, spider naevi, palmar erythema , testicular atrophy hepatic flap, splenomegaly and ascites, were noted.

Laboratory Investigations:

All patients underwent biochemical tests, like liver function tests (serum bilirubin, ALT, AST, ALP, serum albumin), complete blood counts (haemoglobin, PCV, total and differential count, thrombocytopaenia), renal function tests(blood urea, serum creatinine), prothrombin time. Hepatitis B surface antigen and anti-HCV antibody were also investigated in all blood samples. ultrasonography of the abdomen was done to confirm the presence of cirrhosis and to find portal vein diameter, ascites and presence of collaterals and Ascitic fluid analysis including SAAG in patients with ascites.

Chest X-ray and ECG were taken for all patients. Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them.

Statistical Analysis:

Statistical analysis was done with

1. SPSS software version 19

2. Microsoft Excel 2010.

Conflicts of interest: None

OBSERVATION & RESULTS

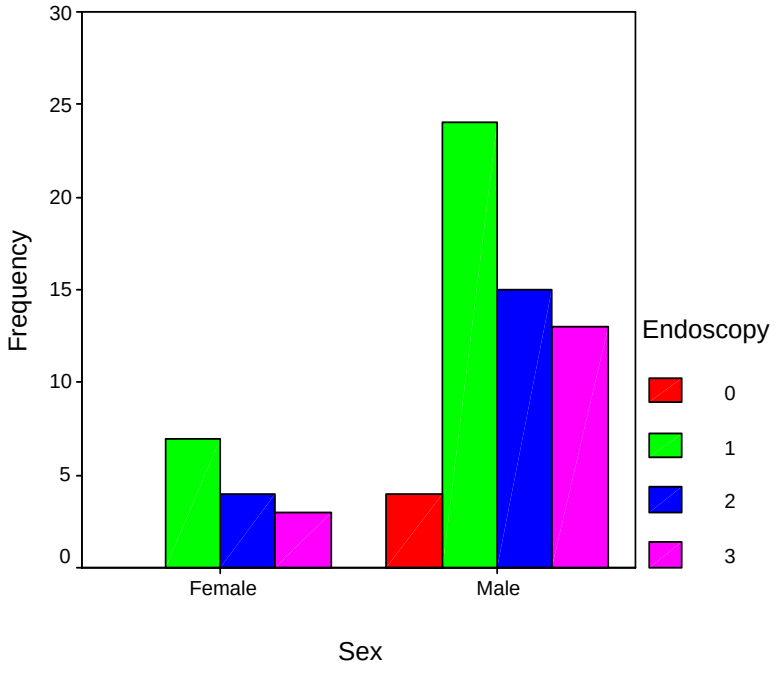
RELATION BETWEEN SEX AND GRADE OF VARICES

Sex * Endoscopy Cross tabulation(Table 1)

SEX			Endoscopy-Grade of varices				Total
			0	1	2	3	
	F	No. of patients	0	7	4	3	14
		% within Sex	0	50.0	28.6	21.4	100.0
		% within Endoscopy	0	22.6	21.1	18.8	20.0
	M	No. of patients	4	24	15	13	56
		% within Sex	7.1	42.9	26.8	23.2	100.0
		% within Endoscopy	100.0	77.4	78.9	81.3	80.0
Total		No. of patients	4	31	19	16	70
		% within Sex	5.7	44.3	27.1	22.9	100.0
		% within Endoscopy	100.0	100.0	100.0	100.0	100.0

P=0.763

No significant gender difference in the distribution of grade of varices was found in our study.

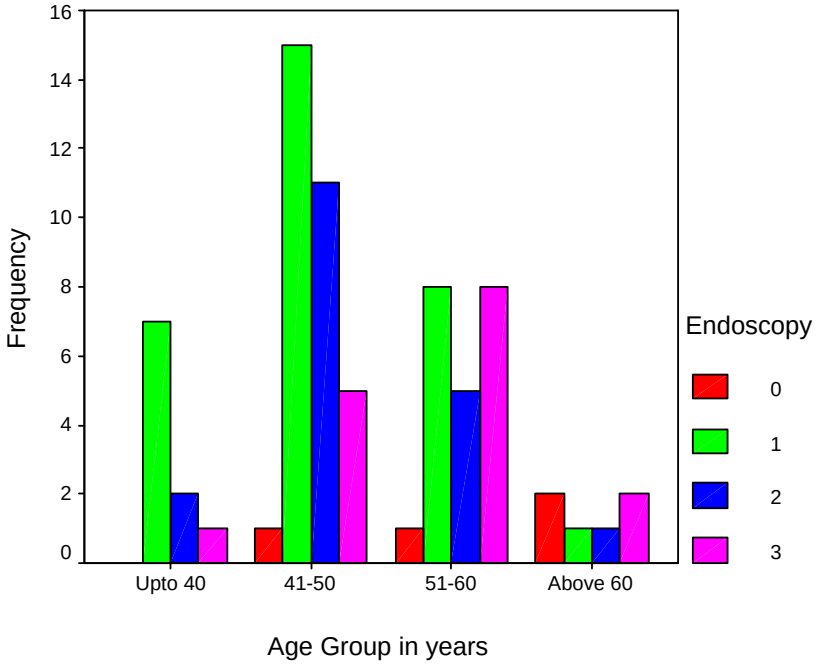


RELATION BETWEEN AGE AND GRADE OF VARICES

Age Group in years * Endoscopy (Table 2)

Age Group in years		Endoscopy-Grade of varices				Total
		0	1	2	3	
Upto 40	No. of patients	0	7	2	1	10
	% within Age Group in years	0	70.0	20.0	10.0	100.0
	% within Endoscopy	0	22.6	10.5	6.3	14.3
41-50	No. of patients	1	15	11	5	32
	% within Age Group in years	3.1	46.9	34.4	15.6	100.0
	% within Endoscopy	25.0	48.4	57.9	31.3	45.7
51-60	No. of patients	1	8	5	8	22
	% within Age Group in years	4.5	36.4	22.7	36.4	100.0
	% within Endoscopy	25.0	25.8	26.3	50.0	31.4
Above 60	No. of patients	2	1	1	2	6
	% within Age Group in years	33.3	16.7	16.7	33.3	100.0
	% within Endoscopy	50.0	3.2	5.3	12.5	8.6
Total	No. of patients	4	31	19	16	70
	% within Age Group in years	5.7	44.3	27.1	22.9	100.0
	% within Endoscopy	100	100	100	100	100

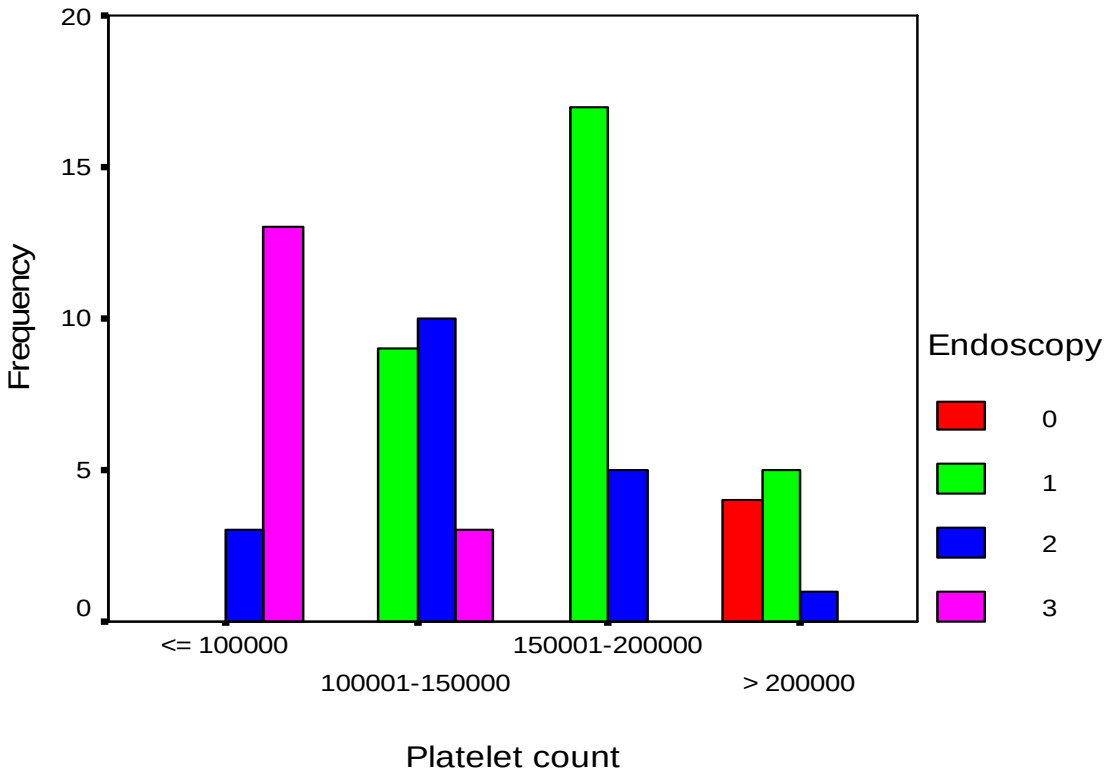
Pearson Chi-Square-16.600, P value-.055. No significance in the distribution of age and grade of varices was found in our study.


16
14
12
10
8
6
4
2
0
Frequency
Upto 40
41-50
51-60
Above 60
Age Group in years
Endoscopy
0
1
2
3

RELATIONSHIP BETWEEN PLATELET COUNT AND GRADE OF VARICES

Platelet count * Endoscopy Crosstabulation (Table 3)

Platelet count/μL		Endoscopy-Grade of varices				Total	P value
		0	1	2	3		
<= 100000	No. of patients	0	0	3	13	16	P <.001
	% within Platelet Count	0	0	18.8	81.3	100.0	
	% within Endoscopy	0	0	15.8	81.3	22.9	
100001-150000	No. of patients	0	9	10	3	22	
	% within Platelet count	0	40.9	45.5	13.6	100.0	
	% within Endoscopy	0	29.0	52.6	18.8	31.4	
150001-200000	No. of patients	0	17	5	0	22	
	% within Platelet count	0	77.3	22.7	0	100.0	
	% within Endoscopy	0	54.8	26.3	0	31.4	
> 200000	No. of patients	4	5	1	0	10	
	% within Platelet count	40.0	50.0	10.0	0	100.0	
	% within Endoscopy	100	16.1	5.3	0	14.3	
Total	No. of patients	4	31	19	16	70	
	% within Platelet count	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100.0	100.0	100.0	100.0	100.0	



Pearson Chi-Square-72.996,P value-<.001,significant

Out of the 70 patients,16 patients had platelet count less than 1 lakh of which 13 patients had grade 3 varices, and 3 patients with grade 2 varices. And patients with platelet count above 2 lakhs none of them had grade 3 varices and one patient with grade 2 varices. The above observations suggested a strong association between a low platelet count and large varices, and a significant `P' value.

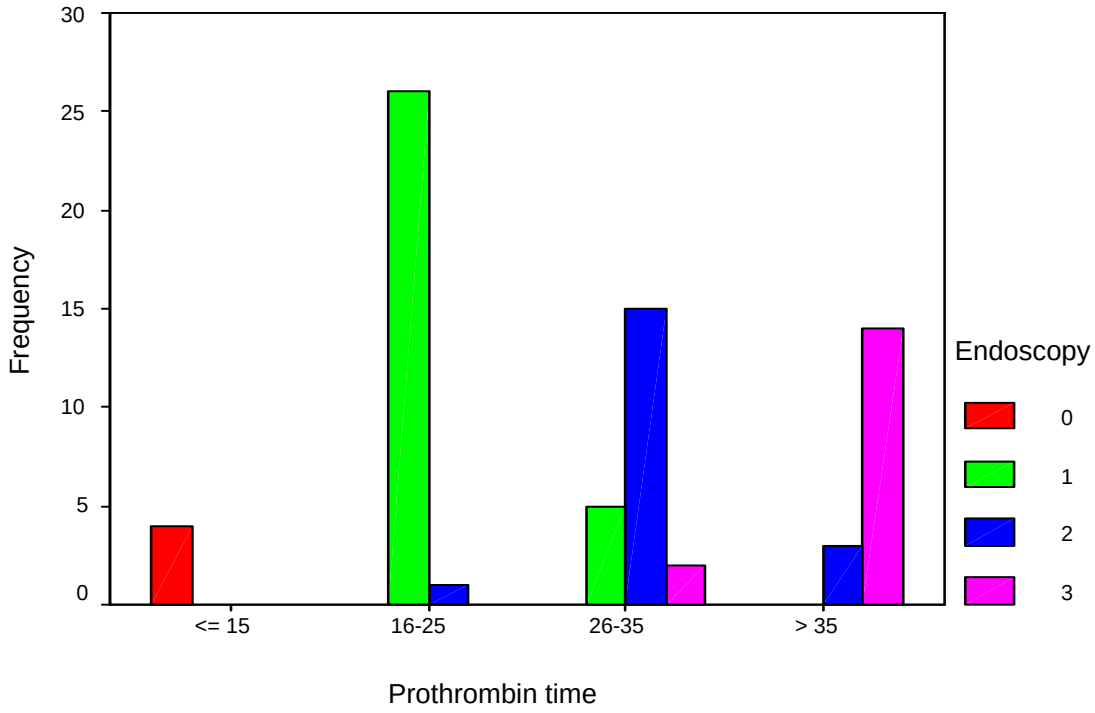
RELATIONSHIP BETWEEN PROTHROMBIN TIME AND GRADE OF VARICES

Prothrombin time * Endoscopy Cross tabulation(Table 4)

Prothrombin time(seconds)	Endoscopy- Grade of varices					Total	P value
		0	1	2	3		
<= 15	No. of patients	4	0	0	0	4	P < .001
	% within Prothrombin time	100	0	0	0	100.0	
	% within Endoscopy	100	0	0	0	5.7	
16-25	No. of patients	0	26	1	0	27	
	% within Prothrombin time	0	96.3	3.7	0	100.0	
	% within Endoscopy	0	83.9	5.3	0	38.6	
26-35	No. of patients	0	5	15	2	22	
	% within Prothrombin time	0	22.7	68.2	9.1	100.0	
	% within Endoscopy	0	16.1	78.9	12.5	31.4	
> 35	No. of patients	0	0	3	14	17	
	% within Prothrombin time	0	0	17.6	82.4	100.0	
	% within Endoscopy	0	0	15.8	87.5	24.3	
Total	No. of patients	4	31	19	16	70	
	% within Prothrombin time	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100	100.0	100.	100.0	100.0	

Pearson Chi-Square-150.104 , P value < .001

34 out of 39 patients with Grade 2,3 varices had a prolonged prothrombin time more than 25 seconds, while in patients with a prothrombin time of less than 25 seconds majority had grade 1,0 varices. A significant 'p' value was observed.



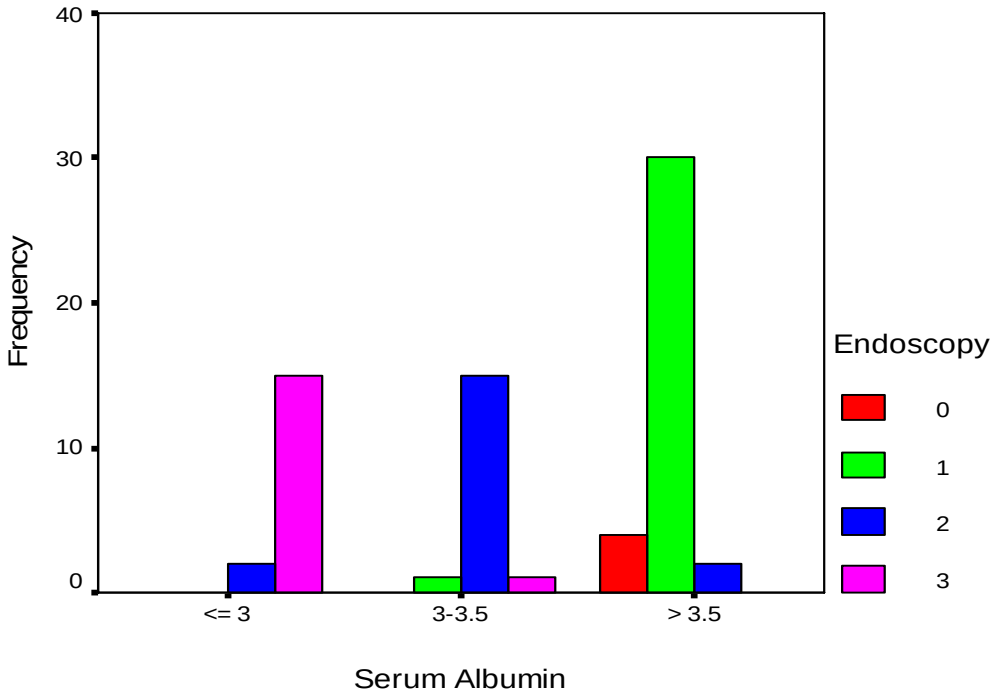
RELATIONSHIP BETWEEN SERUM ALBUMIN AND GRADE OF VARICES

Serum albumin * Endoscopy Cross tabulation(Table 5)

Serum albumin (g/dl)	Endoscopy- Grade of varices					Total	P value
		0	1	2	3		
<= 3	No. of patients	0	0	2	15	17	P < .001
	% within S.albumin	0	0	11.8	88.2	100.0	
	% within Endoscopy	0	0	10.5	93.8	24.3	
3-3.5	No. of patients	0	1	15	1	17	
	% within S.albumin	0	5.9	88.2	5.9	100.0	
	% within Endoscopy	0	3.2	78.9	6.3	24.3	
> 3.5	No. of patients	4	30	2	0	36	
	% within S.albumin	11.1	83.3	5.6	0	100.0	
	% within Endoscopy	100.0	96.8	10.5	0	51.4	
Total	No. of patients	4	31	19	16	70	
	% within S.albumin	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100.0	100.0	100.0	100.0	100.0	

Pearson Chi-Square-102.562, P < .001

In our sample with 70 patients, 17 patients had their serum albumin less than 3g/dl, who had grade 2,3 varices, in 36 patients the serum albumin is more than 3.5 with no varices or grade one varices. Value of serum albumin for patients showed inverse relationship with increasing grade of varices. `P' value was significant.


40
30
20
10
0
Frequency
<= 3
3-3.5
> 3.5
Serum Albumin
Endoscopy
0
1
2
3

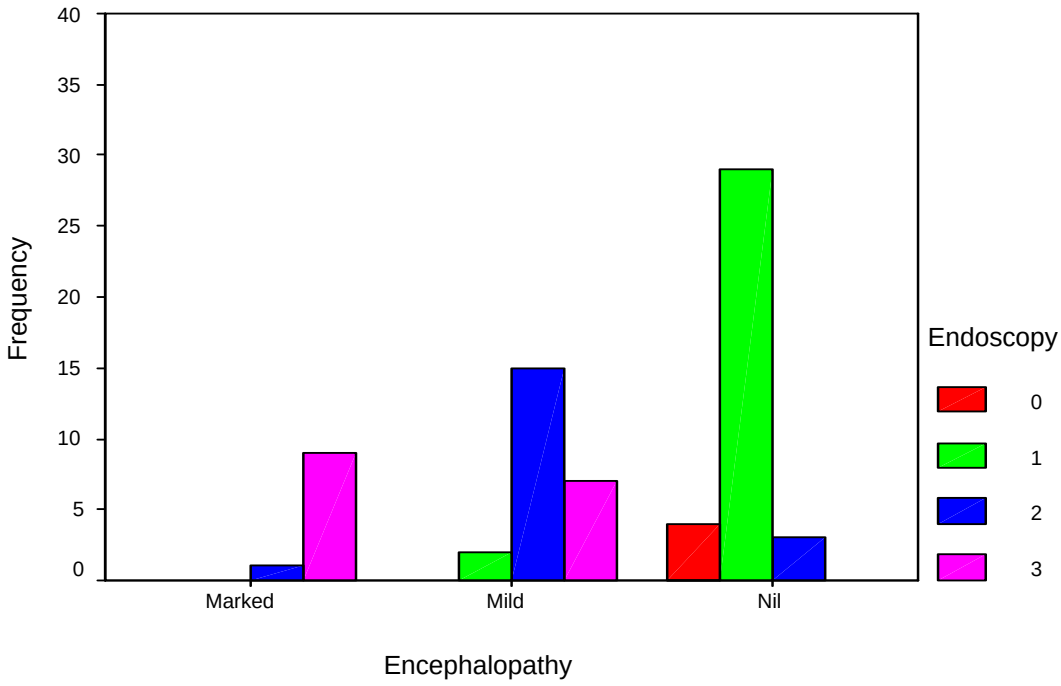
RELATIONSHIP BETWEEN ENCEPHALOPATHY AND GRADE OF VARICES

Encephalopathy * Endoscopy Crosstabulation (Table 6)

Encephalopathy	Endoscopy- Grade of varices					Total	P value
		0	1	2	3		
Marked	No. of patients	0	0	1	9	10	P< .001
	% within Encephalopathy	0	0	10.0	90.0	100.0	
	% within Encephalopathy	0	0	5.3	56.3	14.3	
Mild	No. of patients	0	2	15	7	24	
	% within Encephalopathy	0	8.3	62.5	29.2	100.0	
	% within Endoscopy	0	6.5	78.9	43.8	34.3	
No	No. of patients	4	29	3	0	36	
	% within Encephalopathy	11.1	80.6	8.3	0	100.0	
	% within Endoscopy	100	93.5	15.8	0	51.4	
Total	No. of patients	4	31	19	16	70	
	% within Encephalopathy	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100	100	100	100	100	

Pearson Chi-Square-71.104, P < .001

Hepatic encephalopathy had a linear relation with grade of varices. In our sample with 70 patients ,10 patients had marked hepatic encephalopathy, 90% had grade 3 varices, in 24 patients there is mild hepatic encephalopathy with 2/3 rd of patients having grade 2 varices. `P' value was significant.


40
35
30
25
20
15
10
5
0
Frequency
Marked
Mild
Nil
Encephalopathy
Endoscopy
0
1
2
3

RELATIONSHIP BETWEEN PORTAL VEIN DIAMETER AND GRADE OF VARICES

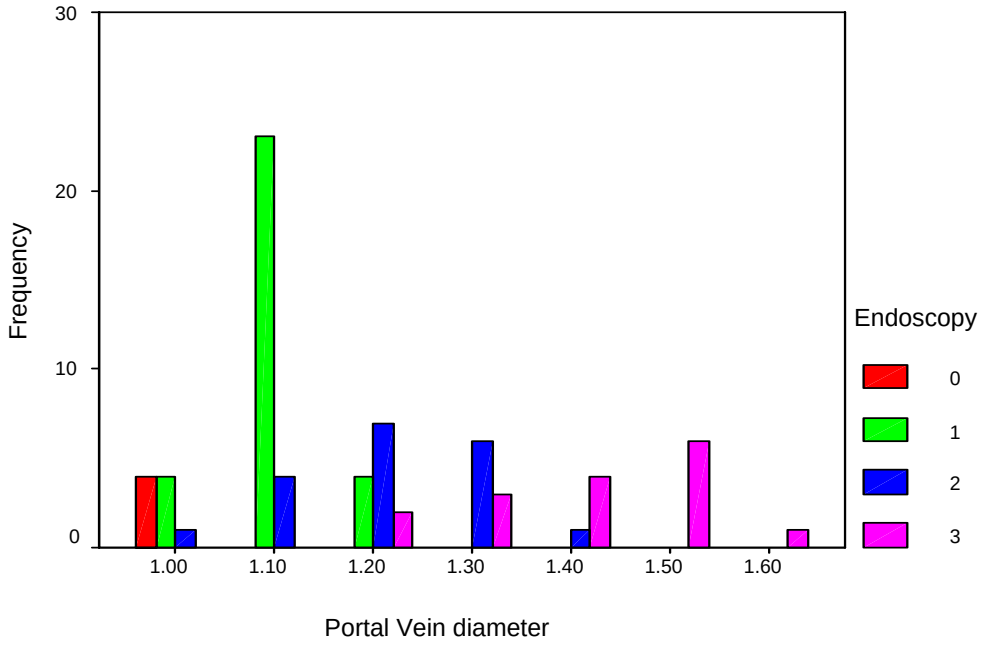
Portal Vein diameter * Endoscopy Cross tabulation (Table 7)

Portal Vein Diameter(cms)	Endoscopy- Grade of varices					Total	P value
		0	1	2	3		
1.00	No. of patients	4	4	1	0	9	P< .001
	% within Portal Vein diameter	44.4	44.4	11.1	0	100.0	
	% within Endoscopy	100.0	12.9	5.3	0	12.9	
1.10	No. of patients	0	23	4	0	27	
	% within Portal Vein diameter	0	85.2	14.8	0	100.0	
	% within Endoscopy	0	74.2	21.1	0	38.6	
1.20	No. of patients	0	4	6	2	12	
	% within Portal Vein diameter	0	33.3	50.0	16.7	100.0	
	% within Endoscopy	0	12.9	31.6	12.5	17.1	
1.30	No. of patients	0	0	6	3	9	
	% within Portal Vein diameter	0	0	66.7	33.3	100.0	
	% within Endoscopy	0	0	31.6	18.8	12.9	
1.40	No. of patients	0	0	1	4	5	
	% within Portal Vein diameter	0	0	20.0	80.0	100.0	
	% within Endoscopy	0	0	5.3	25.0	7.1	
1.50	No. of patients	0	0	0	6	6	
	% within Portal Vein diameter	0	0	0	100.0	100.0	
	% within Endoscopy	0	0	0	37.5	8.6	
1.60	No. of patients	0	0	0	1	1	
	% within Portal	0	0	0	100.	100.0	

	Vein diameter				0		
	% within Endoscopy	0	0	0	6.3	1.4	
12.00	No. of patients	0	0	1	0	1	
	% within Portal Vein diameter	0	0	100	.0	100.0	
	% within Endoscopy	0	0	5.3	.0	1.4	
Total	No. of patients	4	31	19	16	70	
	% within Portal Vein diameter	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100.0	100.0	100	100	100.0	

Pearson Chi-Square-95.6, P value- < .001

In patients with portal vein diameter <1.1cm none of them had Grade 2,3 varices. Large varices were seen patients with portal vein diameter >1.4cm. The above observations suggested a strong association between a larger portal vein diameter with large varices, and a significant `P' value.

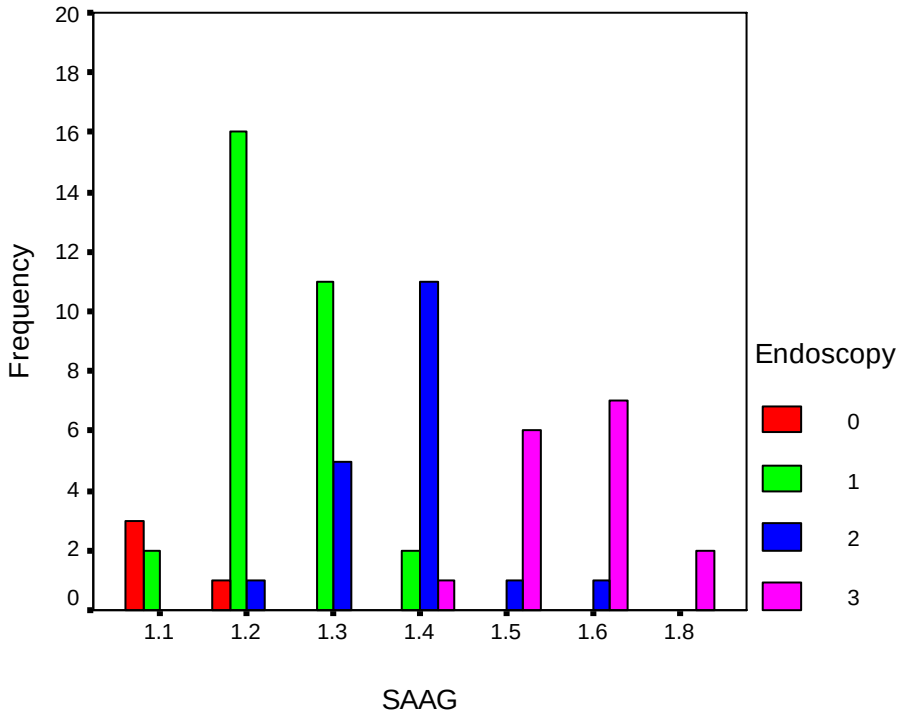


RELATIONSHIP BETWEEN SAAG(Serum Ascites Albumin Gradient) AND GRADE OF VARICES

SAAG gradient * Endoscopy Crosstabulation (Table 8)

SAAG g/dl	Endoscopy – Grade of varices					Total	P value
		0	1	2	3		
1.1	No. of patients	3	2	0	0	5	P < .001
	% within Saag	60.0	40.0	0	0	100.0	
	% within Endoscopy	75.0	6.5	0	0	7.1	
1.2	No. of patients	1	16	1	0	18	
	% within Saag	5.6	88.9	5.6	0	100.0	
	% within Endoscopy	25.0	51.6	5.3	0	25.7	
1.3	No. of patients	0	11	5	0	16	
	% within Saag	0	68.8	31.3	0	100.0	
	% within Endoscopy	0	35.5	26.3	0	22.9	
1.4	No. of patients	0	2	11	1	14	
	% within Saag	0	14.3	78.6	7.1	100.0	
	% within Endoscopy	0	6.5	57.9	6.3	20.0	
1.5	No. of patients	0	0	1	6	7	
	% within Saag	0	0	14.3	85.7	100.0	
	% within Endoscopy	0	0	5.3	37.5	10.0	
1.6	No. of patients	0	0	1	7	8	
	% within Saag	0	0	12.5	87.5	100.0	
	% within Endoscopy	0	0	5.3	43.8	11.4	
	No. of patients	0	0	0	2	2	

1.8	% within Saag	0	0	0	100	100.0	
	% within Endoscopy	0	0	0	12.5	2.9	
Total	No. of patients	4	31	19	16	70	
	% within Saag	5.7	44.3	27.1	22.9	100.0	
	% within Endoscopy	100.0	100.0	100.0	100	100.0	



Pearson Chi-Square-111.265, P < .001.

When the Value of SAAG was between1.1 and 1.3 it was noted that Grade 3 varices were absent. When the SAAG values increased more than 1.3, there was considerable increase in grade 2,3varices.

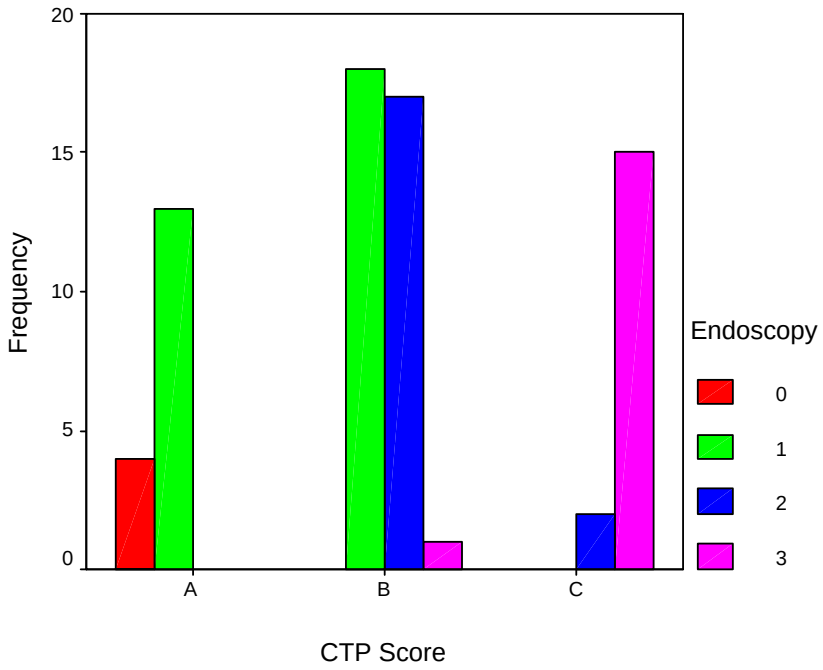
RELATIONSHIP BETWEEN CTP SCORE AND GRADE OF VARICES

CTP Score * Endoscopy Crosstabulation (Table 9)

CTP Score	Endoscopy-Grade of varices					Total
		0	1	2	3	
A	No. of patients	4	13	0	0	17
	% within CTP Score	23.5	76.5	0	0	100.0
	% within Endoscopy	100.0	41.9	0	0	24.3
B	No. of patients	0	18	17	1	36
	% within CTP Score	0	50.0	47.2	2.8	100.0
	% within Endoscopy	0	58.1	89.5	6.3	51.4
C	No. of patients	0	0	2	15	17
	% within CTP Score	0	0	11.8	88.2	100.0
	% within Endoscopy	0	0	10.5	93.8	24.3
Total	No. of patients	4	31	19	16	70
	% within CTP Score	5.7	44.3	27	22.9	100.0
	% within Endoscopy	100.0	100.0	100.0	100.0	100.0

Pearson Chi-Square-, P <77.71 . P<.001.

Child Pugh score had a linear relation with grade of varices. In our sample with 70 patients, CTP score C found in 17 patients of which 15 patients had grade 3 varices. CTP score A found in 17 patients of which 4 patients did not had varices and 13 patients had grade 1 varices. P' value was significant.



DISCUSSION

Our study sample consisted of 70 patients of whom 56 were male and 14 were females. No significant gender difference in the distribution of grade of varices was found in our study (Table 1). Distribution of grade of varices was studied in various age groups and no significant correlation was detected.(Table 2)

We studied the frequency of distribution of varices and found that Grade I predominated (42%),while 6 % of the study population did not have varices.

Our study could find significant association between thrombocytopaenia and varices.(Table 3). An inverse relation between thrombocytopaenia and grade of varices is noted, out of 70 patients 44 patients had platelet count less than 1.5lakhs,had grade 3,2 varices. Especially thae number of grade 3 varices increases when the platelet count was below 1 lakh. In patients with platelet count above 2 lakhs grade 3 varices were not present and only one patient had grade 2 varices.

PLATELET COUNT IN OTHER STUDIES PREDICTING OESOPHAGEAL VARICES

Garcia- Tsao *et al*.[53](180 patients), **Pilette *et al*.**[54](116 patients) and K.**Thomopoulos *et al*.**[55](184 patients) reported a low platelet count to

be an independent risk factor for the presence of varices. Mohammad **Khuram *et al*.**[56](200 patients) found esophageal varices in 146 with 121 having thrombocytopenia (94.5%).**Chalasani et al** found that of 346 patients, the presence of splenomegaly on physical examination (OR, 2.0; 95% CI, 1.1-3.8) and a platelet count less than 88103/μL (OR, 1.6; 95% CI, 1.0-3.0) were independent risk factors for the presence of large varices.

PROTHROMBIN TIME IN VARIOUS STUDIES PREDICTING OESOPHAGEAL VARICES

Our study could find significant association between prothrombin time and varices. Higher the prothrombin time greater is the grade of varices (Table4)..**Filippo Schepis[et]** al reported that the presence of esophageal varices was independently predicted by prothrombin activity less than 70% (odds ratio [OR]: 5.83; 95% CI: 2.6-12.8). In a study by **Pilette et al** in a study of 116 patients with cirrhosis, a low platelet count, high prothrombin time, and the presence of spider angiomata were independent risk factors for the presence of varices. **Paquet KJ.et al,[58]** A prospective controlled trial, showed the importance of high prothrombin time and association of varices.

SERUM ALBUMIN AND OESOPHAGEAL VARICES

Our study could find significant association between serum albumin and varices. Lower the serum albumin levels the greater is the grade of varices (Table 5). In our sample with 70 patients, 17 patients had their serum albumin less than 3g/dl, had grade 2,3 varices. In a logistic regression study by **Garcia-Tsao et a**l of 180 patients, the presence of spider angiomata, a low albumin level, and a low platelet count were independent risk factors for the presence of varices.

HEPATIC ENCEPHALOPATHY AND OESOPHAGEAL VARICES

Our study could find significant association between hepatic encephalopathy and varices. Higher the encephalopathy grade greater is the grade of varices (Table 6).

PORTAL VEIN DIAMETER IN OTHER STUDIES PREDICTING OESOPHAGEAL VARICES

Our study could find significant association between Portal vein diameter and grade of varices. As the portal vein diameter increases the grade of varices also increases (Table 7). Grade 2,3 varices are seen with portal vein diameter more than 1.4cm.

Arulprakash Sarangapani et al, 2009, The study analyzed 106 patients with liver diseases. On multivariate analysis, independent predictors for the presence of Large varices were, spleen size >13.8 mm, portal vein >13 mm, splenic vein >11.5 mm.

Schepis et al [57] suggested that cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity was less than 70%, platelet count less than 100 × 10^9/L, and ultrasonographic portal vein diameter greater than 13 mm are observed, whereas those without any of these predictors should not undergo endoscopy.

SAAG IN VARIOUS STUDIES PREDICTING OESOPHAGEAL VARICES

Our study could find that, when the value of SAAG was between1.1 and 1.3 it was noted that Grade 3 varices were absent. When the SAAG values increased more than 1.3, there was considerable increase in grade 2,3varices. **Kajani et al.** [59] reported that the portal pressure correlated with the SAAG only in patients with PHT caused by alcoholic liver disease.

The SAAG is able to define the presence or absence of PHT with an accuracy of 96.7%. This test is accurate despite ascitic fluid infection,

diuresis, therapeutic paracentesis, albumin infusion, and etiology of liver diseases. **Gurubacharya et al** the study included 32 patients with ascites, demonstrated by ultrasonography, who had measurement of the SAAG. All had upper gastrointestinal endoscopy with assessment of the presence and size of EV. High SAAG was considered to be present when SAAG was >=1.1 g/dl and Low SAAG when it measured < 1.1 g/dl. In a study performed by **Hoefs et al.** (1983)[60], it was shown that an excellent correlation exists between portal hypertension and SAAG .According to **Goyal et al** (1989) Serum ascites albumin gradient, showed a strong correlation to portal pressure, and was found to be the best diagnostic index (with an overall accuracy of 97 per cent). **Demyrel et al** (2003) study supports the observation that SAAG values increase in ascites due to portal hypertension.

CTP IN VARIOUS STUDIES PREDICTING OESOPHAGEAL VARICES

Our study could find that when the CTP score increases the variceal grade also increases. Of the 17 patients with CTP score C,15 patients had grade 3 varices and similarly of the 17 patients with CTP score A none of the patients had grade 2,3 varices. (Table 9).The P value was significant.

In a study by **Atif Zaman, et al**. patients in CTP score B or C are nearly 3 times more likely to have large varices on upper endoscopy than are those in Child-Pugh score A. **Cales et al,** . In their study, multivariate analysis revealed that initial size of varices and interval worsening of the Child-Pugh score predicted the development of varices.

LIMITATIONS OF THE STUDY

- The major limitation of the study was the smaller number of subjects.
- Being a tertiary care center, the proportion of patients with more severe disease and multiple risk factors were getting admitted more than those with milder disease.
- In our study female subjects were relatively less because of overall lesser incidence of cirrhosis among female population.

SUMMARY AND CONCLUSION

We studied seventy patients to find out non endoscopic predictors of esophageal varices in patients with cirrhosis who did not have previous history of upper gastrointestinal bleed. Presence of varices increases as patients progress to decompensated liver disease (Child Pugh grade B & C). Decrease in platelet count below 100000/μL was found to be a predictor of esophageal varices in patients with cirrhosis. Increase in prothrombin time more than 25 seconds is associated with grade 2,3 varices. Value of serum ascitic albumin gradient (SAAG) more than 1.4g/dl is found to be a predictor for presence and large grade of esophageal varices .Portal vein diameter more than 1.3cm is associated with linear increase in grade of varices. Majority of patients with marked hepatic encephalopathy had grade 3 varices. In patients with serum albumin less than 3g/dl most of the patients had grade 3 varices.

A combination of these non invasive parameters in cirrhotic patients like platelet count, portal vein diameter, SAAG, Prothrombin time along with serum albumin, encephalopathy grade, Child pugh score for screening esophageal varices can substantially reduce the cost of health care and discomfort for patients as well as reduce burden on endoscopy units.

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ANNEXURES

PROFORMA

NON ENDOSCOPIC PREDICTORS OF OESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

1. Name

2. Age/Sex:

3. Address:

4. IP No.

5. Occupation:

6. **Presenting illness**

   Blood vomitting

   Black tarry stools

   Abdominal distension

   Pedal edema

   Jaundice

   Oliguria

   Altered sleep pattern/ consciousness level

7. **Past history**

   (DM/HT/Asthma/Seizures/Others/history of liver disease)

8. **Personal history:**

(Alcohol, Smoking, IV drug abuse/Exposure to STD, Blood transfusion)

9**. Clinical examination:**

Pallor

Icterus

Clubbing

Cyanosis

Pedal Edema

Significant lymphadenopathy

KF ring

Signs of Liver cell failure

Vitals

Pulse rate

Blood Pressure

Respiratory rate

Temperature

Signs of bleeding

JVP

10. **SYSTEM EXAMINATION**

Abdomen: Ascites, liver span, splenomegaly

Respiratory system:

CVS Examination:

CNS Examination:

11. **Investigations:**

Blood Biochemistry

Complete Hemogram

TC, DC, Hb, Platelet count

Coagulation Profile

Blood sugar

RFT

Urea

Creatinine

Electrolytes

LFT

Total/Direct Bilirubin

SGPT

SGOT

SAP

Total protein, S.Albumin

Viral markers (HBsAg, Anti HCV)

Ascitic Fluid Analysis

Protein/Sugar

Cell Count

Cytology

Gramstain/AFB

Culture

SAAG ratio

Chest X-ray

ECG

USG abdomen

Portal vein size

Spleen size

Ascites

Child's Grading: A/B/C

UGI Endoscopy

Varices grade

12. Treatment

13. Outcome

Discharge

Death