"NON INVASIVE INDEX USING COMPLETE BLOOD COUNTS (P2/MS) FOR DETECTING OESOPHAGEAL VARICES IN CIRRHOSIS"

Dissertation submitted in partial fulfillment of the

Requirement for the award of the Degree of

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BRANCH I - GENERAL MEDICINE

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CHENNAI, TAMILNADU

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled "**NON INVASIVE INDEX USING COMPLETE BLOOD COUNTS (P2/MS) FOR DETECTING OESOPHAGEAL VARICES IN CIRRHOSIS**" is the bonafide work of **DR. K.LOGANATHAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M. G. R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in April 2018.

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DECLARATION

I, **Dr.K.LOGANATHAN** declare that, I carried out this work on "**NON INVASIVE INDEX USING COMPLETE BLOOD COUNTS (P2/MS) FOR DETECTING OESOPHAGEAL VARICES IN CIRRHOSIS**" at the Department of General Medicine, Government Rajaji Hospital, Madurai during the period from may 2017 to august 2017. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, Diploma to any other University, Board either in India or abroad.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I, examination to be held in April 2018.

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CONTENTS

INTRODUCTION

INTRODUCTION

Portal hypertension is a progressive complication of liver cirrhosis and it is the cause of high morbidity and mortality. Approximately 50% of patients with cirrhosis have gastroesophageal varices. The management of cirrhotic patients with varices differs according to the grade of varices or the presence of acute variceal bleeding. While varices are found in 40% of Child A patients, they can be present in up to 85% of Child C patients. Cirrhotic patients develop varices at a rate 8% per year and in those who have no varices at the time of initial endoscopic screening, and have a portal-hepatic venous pressure gradient (HVPG) more than 10 mmHg is the strongest predictor for their development.Variceal hemorrhage occurs at a yearly rate 5% - 15%, and its most important predictor is the size of varices, of which hemorrhage with the highest risk occurring in patients with large varices. The gold standard for the diagnosis of varices is esophagogastroduodenoscopy (EGD). It is recommended that cirrhosis patients undergo endoscopic screening for varices at the time of diagnosis. Since the point prevalence of medium/large varices is approximately 15% - 20%, the majority of patients undergoing screening EGD either do not have varices or have varices that do not require prophylactic therapy. Thus, several models have been proposed

to predict the presence of high risk varices by non-invasive methods and have excited considerable interest among researchers. Multiple studies have evaluated possible noninvasive markers of esophageal varices in cirrhosis patients such as: the platelet count, spleen size, Fibro test, diameter of portal vein, and transient elastography. Lee and coworkers recently proposed a simple noninvasive test, P2/MS, which they developed in a study of patients with virus-related chronic liver disease (CLD).They used the following formula: (platelet count)2/[monocyte fraction (%) − segmented neutrophil fraction (%)]. However, P2/MS has received little external validation of its diagnostic accuracy and cut-off values for detection of esophageal varices. We, therefore, conducted the current study to externally validate P2/MS, to determine optimal thresholds to predict high risk esophageal varices (HREV) in patients with liver cirrhosis.

The diagnosis of EV is required for patients with liver cirrhosis to detect those who will benefit from variceal bleeding primary prophylaxis. Currently, esophago-gastro-duodenoscopy (EGD) remains the gold standard test for such diagnosis. However, EGD is limited by its invasiveness and high cost. A simple non-invasive widely available and cheap test would be ideal if proved to have sufficient specificity and sensitivity. Therefore, we aimed to study the diagnostic value of an

index derived from the patients' complete blood count; namely the P2/MS ratio as a predictive tool for the presence of varices and if they are at high risk of bleeding**.**

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

To evaluate the predictive value of P2/MS index (platelet count)2/[monocyte fraction (%) × segmented neutrophil fraction (%)] derived from the patient's complete blood count for detecting oesophageal varices in cirrhosis patients presenting to Government Rajaji Hospital, Madurai.

To compare the P2/MS index in cirrhosis paients with portal hypertension and without portal hypertension

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Cirrhosis is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules,which is a final pathway for a wide variety of chronic liver diseases. The diagnosis of cirrhosis in clinical practice is based on risk factors, history and clinical findings, biochemical tests, imaging, endoscopic and histologic findings

PATHOGENESIS

The most common cell type involved in the pathogenesis of fibrosis is hepatic stellate cell.on activation stellate cell transforms into myofibroblast.these cell generate various forms of matrix of which fibronectin is earliest form which produce other forms of matrix including collagen 1.matrix deposition leads to further stellate cell activation and changes in the angioarchitecture.

The canonical pathways involved are kinase activation pathwaysmediated through PDGF and TGF-beta and integrin signaling pathways.portal fibroblast is implicated in fibrosis that develop in response to cholestatic injury as in primary biliary cirrhosis and primary sclerosing cholangitis

Epithelial cell injury is the initiating step in liver injury and leads to fibrosis.macrophage release inflammatory cytokines that activate stellate cells into myofibroblast.sinusoidal endothelial cells also involved in the development of fibrosis through autocrine and paracrine signaling pathways.

CAUSES OF CIRRHOSIS

Viral

Hepatitis B

Hepatitis C

Hepatitis D

Autoimmune

Autoimmune hepatitis

Primary biliary cirrhosis

Primary sclerosing cholangitis

Toxic

Alcohol

Arsenic

Metabolic

Alpha1antitrypsin deficiency

Galactosemia

Glycogen storage disease

Hemochromatosis

Nonalcoholic fatty liver disease

Wilson disease

Biliary

Atresia

Stone

Tumor

Vascular

Budd chiari syndrome

Cardiac fibrosis

Genetic

Cystic fibrosis

Lysosomal acid lipase deficiency

Iatrogenic

biliary injury

drugs-high dose vit A,methotrexate

CLINICAL FEATURES

Cirrhosis can be either compensated or decompensated

The development of ascites,jaundice,encephalopathy,variceal hemorrhage,hepatocellular carcinoma characterizes decompensated cirrhosis.

Four clinical stages have been proposed

Stage 1 and 2 represents compensated cirrhosis

Stage 3 and 4 represents decompensated cirrhosis

Stage 1-absence of both ascites and varices

Stage 2-presence of varices without bleeding

Absence of ascites

Stage 3-ascites with or without varices

Stage 4-variceal bleeding with or without ascites

COMPENSATED CIRRHOSIS:

The cirrhotic process of the liver is not enough severe to alter the function significantly and so the patients may be asymptomatic or present only with non-specific symptoms or finding incidentally due to alteration in biochemical parameters or imaging studies. Patients may be presented with fatigue, anorexia, weight loss, flatulence, dyspepsia or abdominal pain. palmar erythema, pedal edema, spider naevi, unexplained epistaxis may be present.

Abdominal examination - epigastric mass which is the enlarged left lobe of the liver and splenomegaly may be present. Biochemical tests are usually normal . The most common abnormality noticed in this group include mildly elevated transaminases, or GGT.cirrosis is confirmed by liver imaging or liver biopsy. Factors which may precipitate decompensation in a compensated cirrhosis are bacterial infection, trauma, medications, surgery etc.,

DECOMPENSATED CIRRHOSIS:

These patients may present with ascites, jaundice, altered sensorium,gastrointestinal bleeding .

SYMPTOMS AND SIGNS

General weakness,muscle wasting,weight loss

Mild fever(37.5-38* c)-due to gram negative bacteremia

Jaundice-liver cell destruction exceeds the capacity for regeneration

Skin pigmentation

Clubbing

Purpura –low platelet count

Sparse body hair

Vascular spiders

Palmar erythema

White nails

Gonadal atrophy

Ascites

Pedal edema

Hepatomegaly

spleenomegaly

blood pressure low

Dupuytrens contracture”

Parotid enlargement, alopecia, fetor hepaticus, KF ring

Gynecomastia in males

loss of axillary hair and chest hair

11% of cirrhosis patients have peptic ulcers -duodenal ulcers are more frequentiy encountered than *gastric* ulcers

Asterixis or flapping tremors are present in hepatic encephalopathy.

In about 80% of cirrhotic patients hyperglycemia occurs in the form of glucose intolerance

INVESTIGATIONS*:*

LIVER FUNCTION TEST ABNORMALITIES-

“Aminotransferases” —ALT is increased more than AST in chronic hepatitis, AST becomes more elevated than ALT when hepatitis progresses to cirrhosis and thus the ratio of AST to ALT is reversed from <1 to > 1.In cirrhosis patients the enzymes may be within normal values or become moderately elevated.

“Alkaline phosphatase” - Alkaline phosphatase enzyme elevated 2 to 3 times than normal in cirrhosis. If elevated greater than that, primary biliary cirrhosis or sclerosing cholangitis should be considered as etiology.

“Gammaglutamyl transpeptidase” — GGT and alkaline phosphatase are usually proportionately elevated.Disproportionately high levels of GGT are seen in alcoholic discease.GGT present in the rnicrosomes gets induced due to alcohol intake.

“Bilirubin” — In compensated cirrhosis, the bilirubin levels are usually normal. Decompensation - characterized by increasing levels of bilirubin and it is one of the prognostic indicators used in Child Pugh score.

“Albumin” - exclusively synthesised in the liver. With worsening cirrhosis, albumin level will be low due to the decline in the synthetic function of the liver.It is also one of the prognostic indicators for survival in child pugh scoring system.

“Prothrombin time” -most of the coagulation factors are synthesized in liver.Prothrombin time which measures the extrinsic pathway, is a marker for the synthetic function of the liver. coagulopathy worsens as the cirrhosis progresses.

Serum electrolytes – "hyponatremia" can occur in patients with ascites. Severity can be correlated with worsening cirrhosis.

Hematologic abnormalities-Thrornbocytopenia, anemia and leucopenia can occur.

"Anemia" - mainly because of upper G1 bleed. Anemia can also be present as a result of direct suppression of bone marrow by alcohol,splenic sequestration , hemolysis,and folate deficiency.

Other abnormalities - In cirrhosis, the globulin levels- high. This is because of shunting of bacterial antigens in the portal venous blood which are normally filtered by the liver in to systemic circulation leading which induces production of immunoglobulins. Marked elevations of IgG may point towards the presence of autoimmune hepatitis.

Imaging studies:

Cirrhosis can be diagnosed radiologically by ultrasound, portal vein Doppler, CT and MRI in specific cases.

• Ultrasonography — Ultrasonography is a non-invasive routinely used to diagnose cirrhosis. The size of the liver, the nodularity, the portal vein diameter, ascites and splenomegaly can be assessed. Doppler studies to

check the direction of blood flow in the portal vein aids in the diagnosis of portal hypertension. Presence HCC and portal vein thrombosis can also be made out.

• CT is not the first choice in the diagnosis of cirrhosis, may be useful when investigating liver malignancy or secondaries or pancreatic pathology.

• MRI- useful in hermochromatosis to reveal iron overload. MRA can determine portal vein flow and dynamics.

• Elastography - assess the stiffness of the liver tissue is also available.

Liver biopsy:

The gold standard investigation for diagnosing cirrhosis is liver biopsy ,is rarely required nowadays to diagnose cirrhosis.Only certain situations may require performing liver biopsy such as for dermonstrating the underlying metabolic cause of cirrhosis such as NASH, Wilson disease, hemochromatosis, and alpha 1 antitrypsin deficiency.

PROGNOSIS:

Modified Child-Turcotte-Pugh Store (CTP): This simple scoring system is now widely in use in clinical practice, for predicting the

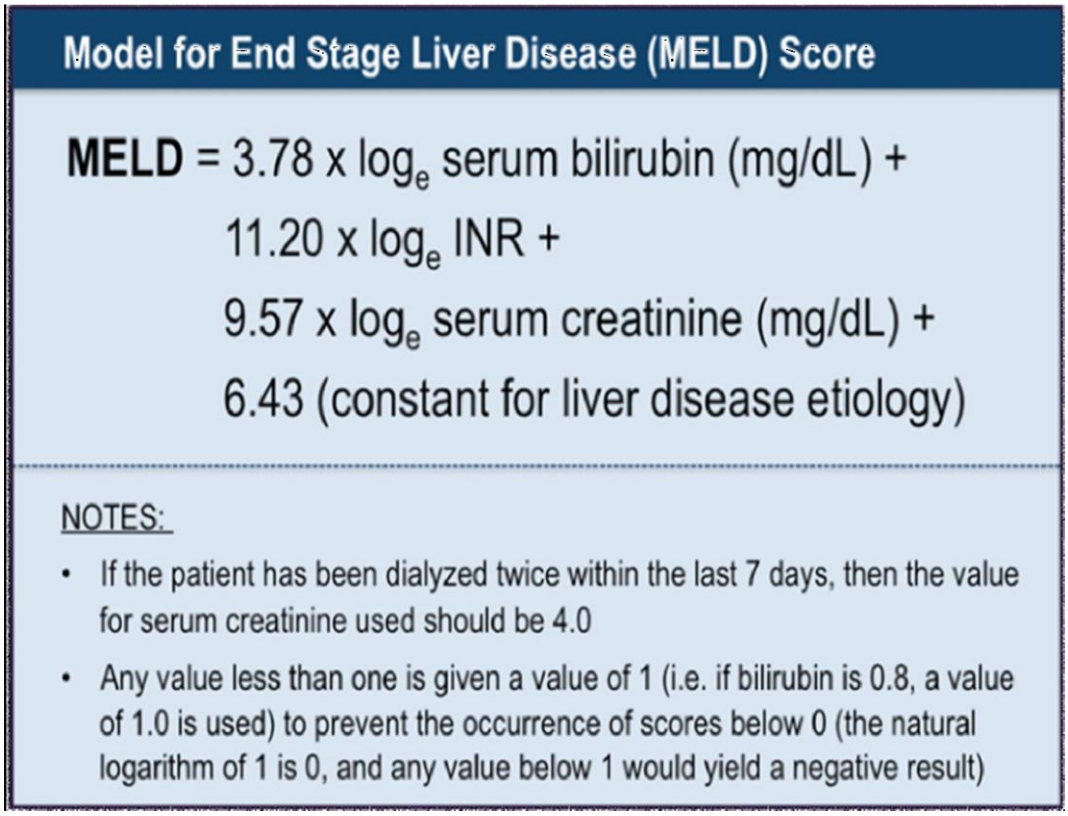
prognosis and mortality from the major complications of the cirrhosis patients. Even though it is not derived based on statistically significant studies and is only derived in an empirical manner, this score can predict the outcomes in patients with liver cirrhosis with reasonable accuracy.

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

Initially this scoring system used for the stratification of patients in to risk groups before taking them up for portosystermic shunt surgeries. Then in clinical practice this system was used to prioritize the patients to be taken up for liver transplantation (Child Pugh class B) but now this system has been replaced by MELD score for selection of patients for liver transplantation.

MODEL FOR END STAGE LIVER DISEASE (MELD) SCORE -

MELD score is calculated using three noninvasively obtained variables: serum bilirubin, serum creatinine and PT INR.



Patients with cirrhosis are given priority for liver transplantation based on this particular score in the United States. Patient with a score more than 10 is to be considered for 1iver transplantation. This scoring system has the advantage that it is completely objective for assessment of severity of the disease and does not result in inter observer variations .Moreover the score has a wider range of values,thereby severity can be graded precisely.

MAJOR COMPLICATIONS OF CIRRHOSIS:

With the progression of cirrhosis and development of portal hypertension, various complications occur as a result of either the decreased synthetic, excretory,metabolic functions of the liver and also some secondary to portal hypertension.

COMPLICATIONS OF CIRROSIS

Portal Hypertension

Ascites

Variceal bleeding

Malignancy

Colangiocarcinoma

Hepatocellular carcinoma

Bacterial infections

Bacteremia

c.difficile infection

celluliis

pneumonia

SBP

UTI

Cardiopulmonary disorder

Cardiomyopathy

Hepatic hydrothorax

Hepatopulmonary syndrome

Portopulmonary hypertension

GI Disorders

GI bleeding

Protein losing enteropathy

Venous thrombosis

Renal disorders

Hepatorenal syndrome

Other causes of acute kidney injury

Metabolic

Adrenal insufficiency

Hypogonadism

Malnutrition

Osteoporosis

Neuropsychiatric

Depression

Hepatic encephalopathy

Hematologic

Anemia

Hyper coagulability

Hypersplenism

Impaired coagulation

Unclear etiology

Erectile dysfunction

Fatigue

Muscle cramps

PORTAL HYPERTENSION

Portal venous system carries capillary blood from the esophagus, stomach, small and large intestine, pancreas, gallbladder, and spleen to the liver. The portal vein is formed by the confluence of the splenic vein and the superior mesenteric vein behind the neck of the pancreas . The inferior mesenteric vein usually drains into the splenic vein. The left gastric vein, also called the left coronary vein,usually drains into the portal vein at the confluence of the splenic vein and superior mesenteric vein . The portal vein is approximately 7.5 cm in length and runs dorsal to the hepatic artery and bile duct into the hilum of the liver. The uppermost 5 cm of the portal vein does not receive any tributaries. In the hilum of the liver, the portal vein divides into the left and right portal vein branches,which supply the left and right sides of the liver, respectively.The umbilical vein drains into the left portal vein.

The cystic vein from the gallbladder drains into the right portal vein, whereas the portal venules drain into hepatic sinusoids that, in turn, are drained by the hepatic veinsinto the inferior vena cava. The left and middle hepatic veins usually join and drain into the inferior vena cava separately but adjacent to the confluence of the right hepatic vein with the inferior vena cava. The caudate lobe drains separately into the inferior vena cava.

The circulatory system of the normal liver is a high compliance,low-resistance system that is able to accommodate a large blood volume, as occurs after a meal, without substantially increasing portal pressure. The liver receives a dual blood supply from the portal vein and the hepatic artery that constitutes nearly 30% of total cardiac output. Portal venous blood derived from the mesenteric venous circulation constitutes approximately 75% of total hepatic blood flow, whereas the remainder of blood to the liver is derived from the hepatic artery, which provides highly oxygenated blood directly from the celiac trunk of the aorta.Portal vein–derived and hepatic artery–derived blood flow converge in high-compliance, specialized vascular channels termed *hepatic sinusoids*. A dynamic and compensatory interplay occurs between hepatic blood flow derived from the portal vein and that from the hepatic artery. Specifically, when portal venous blood flow to the liver is diminished, as occurs in portal vein thrombosis, arterial inflow increases in an attempt to maintain total hepatic blood flow at a constant level. Similarly, after hepatic artery occlusion, portal venous inflow increases in a compensatory manner. This autoregulatory mechanism, aimed at maintaining total hepatic blood flow at a constant level, is termed the *hepatic arterial buffer response*.

The sinusoids are highly permeable and thus facilitate the transport of macromolecules to the parenchymal hepatocytes that reside on the extraluminal side of the endothelial cells. The hepatic sinusoids are highly permeable because they lack a proper basement membrane and because the endothelial cells that line the sinusoids contain fenestrae. Other unique aspects of the hepatic sinusoids are the space of Disse, a virtual space located extraluminal to the endothelial cell and adjacent to the hepatocyte, and its cellular constituents, the hepatic stellate cell and the Kupffer cell. These two cell types probably play an important role, in concert with the endothelial cell, in regulating sinusoidal hemodynamics and homeostasis and may contribute to the sinusoidal derangements that occur in portal hypertension. In cirrhosis, as well as in most noncirrhotic causes of portal hypertension, portal hypertension results from changes in portal resistance in combination with changes in portal inflow. The influence of flow and resistance on pressure can be represented by the formula for Ohm's law:

$_P = F \times R$

in which the pressure gradient in the portal circulation (ΔP)

is a function of portal flow (F) and resistance to flow (R).

Increases in portal resistance or portal flow can contribute to increased pressure. Portal hypertension almost always results from increases in both portal resistance and portal flow.

Portal hypertension is defined as the elevation of the hepatic venous pressure gradient (HVPG)>5 mmHg .

Portal hypertension occurs as a result of two processes happening simultaneously:

I) The altered architecture of the liver due to fibrosis and regenerating nodules, results in increased resistance to the flow of portal blood.

2) Increased blood flow secondary to splanchnic vasodilatation.

This portal hypertension results in variceal bleeding and ascites. Causes of portal hypertension

Prehepatic

Portal vein thrombosis

Splenic vein thrombosis

Intra hepatic

Presinusoidal

Idiopathic portal hypertension

Primary biliary cirrhosis

Sarcoidosis

Schistosomiasis

Sinusoidal

Alcoholic cirrhosis

Alcoholic hepatitis

Cryptogenic cirrhosis

Postnecrotic cirrhosis

Postsinusoidal

Sinusoidal obstruction syndrome

Post hepatic

Budd-Chiari syndrome

Constrictive pericarditis

Inferior vena caval obstruction

Right-sided heart failure

Severe tricuspid regurgitation

Clinically significant portal hypertension occurs in around 60% of cirrhosis patients.

The primary complications of portal hypertension include ascites, bleeding varices splenomegaly, hypersplenism etc. Splenomegaly results from congestion due to increased portal pressure. Hypersplenism with development of thrombocytopenia may be the first presentation of portal hypertension even before ascites may develop.

PATHOPHYSIOLOGY:

Portal hypertension results due to increased intrahepatic resistance and increased portal blood flow. As there is increased hepatic resistance, hepatic compliance decreases. Increase in portal pressure causes small changes in blood flow. A normal liver can adapt to it. But it can have a prominent stimulatory effect on portal pressure in the cirrhotic liver. Due to hyperdynamic state there is an increase in portal venous inflow. The Collateral vessels get dilated and new vessels sprouts. There is an increase in flow from high pressure portal veins to low pressure systemic veins. This process of angiogenesis and collateral vessel formation can cause esophageal varices. These changes in portal flow and resistance are mainly originating from mechanical and vascular factors.

MEASUREMENT OF PORTAL PRESSURE

Portal pressure may be measured indirectly or directly. The most commonly used method of measuring portal pressure is determination of the hepatic vein pressure gradient (HVPG), which is an indirect method. Measurement of splenic pulp pressure and direct measurement of the portal vein pressure are invasive, cumbersome, and infrequently used approaches. Variceal pressure also can be measured but is not routinely performed in clinical practice. Measurement of liver stiffness using ultrasound fibroelastography or magnetic resonance elastography (MRE) may indicate the presence of portal hypertension but cannot yet be used to measure portal pressure.

HEPATIC VEIN PRESSURE GRADIENT

The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP). The HVPG has been used to assess portal hypertension since its first description in 1951, and has been validated as the best predictor for the development of complications of portal hypertension.

Measurement of the HVPG requires passage of a catheter into the hepatic vein under radiologic guidance until the catheter can be passed no further, that is, until the catheter has been “wedged” in the hepatic

vein. The catheter can be passed into the hepatic vein through the femoral vein or using a transjugular venous approach. The purpose of wedging the catheter is to form a column of fluid that is continuous between the hepatic sinusoids and the catheter.

Therefore, the measured pressure of fluid within the catheter reflects hepatic sinusoidal pressure. One of the drawbacks of using a catheter that is wedged in the hepatic vein is that the WHVP measured in a more fibrotic area of liver may be higher than the pressure measured in a less fibrotic area because of regional variation in the degree of fibrosis.

Using a balloon-occluding catheter in the right hepatic vein to create a stagnant column of fluid in continuity with the hepatic sinusoids eliminates this variation in measurement of WHVP because the balloon catheter measures the WHVP averaged over a wide segment of the liver. HVPG is not effective for detecting presinusoidal causes of portal hypertension.

For example, in portal hypertension secondary to portal vein thrombosis, the HVPG is normal. Moreover, the HVPG may underestimate sinusoidal pressure in

primary biliary cirrhosis and other presinusoidal causes of portal hypertension .Therefore, HVPG is accurate for detecting only sinusoidal and postsinusoidal causes of portal hypertension.

The HVPG represents the gradient between the pressure in the portal vein and the intra-abdominal inferior vena caval pressure. An elevation in intra-abdominal pressure increases both WHVP and FHVP equally, so that the HVPG is unchanged. The advantage of the HVPG is that variations in the “zero” reference point have no impact on the HVPG.The HVPG is measured at least three times to demonstrate that the values are reproducible. Total occlusion of the hepatic vein by the inflated balloon to confirm that the balloon is in a wedged position is demonstrated by injecting contrast into the hepatic vein. A sinusoidal pattern should be seen, with no collateral circulation to other hepatic veins.

The contrast washes out promptly with deflation of the balloon. Correct positioning of the balloon also is demonstrated by a sharp increase in the recorded pressure on inflation of the balloon. The pressure then becomes steady until the balloon is deflated, when the pressure drops sharply. In experienced hands, measurement of the HVPG is highly reproducible, accurate, and safe.

Measurement of the HVPG has been proposed for the following

indications: (1) to monitor portal pressure in patients taking drugs used to prevent variceal bleeding;

(2) as aprognostic marker;

(3) as an end-point in trials using pharmacologic agents for the treatment of portal hypertension;

(4) to assess the risk of hepatic resection in patients with

cirrhosis; and

(5) to delineate the cause of portal hypertension(i.e., presinusoidal, sinusoidal, or postsinusoidal) usually in combination with venography, right-sided heart pressure measurements, and transjugular liver biopsy. Although the indication for HVPG measurement with the most potential for widespread use is monitoring the efficacy of therapies to reduce portal pressure, HVPG monitoring is not done routinely in clinical practice because no controlled trials have yet demonstrated its usefulness.

SPLENIC PULP PRESSURE

Determination of splenic pulp pressure is an indirect method of measuring portal pressure and involves puncture of the splenic pulp with a needle catheter. Splenic pulp pressure is elevated in presinusoidal portal hypertension, when the HVPG is normal. Because of the potential risk of complications, especially bleeding, associated with splenic puncture, however, the procedure is rarely used.

PORTAL VEIN PRESSURE

Direct measurement of the pressure in the portal vein is a rarely used method that can be carried out through a percutaneous transhepatic route, transvenous approach, or, rarely, intraoperatively (although anesthesia can affect portal pressure). The transhepatic route requires portal vein puncture performed under ultrasound guidance. A catheter is then threaded over a guidewire into the main portal vein.With increasing use of the transjugular intrahepatic portosystemic shunt (TIPS) , radiologists have gained expertise in puncturing the portal vein and measuring portal vein pressure by a transjugular route. Direct portal pressure measurements are carried out when HVPG cannot be measured, as in patients with occluded hepatic veins caused by the Budd-Chiari syndrome, in whom a surgical portosystemic shunt is being

contemplated, or in patients with intrahepatic, presinusoidal causes of portal hypertension, such as idiopathic portal hypertension, in which the HVPG may be normal

Idiopathic Portal Hypertension

Idiopathic portal hypertension is uncommon in Western countries but is common in parts of Asia such as India and Japan. This disorder is diagnosed when the portal pressure is elevated in the absence of significant histologic changes in the liver or extrahepatic portal vein obstruction. A liver biopsy specimen from affected patients may be entirely normal although increased concentrations of ET-1 have been noted in the periportal hepatocytes, portal venules, and hepatic sinusoids of patients with idiopathic portal hypertension. Various terms used to describe idiopathic portal hypertension include *hepatoportal sclerosis*, *noncirrhotic portal fibrosis*, and *Banti's syndrome*. Use of the term *idiopathic portal hypertension* probably is best restricted to portal hypertension in patients in whom no hepatic lesion is found on light microscopy.

The term *hepatoportal sclerosis* suggests obliterative portal venopathy with subendothelial thickening of the intrahepatic portal

veins; thrombosis and recanalization of these veins may follow. Fibrosis of the portal tracts is prominent later in the course.

The cause of idiopathic portal hypertension is unclear in a majority of patients, although chronic arsenic intoxication, exposure to vinyl chloride, and hypervitaminosis A have been implicated . These etiologic factors are present in only a minority of patients. The dominant clinical features of the condition are variceal bleeding and hypersplenism related to a markedly enlarged spleen. Liver biochemical test levels are usually normal, although the serum alkaline phosphatase level may be mildly elevated. Ascites is" "uncommon. The HVPG in this disorder usually is normal because the site of increased resistance is presinusoidal. Surgical portosystemic shunts are well tolerated in these patients, although hepatic encephalopathy may occur on long-term follow-up evaluation. Liver transplantation is rarely required in these patients"

HEPATIC ENCEPHALOPATHY

"The term hepatic encephalopathy (HE) encompasses a wide array of transient and reversible neurologic and psychiatric manifestations usually found in patients with chronic liver disease and portal hypertension, but also seen in patients with acute liver failure. HE

develops in 50% to 70% of patients with cirrhosis, and its occurrence is a poor prognostic indicator, with projected one- and three-year survival rates of 42% and 23%, respectively, without liver transplantation. Symptoms may range from mild neurologic disturbances to overt coma. HE is often triggered by an inciting event that results in a rise in the serum ammonia level. The precise underlying pathophysiologic mechanisms are not well understood, and the mainstay of therapy is the elimination" "of the precipitating event and excess ammonia. Liver transplantation generally reverses HE.

PATHOPHYSIOLOGY

A number of factors, occurring alone or in combination, have been implicated in the development of HE. These factors may differ in acute and chronic liver disease and include the production of eurotoxins, altered permeability of the blood-brain barrier, and abnormal neurotransmission.

The best-described neurotoxin involved in HE is ammonia, which is produced primarily in the colon, where bacteria metabolize proteins and other nitrogenbased products into ammonia. Enterocytes synthesize ammonia from glutamine. Once produced, ammonia enters the portal circulation and, under normal conditions, is metabolized and cleared by

hepatocytes. In cirrhosis and portal hypertension, reduced hepatocyte function and portosystemic shunting contribute to increased circulating ammonia levels. Arterial hyperammonemia is observed in up to 90% of patients with HE, although serum levels are neither sensitive nor specific indicators of its presence".

"Increased permeability of the blood-brain barrier increases the uptake and extraction of ammonia by the cerebellum and basal ganglia.Acute hyperammonemia appears to have a direct effect on brain edema, astrocyte swelling and the transport of neurally active compounds such as myoinositol, and thereby contributes to HE. Other alterations in HE affect neuronal membrane fluidity, central nervous system (CNS) neurotransmitter expression, and neurotransmitter receptor expression and activation. The γ-aminobutyric acid (GABA)–system has been the most well studied. Although CNS benzodiazepine levels and GABA receptor concentrations are unchanged in animal models of HE, increased" sensitivity of the astrocyte (peripheral-type) benzodiazepine receptor enhances activation of the GABA-benzodiazepine system. This activation occurs in part through a feed-forward system in which production of neurosteroids" "(allopregnanolone and tetrahydrodeoxycorticosterone) by astrocytes further activates the GABAA-benzodiazepine receptor system. Other

factors that influence CNS neurotransmission, including serotonin (5-hydroxytryptamine, 5-HT), nitric oxide (NO), circulating opioid peptides, manganese, and increased oxygen free radical production, have also been postulated to contribute to HE. Finally, hyperammonemia, particularly in acute liver failure, also increases astrocyte glutamine production via glutamine synthetase. The rise in astrocyte glutamine and glutamate concentrations contributes to factors associated with CNS dysfunction

CLINICAL FEATURES AND DIAGNOSIS

HE may present as a spectrum of reversible neuropsychiatric symptoms and signs, ranging from mild changes in cognition to profound coma, in patients with acute or chronic liver disease. It is often precipitated by an inciting event (e.g., gastrointestinal bleeding, electrolyte abnormalities, infections, medications, dehydration). The diagnosis of HE, therefore, requires careful consideration in the appropriate" "clinical situation. Occasionally, HE may be the initial presentation of chronic liver disease. Subtle findings in HE may include forgetfulness, alterations in handwriting, difficulty with driving, and reversal of the sleep-wake cycle".

“Overt findings may include asterixis, agitation, disinhibited behavior, seizures, and coma. Other causes of altered mental status, particularly hypoglycemia, hyponatremia, medication ingestion, and structural intracranial abnormalities resulting from coagulopathy or trauma, should be considered and rapidly excluded in patients suspected of having HE”.

“No specific laboratory findings indicate the presence of HE definitively. The most commonly used test to assess a patient with possible HE is the blood ammonia level. An elevation in the blood ammonia level in a patient with cirrhosis and altered mental status supports a diagnosis of HE. Blood ammonia levels may be elevated in the absence of HE, however, because of gastrointestinal bleeding or the ingestion of certain medications (e.g., diuretics, alcohol, narcotics”, “valproic acid). In addition, blood ammonia levels may be elevated in the presence of HE, even in the absence of cirrhosis and portal hypertension, in patients with metabolic disorders that influence ammonia generation or metabolism,” such as urea cycle disorders and disorders of proline metabolism

Use of a tourniquet when blood is drawn and delayed processing and cooling of a blood sample may raise the blood ammonia level. Measurement of arterial ammonia offers no advantage over

measurement of venous ammonia levels in patients with chronic liver disease. In patients with acute liver failure, however, elevated arterial ammonia levels (150 to 200 mg/dL or higher) may be predictive of the presence of brain edema and herniation Of the scoring systems used to grade the severity of HE, the West Haven system, based on a scale of 0 to 4, is the most widely used in clinical practice Although clinically useful, the West Haven criteria are insensitive and have led to the development of standardized" "psychometric tests and rapid bedside mental status assessments to aid in the diagnosis of HE and facilitate research.

One simple paper and pencil test, the portosystemic ence encephalopathy syndrome test (PSET), evaluates the patient's attention, concentration, fine motor skills, and orientation and has been shown to be highly specific for the diagnosis of HE The development of these tests has led to recognition of the syndrome of *minimal HE*, in which abnormalities are observed on testing but clinically recognizable alterations of HE are minimal or not detected. The presence of minimal HE is common in patients with cirrhosis, appears" "to influence the patient's quality of life and driving ability, and confers an increased risk that overt HE will develop in the patient. Whether treatment of minimal HE confers any benefit is an area of active investigation.

A number of novel imaging and functional tests have been studied in the diagnosis of HE. Magnetic resonance spectroscopy (MRS) has been used to measure brain concentrations of choline and glutamine noninvasively. Magnetic resonance (MR) T1 mapping with partial inversion recovery" "(TAPIR) has been investigated as a means to measure changes in the brain quantitatively over clinically relevant measurement times. Whether MR-based techniques can be standardized and become practical diagnostic tests is uncertain. The critical flicker frequency test, a simple light-based test that has been used to assess cerebral cortex function in a number of disorders, has been shown to be a reliable marker of minimal HE and may become a clinically useful screening test".

TREATMENT

"Current treatments for HE are directed primarily toward the elimination or correction of precipitating factors bleeding, infection, hypokalemia, medications, dehydration), reduction in elevated blood ammonia levels, and avoidance of the toxic effects of ammonia in the CNS. In the past, dietary protein restriction was considered an important component of the treatment of HE. Subsequent work, however, has suggested that limiting protein-calorie intake is not beneficial in patients with HE.Vegetable and dairy proteins are preferred to animal proteins

because of a more" "favorable calorie-to-nitrogen ratio. Although branchedchain amino acid supplementation may improve symptoms modestly, the benefits of such supplementation are not sufficient to justify its routine use."

"Nonabsorbable disaccharides have been the cornerstone of the treatment of HE. Oral lactulose or lactitol (the latter is not available in the United States) are metabolized by colonic bacteria to byproducts that appear to have beneficial effects by causing catharsis and reducing intestinal pH, thereby inhibiting ammonia absorption. These agents improve symptoms in patients with acute and chronic HE when compared with placebo but do not improve psychometric test performance or mortality. The most common" "side effects experienced by patients who take lactulose are abdominal cramping, flatulence, diarrhea, and electrolyte imbalance. Lactulose may also be administered per rectum (as an enema) to patients who are at increased risk of aspiration, although the efficacy of enema administration has not

been evaluated.

Oral antibiotics also have been used to treat HE, with the" 'aim of modifying the intestinal flora and lowering stool pH to enhance the excretion of ammonia. Antibiotics are generally used as second-line

agents after lactulose or in patients who are intolerant of nonabsorbable disaccharides. Neomycin has been approved by the U.S. Food and Drug Administration (FDA) for use in acute HE in a dose of 1 to 3 g orally every six hours for up to six days but has been used more commonly off-label to treat chronic HE in doses of 0.5 to 1 g every 12 hours, in addition to lactulose. The efficacy of neomycin in acute or chronic HE, however, is not clearly" "established,47 and ototoxicity and nephrotoxicity caused by neomycin have been reported, particularly in patients with preexisting renal dysfunction.4 Rifaximin has been studied and approved by the FDA for the treatment of chronic HE on the basis of the results of a multicentered, randomized, controlled trial in which the overall clinical efficacy and rate of side effects were similar in patients treated with lactitol and those treated with rifaximin.48 The usual dose is 400 mg orally three times daily. Two systematic reviews" "of randomized controlled trials that compared rifaximinwith other therapies (nonabsorbable disaccharides and other antibiotics) for the treatment of acute or chronic HE have confirmed that the efficacy and side effect profiles are comparable. Other antibiotics, including metronidazole and vancomycin, have been reported to be effective in small trials and case series, but the data to support their use are insufficient. In addition to antibiotics, several other agents that may

modify intestinal flora and modulate ammonia generation or absorption have been evaluated as potential treatments for HE. Acarbose, an intestinal α-glucosidase inhibitor used to treat type 2 diabetes mellitus, inhibits the intestinal absorption of carbohydrates and glucose and results in their enhanced delivery to the colon. As a result, the ratio of saccharolytic to proteolytic bacterial flora is increased, and blood ammonia levels are decreased. A randomized, controlled, double-blind, crossover trial has demonstrated that acarbose improves mild HE in patients with cirrhosis and adult-onset diabetes mellitus.Similarly, probiotic regimens have been used to modify intestinal flora and" "diminish ammonia generation. Four small studies have suggested that these agents may be beneficial in humans with mild HE. These agents merit further evaluation and may be alternatives for patients who do not tolerate lactulose.

Strategies to enhance ammonia clearance may also be useful in the treatment of HE. Sodium benzoate, sodium phenylbutyrate, and sodium phenylacetateall of which increase ammonia excretion in urine, are approved by the FDA for the treatment of hyperammonemia resulting from urea cycle enzyme defects and may improve HE in cirrhosis . Administration of sodium benzoate, however, results in a high sodium load, and the efficacy of this agent is not clearly established. The

combination of intravenous sodium phenylacetate and sodium benzoate (Ammonul, Ucyclyd Pharma, Scottsdale, Ariz) in HE is being studied. Administration of zinc, which has been used because zinc deficiency is common in patients with cirrhosis and because zinc increases the activity of ornithine transcarbamylase, an enzyme in the urea cycle, may also" "improve HE; however, clear efficacy has not been established.

Extracorporeal albumin dialysis using the molecular adsorbent recirculating system (MARS) has resulted in a reduction in blood ammonia levels and improvement in severe HE in patients with acute-on-chronic liver failure Further studies are needed to clarify whether albumin dialysis has a role in treatment of HE. Finally, l-ornithine–l-aspartate (LOLA), a salt of the amino acids ornithine and aspartic acid that activates the urea cycle and enhances ammonia clearance, has been shown in several randomized controlled studies to improve HE compared with lactulose. Flumazenil is a specific benzodiazepine (GABAA receptor) antagonist that has been used in patients with HE. It improves the degree of encephalopathy and electrophysiologic findings in approximately one fourth of patients with grade 3 or 4 HE. It has a short half-life and a number of potential side effects, including seizures, arrhythmias, and withdrawal symptoms, that limit its clinical usefulness."

GASTROESOPHAGEAL VARICES:

Varices -dilated and tortous veins that commonly develop within the oesophagus and stomach of patients with cirrhosis. They are Porto-systemic collaterals — ie.vascular channels that link the portal venous and the systemic venous circulation and develop as a result of portal hypertension, preferentially in the submucosa of the lower esophagus and also in stomach.

Sites of portal collaterals:"

1. Oesophageal and gastric varices
2. Hemorrhoids.
3. Caput medusae.
4. Retroperitoneal sites

bleeding from esophageal varices are associated with a high mortality , the mortality rate still remains high (20%-35%) . bleeding contributes to 10–30% of all cases of UGI bleeding .

EPIDEMIOLOGY:

Most common location - distal oesophagus,but varices occur in anywhere along the gastrointestinal tract. 50% of patients with cirrhosis

may develop gastroesophageal varices, Gastric varices are present in 5–33% of patients with portal hypertension.The frequency of esophageal varices varies from 30% to 60% in patients with Cirrhosis and 9–38% of patients have “high-risk”varices.

Annual rate of development of varices in patients with cirrhosis is around 5–8%, but the risk of bleeding in only 1–2% of cases.

PATHOPHYSIOLOGY:

Four distinct zones of venous drainage at the gastroesophageal junction are particularly relevant to the formation of esophageal varices. The “gastric zone”, which extends for 2 to 3 cm below the gastroesophageal junction, comprises veins that are longitudinal and located in the submucosa and lamina propria. They come together at the upper end of the cardia of the stomach and drain into short gastric and left gastric veins.The “palisade zone” extends 2 to 3 cm proximal to the gastriczone into the lower esophagus. Veins in this zone run longitudinally and in parallel in 4 groups corresponding to the esophageal mucosal folds. These veins anastomose with “veins” in the lamina propria. The perforating veins in the palisade zone do not communicate with extrinsic (periesophageal) veins in the distal esophagus,hence more chance of bleeding. The palisade zone is the

dominant watershed area between the portal and systemic circulations.More proximal to the palisade zone in the esophagus is the “perforating zone”, where there is a network of veins. These veins are less likely to be longitudinal and are termed “*perforating veins”* because they connect the veins in the esophageal submucosa and the external veins. The “truncal zone”, the longest zone, is approximately 10 cm in length, located proximal to the perforating zone in the esophagus, and usually characterized by 4 longitudinal veins in the lamina propria and they are unlikely to bleed.The periesophageal veins drain into the azygos system, and as a result, an increase in azygos blood flow is a hallmark of portal hypertension. The venous drainage of the lower end of the esophagus is through the coronary vein, which also drains the cardia of the stomach, into the portal vein.

The fundus of the stomach drains through short gastric veins into the splenic vein. In the presence of portal hypertension , varices may therefore form in the fundus of the stomach.Splenic vein thrombosis usually results in isolated “gastric fundal varices”

“Because of the proximity of the splenic vein to the renal vein, spontaneous splenorenal shunts may develop and are more common in patients with gastric varices than in those with esophageal varices.

The development of gastroesophageal varices requires a portal pressure gradient of at least 10 mm Hg. Furthermore, a portal pressure gradient of at least 12 mm Hg is thought to be required for varices to bleed; other local factors that increase variceal wall tension are also needed because not all patients with a portal pressure gradient of greater than 12 mm Hg bleed. Factors that influence variceal wall tension can be viewed in the context of "Laplace's law":

$T = Pr/w$

T is variceal wall tension

P is the transmural pressure gradient between the variceal and

esophageal lumen

r is the variceal radius

w is the variceal wall thickness.

When the variceal wall thins and the varix increases in diameter and pressure, the tolerated wall tension is exceeded and the varix ruptures. These physiologic observations are manifested clinically by the observation that patients with larger varices (r) in sites of limited soft tissue support (w), with elevated portal pressure" "(P), tend to be at greatest risk for variceal rupture from variceal wall tension (T) that

becomes excessive. One notable site in which soft tissue support is limited is at the gastroesophageal junction..

DIAGNOSIS OF VARICES:

"Upper GI endoscopy" is the most commonly used method and also gold standard to detect varices. The consensus is that all patients diagnosed with cirrhosis of the liver should be screened for esophageal varices by endoscopy. Surveillance endoscopies are recommended on the basis of the level of cirrhosis and the presence and size of the varices

Patients with Compensated cirrhosis and No varices - Every 2–3 years Compensated cirrhosis with small varices - Every 1–2 years Decompensated cirrhosis - Yearly intervals

Wireless video capsule endoscopy, CT imaging,Doppler ultrasonography, radiography/barium swallow of the esophagus and stomach, and portal vein angiography and manometry are alternative screening modalities in patients who are not candidates for upper endoscopy".

"ESOPHAGEAL VARICES

Endoscopic grading of esophageal varices is subjective.Various criteria have been used to try to standardize the reporting of esophageal

varices. The most commonly used criteria are those compiled by the “Japanese Research Society for Portal Hypertension . The descriptors include

- red color signs,
- color of the varix,
- size of the varix, and
- location of the varix.

“Red color signs” include

1) “red wale markings”, which are longitudinal whip-like marks on the varix

2) “cherry-red spots”, which usually are 2 to 3 mm or less in diameter

3) “hematocystic spots”, which are blood-filled blisters 4 mm or greater in diameter

4) diffuse redness.

The color of the varix can be white or blue. The form of the varix at endoscopy is described most commonly as

- small and straight(grade I)

 tortuous and occupying less than one third of theesophageal lumen (grade II)”

“ large and occupying more than one third of the esophageal lumen (grade III).

Varices can be in the lower third, middle third, or upper third of the esophagus. Of all of the aforementioned descriptors, the size of the varices in the lower third of the esophagus is the most important. The size of the varices in the lower third of the esophagus is determined during withdrawal of the endoscope. Small varices are less than 5 mm in diameter, whereas large varices are greater than 5 mm in diameter.

Another grading which is used in this study is the Paquet classification, where varix size is graded on a 4-point Likert scale:

 grade 1 varices are small and flattened by insufflation of air;

 grade 2 varices are slightly larger and do not flatten;

 grade 3 varices are larger but do not touch in the middle of the lumen.

 grade 4 varices are large and touch each other in the middle of the lumen.

Grade 1 and 2 are small varices and grade 3 and 4 are large varices.Others are two size ,three size classifications.

Patients with large esophageal varices, Child-Pugh class C cirrhosis, and red color signs on varices have the highest risk of variceal bleeding within 1 year “Progression from small to large varices” are associated with”

• Decompensated cirrhosis

• Alcoholic cirrhosis

• Presence of red wale marks at baseline endoscopy

Risk factors for “Initial variceal bleeding” are:

• large varices (>5 mm) with red color signs

• high CTP or MELD score

• continuing alcohol consumption

• high HVPG >16 mm hg

• coagulopathy

“Variceal haemorrhage” is diagnosed on the basis of one of the following findings on endoscopy:

 Active bleeding from a varix

 “White nipple” overlying a varix

- Clots overlying a varix
- Varices with no other potential source of bleeding

GASTRIC VARICES:

There are three types of classification commonly used for GV.

1. Sarin's classification
2. Hashizome classification
3. Arakawa's classification.

Most commonly used classification is Sarin's classification.

SARIN'S CLASSIFICATION

Gastric varices are categorized into four types based on the relationship with esophageal varices, as well as by their location in the stomach .

a. Gastroesophageal varix (GOV) type 1: Extension of esophageal varices along lesser curve.

b. Gastroesophageal varix type 2: Extension of esophageal varices along greater curve.

c. isolated gastric varices type1 in stomach

d.isolated gastric varices type 2 in duodenum

GV drain into the systemic vein via the esophageal paraesophageal varices (gastroesophageal venous system), the inferior phrenic vein (IPV) (gastrophrenic venous system), or both. These drainage types generally correspond to the classification system of Sarin *et al*. GOV1 drains via esophageal and paraesophageal varices, IGV1 drains via the left IPV, and GOV2 drains via both esophageal varices and the IPV. GV form at the hepatopetal collateral pathway that develops secondary to localized portal hypertension and drain via the gastric veins, thereby corresponding with IGV2 .

TREATMENT :

The treatment of portal hypertension is aimed either at reducing portal blood flow with pharmacologic agents, such as beta blockers or vasopressin and its analogs, or at decreasing intrahepatic resistance with pharmacologic agents, such as nitrates, or by radiologic or surgical creation of a portosystemic shunt.Treatment also may be directed at the varices with use of endoscopic or radiologic techniques.

PHARMACOLOGIC THERAPY:

It consist of “splanchnic vasoconstrictors” (vasopressin and analogues,somatostatin analogues, nonselective beta-blockers) and “venodilators” (nitrates).

Vasoconstrictors act by producing splanchnic vasoconstriction and reducing portal venous inflow. Venodilators theoretically act by decreasing intrahepatic and/or portocollateral resistance.

Drugs That Decrease Portal Blood Flow

- Nonselective β-adrenergic blocking agents
- Somatostatin and its analogs
- Vasopressin and terlipressin

Drugs That Decrease Intrahepatic Resistance

- α1-Adrenergic blocking agents (e.g., prazosin)
- Angiotensin receptor blocking agents
- Nitrates

ENDOSCOPIC THERAPIES -

"sclerotherapy or endoscopic variceal ligation (EVL)

SHUNTING THERAPY

radiological (transjugular intrahepatic portosystemic shunt) or surgical, markedly reduces portal pressure by bypassing the site of increased resistance.

"Vasopressin" is an endogenous peptide hormone that causes splanchnic vasoconstriction, reduces portal venous inflow, and reduces portal pressure. This drug is associated with serious systemic side effects. "Terlipressin" is another semisynthetic analogue with lesser side effects.

"Somatostatin" is a 14–amino acid peptide. Following IV injection, somatostatin has a half-life in the circulation of 1 to 3 minutes; therefore, longer-acting analogs of somatostatin have been synthesized. The best known of these analogs are octreotide, lanreotide, and vapreotide. Somatostatin decreases portal pressure and collateral blood flow by inhibiting release of glucagon. Somatostatin also decreases portal pressure by decreasing postprandial splanchnic blood flow.

“Octreotide” has a half-life in the circulation of 80 to 120 minutes following iv administraton. Its effect on portal pressure is not prolonged,however. Moreover, continuous infusion of octreotide does not decrease portal pressure despite decreasing the postprandial increase in portal pressure. Long-acting octreotide does not reliably reduce portal pressure, and side effects with higher doses preclude use of this agent for the treatment of portal hypertension. Some randomized controlled trials support the view that somatostatin or octreotide may be equivalent in efficacy to terlipressin or sclerotherapy for controlling acute variceal bleed. In clinical practice,somatostatin or octreotide administration is combined with endoscopic management of variceal bleeding.

“ Nonselective beta blockers” such as propranolol or nadolol are preferred. Blockade of β1-adrenergic receptors in the heart decreases cardiac output.Blockade of β2-adrenergic receptors, which cause vasodilatation in the mesenteric circulation, allows unopposed action of α1-adrenergic receptors and results in decreased portal flow.The combination of decreased cardiac output and decreased portal flow leads to a decrease in portal pressure. The effectiveness of beta blockers is assessed most accurately by monitoring the HVPG. The acute hemodynamic response (decrease in HVPG to < 12 mm Hg, or by 10%) 20 minutes after administration of IV propranolol may be used to predict

the long-term reduction in bleeding risk. The benefit of beta blockers is reduced when hepatic function worsens. The usual method of monitoring the efficacy of beta blockers is to observe a decrease in the heart rate, which is a measure of β1-adrenergic receptor blockade.

“Carvedilol” is a drug that has both nonselective β-blocker and weak α-receptor blockade activity. α-Receptor activity normally increasesresistance within the intrahepatic circulation. Therefore, blockade of the α-receptor decreases intrahepatic vascular resistance, which results in a further reduction in portal pressure Carvedilol is also known to have antioxidant as well as antiproliferative actions and may be superior to endoscopic variceal ligation in the prevention of a first variceal bleed .Carvedilol has been demonstrated to be equivalent to a combination of nadolol and isosorbide mononitrate in reducing variceal rebleeding, with fewer side effects.Carvedilol is started in a dose of 6.25 mg once daily, and the dose is increased stepwise to a maximum of 25 mg daily. Dose increases are usually limited by arterial hypotension. “Nitrates”- Short-acting (nitroglycerin) or long-acting (isosorbide mononitrate) nitrates result in vasodilatation. The vasodilatation results from a decrease in intracellular calcium in vascular smooth muscle cells. Nitrates cause venodilatation, rather than arterial dilatation, and decrease portal pressure predominantly by decreasing portal venous blood flow.

Nitroglycerin has been used in combination with vasopressin to control acute variceal bleeding. The rate of infusion of nitroglycerin is 50 to 400 μg per minute, provided that the systolic blood pressure is greater than 90 mm Hg; however, the combination of vasopressin and nitroglycerin is seldom used nowadays. Nitrates are no longer recommended, either alone or in combination with a beta blocker, for primary prophylaxis to prevent first variceal bleeds. For secondary prophylaxis (to prevent variceal rebleeding), isosorbide mononitrate may be added to a beta blocker if the beta blocker alone has not resulted in an appropriate decrease in HVPG.

Drugs like prazosin,losartan,simvastatin may decrease intrahepatic resistance.

ENDOSCOPIC THERAPY:

Endoscopic therapy is the only treatment modality that is widely accepted for the prevention of variceal bleeding,control of acute variceal bleeding, and prevention of variceal rebleeding. Endoscopic variceal therapy includes variceal sclerotherapy and band ligation.

SCLEROTHERAPY

Endoscopic sclerotherapy has largely been supplanted by endoscopic band ligation, except when poor visualization precludes effective band ligation of bleeding varices. The technique involves injection of a sclerosant into (intravariceal) or adjacent to (paravariceal) a varix.The sclerosants used include sodium tetradecyl sulfate,sodium morrhuate, ethanolamine oleate, and absolute alcohol.Complications include retrosternal discomfort, sclerosant-induced esophageal ulcer-related bleeding, strictures, and perforation.

VARICEAL LIGATION:

Endoscopic variceal ligation is the preferred endoscopic modality for control of acute esophageal variceal bleeding and prevention of rebleeding; however, the utility of band ligation in the treatment of gastric varices is limited.

Variceal ligation is simpler to perform than injection sclerotherapy. The procedure involves suctioning of the varix into a cap fitted on the tip of an endoscope and deploying a band around the varix.The band strangulates the varix, thereby causing thrombosis.

Multi-band devices can be used to apply several bands without requiring withdrawal and reinsertion of the endoscope .Varices at the gastroesophageal junction are banded initially,and then more proximal varices are banded in a spiral manner at intervals of approximately 2 cm; the endoscope is thenwithdrawn. Varices in the mid- or proximal esophagus do not need to be banded.

Endoscopic variceal ligation is associated with fewer complications than sclerotherapy and requires fewer sessions to achieve variceal obliteration. Moreover,esophageal variceal ligation during an acute bleed is not associated with a sustained elevation in HVPG, as occurs with sclerotherapy.Endoscopic variceal ligation can cause local complications including esophageal ulcers , strictures, and dysmotility,less frequently than does sclerotherapy.Banding-induced ulcers can be large and potentially serious if gastric fundal varices are banded. A PPI is usually recommended after variceal ligation.Detachable snares and clips are generally not indicated.

BALLOON TAMPONADE AND STENTS:

From 10% to 15% of patients with an acute variceal bleeding are refractory to pharmacologic and endoscopic treatment.Balloon tamponade is used as a temporizing measure until TIPS can be carried

out. Varices are easily compressed because they are superficial and thin-walled and the flow of blood is via submucosal vessels. The Sengstaken-Blakemore tube is a triple-lumen tube: one tube is for aspirating gastric contents,the other allows inflation of a gastric balloon to 200 to 400 mL in volume, and the third inflates an esophageal balloon. The Minnesota tube is a modified Sengstaken-Blakemore tube. Inflation of a gastric balloon alone is preferred with any of these tubes. Balloon tamponade can control bleeding for up to 24 hours in approximately 80% to 90% of patients.The risk of pulmonary aspiration is reduced by placement of an endotracheal tube. If bleeding cannot be controlled after placement of the tube, reinflate and reposition the gastric balloon than to inflate the esophageal balloon.Because of the risks associated with placement of tamponade balloons, selfexpandable metallic covered stents have been used to tamponade esophageal varices.

These stents may be left in place for up to 2 weeks and then removed.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT:

A “transjugular intrahepatic portosystemic shunt (TIPS)”— also referred to as a transjugular intrahepatic portosystemic stent shunt

(TIPSS)—reduces elevated portal pressure by creating a communication between the hepatic vein and an intrahepatic branch of the portal vein. A percutaneous transjugular approach is used to insert the shunt. A TIPS functions as a side-to-side portacaval shunt and has been used to treat complications of portal hypertension, mainly variceal bleeding and refractory ascites, as well as Budd-Chiari syndrome,hepatic hydrothorax, and hepatorenal syndrome.

"TIPS" has been used to control acute variceal bleeding and to prevent variceal rebleeding when pharmacologic and endoscopic therapies have failed, especially in patients with Child-Pugh class B or C cirrhosis, in whom bleeding is more likely to be refractory to therapy than in patients with Child-Pugh class A cirrhosis. The use of early TIPS (within 72 hours of control of variceal bleeding) in patients at high-risk of rebleeding (Child-Pugh class C, class B with active bleeding, or a MELD score > 18 and a transfusion requirement of > 4 units of red blood cells

[RBCs]) is associated with a reduced rate of treatment failure and mortality, without an increased risk of hepatic encephalopathy, compared with continued pharmacologic and endoscopic therapy. When bleeding from varices cannot be controlled after 2sessions of endoscopic therapy within a 24-hour period, TIPS placement is the usualsalvage

treatment.TIPS is also used to treat bleeding from isolated gastric fundal varices, for both control of bleeding and prevention of rebleeding. Complications following the procedure are classified as procedure related, early (occurring within 30days),or late (after 30days) ,TIPS cannot be recommended as a first choice for preventing variceal rebleeding due to various complications; rather, it is reserved for patients who have failed endoscopic or pharmacologic therapy.

SURGICAL THERAPY:

Surgical treatment of portal hypertension falls into 3 groups:

- non-shunt procedures
- portosystemic shunt procedures
- liver transplantation

Surgical procedures (other than liver transplantation) are used as salvage therapy when standard management with pharmacologic and endoscopic therapy fails in patients with noncirrhotic causes of portal hypertension and in patients with Child-Pugh class A cirrhosis. Liver transplantation should be considered in all patients with cirrhosis and variceal bleeding

NON-SHUNT PROCEDURES :

Non-shunt procedures include “esophageal transection” and “gastroesophageal devascularisation”. They are performed infrequently but may be required in selectedcases.

SURGICAL SHUNTS:

With the increasing availability of TIPS, the use of surgical shunts for refractory variceal bleeding has declined markedly.In children, surgical shunts are carried out almost exclusively for refractory bleeding due to noncirrhotic portal hypertension, such as congenital hepatic fibrosis and portal vein thrombosis. Surgical portosystemic shunts are categorized as selective shunts such as distal splenorenal Shunts(WARRENS SHUNT), partial shunts such as the side-to-side calibrated portacaval shunt, and total portosystemic shunts such as the side-to-side portacaval shunt or end-to-side portacaval shunt.

GASTRIC VARICES TREATMENT:

a. Endoscopic treatment modalities for gastric variceal bleeding.

1. Gastric variceal sclerotherapy (GVS).

2. Gastric variceal obturation (GVO) with glue.

3. Gastric variceal band ligation (GVL) with or without detachable snares.

4. Thrombin injection (bovine or human).

5. Combined endoscopic therapy.

b. Endoscopic ultrasound-guided therapy.

c. Radiologic intervention –

“ transjugular intrahepatic portosystemic shunt (TIPS)”

“ Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)”.

Management Recommendations:

1)PATIENTS WITH CIRRHOSIS BUT NO VARICES:

Bea blockes donot prevent varices

Repeat EGD IN 3 years

Immediate EGD If decompensation occurs

2)PATIENTS WITH CIRRHOSIS AND SMALL VARICES, BUT NO HEMORRHAGE:

Non selective beta blockers to prevent first variceal hemorrhage

3)PATIENTS WITH CIRRHOSIS AND MEDIUM OR LARGE VARICES, BUT NO HEMORRHAGE:

High risk of hemorrhage- Non selective beta blockers or EVL preferred

Not at high risk- beta blockers preferred,if non compliance,intolerance,or contraindication EVL recommended

If a patient is placed on a nonselective beta-blocker, it should be adjusted to the maximal tolerated dose; follow-up surveillance EGD is unnecessary. It is a costeffective form of prophylactic therapy. It does not prevent development or growth from small to large varices and has significant side effects.Patientsreceiving a selective β-blocker (metoprolol, atenolol) for other reasons should switch to a nonselective β-blocker (propranolol, nadolol, or carvedilol).

If a patient is treated with EVL, it should be repeated every

1-2 weeks until obliteration with the first surveillance EGD performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence.Nitrates (either alone or in combination with beta-blockers), shunt therapy, or sclerotherapy should not be used in the primary prophylaxis of variceal haemorrhage.

4) PATIENTS WITH CIRRHOSIS AND ACUTE VARICEAL HEMORRHAGE:

Iv volume support,blood transfusion

Antibiotic prophylaxis-oral norfloxacin,iv ciprofloxacin,iv ceftriaxone

Pharmacological therapy-terlipressin,somatostatin(or octreotide, vapreotide)

Treat varices with ligation or sclerotherapy

In uncontrolled bleeding TIPS indicated

In patients who bleed from gastric fundal varices,endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available.Otherwise, EVL is an option.TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs

despite combined pharmacological and endoscopic therapy

5) PATIENTS WITH CIRRHOSIS WHO HAVE RECOVERED FROM ACUTE VARICEAL HEMORRHAGE:

Secondary prophylaxis-- Non selective beta blockers plus EVL In pt with recurrent hemorrhage-surgical shunt in child A pt and refer to transplant center for evaluation

RECOMMENDATIONS FOR FIRST-LINE MANAGEMENT OF CIRRHOTICPATIENTS AT EACH STAGE IN THE NATURAL HISTORY OF VARICES:

No varices – repeat endoscopy in 2-3 years

Small varices and no hemorrhage- repeat endoscopy in 1-2 years

Medium/large varices and no hemorrhage- beta-blockers,EVL if not tolerated variceal hemorrhage-vasoactive drug plus EVL

WHY THERE IS A NEED FOR NONINVASIVE PREDICTORS OF ESOPHAGEAL VARICES?

The diagnosis of EV is required for patients with liver cirrhosis to detect those who will benefit from variceal bleeding primary prophylaxis.

Currently, esophago-gastro-duodenoscopy (EGD) remains the gold standard test for such diagnosis. However, EGD is limited by its invasiveness and high cost. A simple non-invasive widely available and cheap test would be ideal if proved to have sufficient specificity and sensitivity. Therefore, we aimed to study the diagnostic value of an indexderived from the patients' complete blood count; namely the P2/MS ratio as a predictive tool for thepresence of varices and if they are at high risk of bleeding.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY POPULATION:

The present study was conducted on 50 patients admitted with a diagnosis of cirrhosis of liver at general medicine and medical gastroenterology wards of Government Rajaji Hospital, Madurai during the period of may 2017 to august 2017

Inclusion criteria:

- Liver cirrhosis patients. Diagnosis of cirrhosis was based on clinical, biochemical and ultrasonographic findings.

Exclusion Criteria

Individuals presening with

- previous variceal bleeding
- β-blocker therapy or endoscopic treaments (band ligation or sclerotherapy)
- portal vein thrombosis
- previous surgery for portal hypertension or transjugular intrahepatic porto-systemic shunt stent placement
- hepatocelluar carcinoma.

DATA COLLECTION:

A previously designed proforma was used to collect the demographic and clinical details of the patients. All the patients underwent detailed clinical evaluation, appropriate investigations, imaging studies (ultrasound with Doppler) and upper g.i endoscopy.

STUDY PROTOCOL

DESIGN OF STUDY:

Prospective analytical study

PERIOD OF STUDY:

May 2017 to August 2017

LABORATORY INVESTIGATIONS:

Complete blood count – differential count,platelet count

Liver function test

Ultrasound abdomen

Endoscopy

STUDY METHODOLOGY:

50 liver cirrhosis patients with no previous variceal bleeding and not on beta blocker prophylaxis were subjected to do complete blood count test.

P2/MS index was calculated using platelet count,monocyte fraction and neutrophil fraction.

They were subjected to esophagogastroduodenoscopy for detecting esophageal varices.

Sensitivity, specificity, positive predictive value,negative predictive value were calculated.

COLLABORATING DEPARTMENTS:

Department of Medicine, Department of medical gastroenterology, Department of pathology, Department of Bio chemistry, Department of Radio diagnosis

ETHICAL CLEARANCE:clearance obtained

CONSENT: Individual written and informed consent obtained

ANALYSIS*:*Statistical analysis

CONFLICT OF INTEREST*:*Nil

FINANCIAL SUPPORT: nil

RESULTS AND INTERPRETATION

RESULTSAND OBSERVATIONS

Table 1.Age distribution of the study population (n -50)

Age (in yrs)	
N	50
Mean	49.0
SD	10.6
Minimum	31
Maximum	72

Age group (in yrs)	**No. (%)**
31 – 40	12 (24.0)
41 – 50	18 (36.0)
51 – 60	13 (26.0)
>60	7 (14.0)
Total	50 (100.0)

Comments:

Out of 50 patients 12 patients(24%) are in the age group 31-40,18 patients(36%) are in the age group 41-50,13 patients(26%) are in the age group 51-60,7 patients (14%)are more than 60 years of age

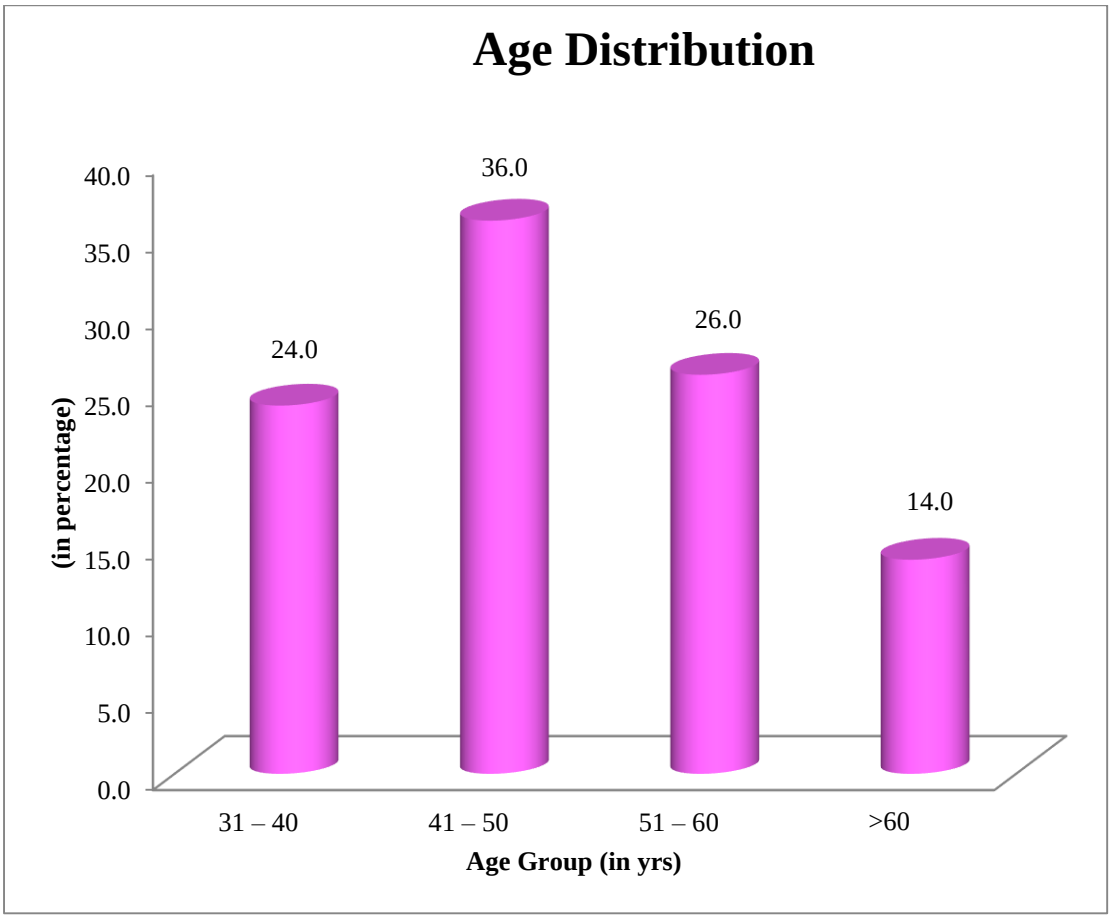

Age Distribution
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
(in percentage)
24.0
36.0
26.0
14.0
31 – 40
41 – 50
51 – 60
>60
Age Group (in yrs)

Table 2. gender distribution of patients

Gender	No. (%)
Male	36 (72.0)
Female	14 (28.0)
Total	50 (100.0)

COMMENTS: out of 50 patients 36 patients(72%) were male patients 14 patients (28%)were female patients

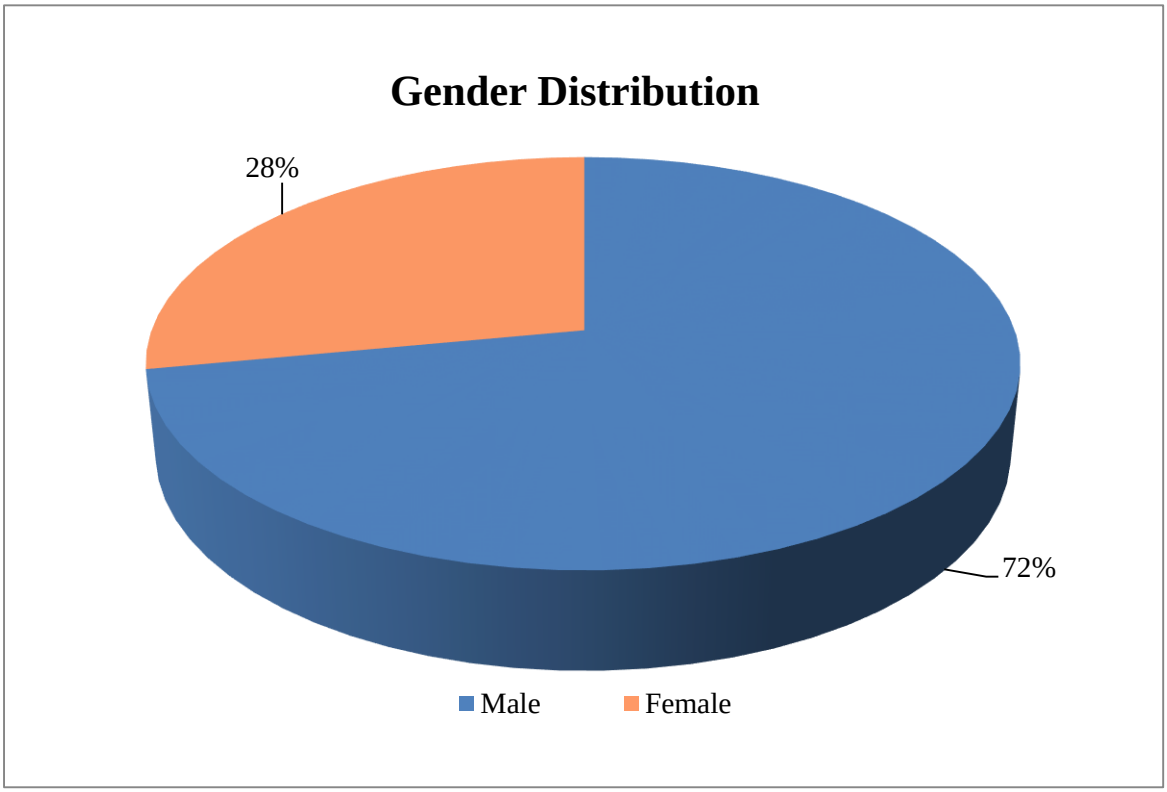


Table 3.distribution of patients with portal hypertension and without portal hypertension

Diagnosis	No. (%)
Cirrhosis with PHT	25 (50.0)
Cirrhosis without PHT	25 (50.0)
Total	50 (100.0)

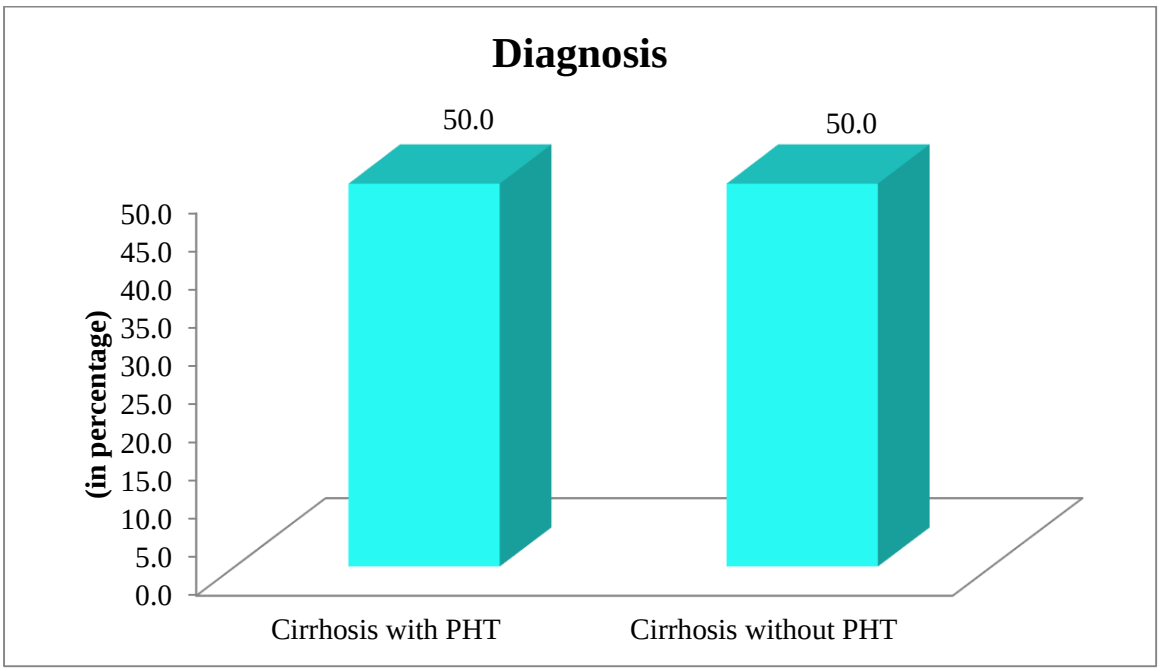
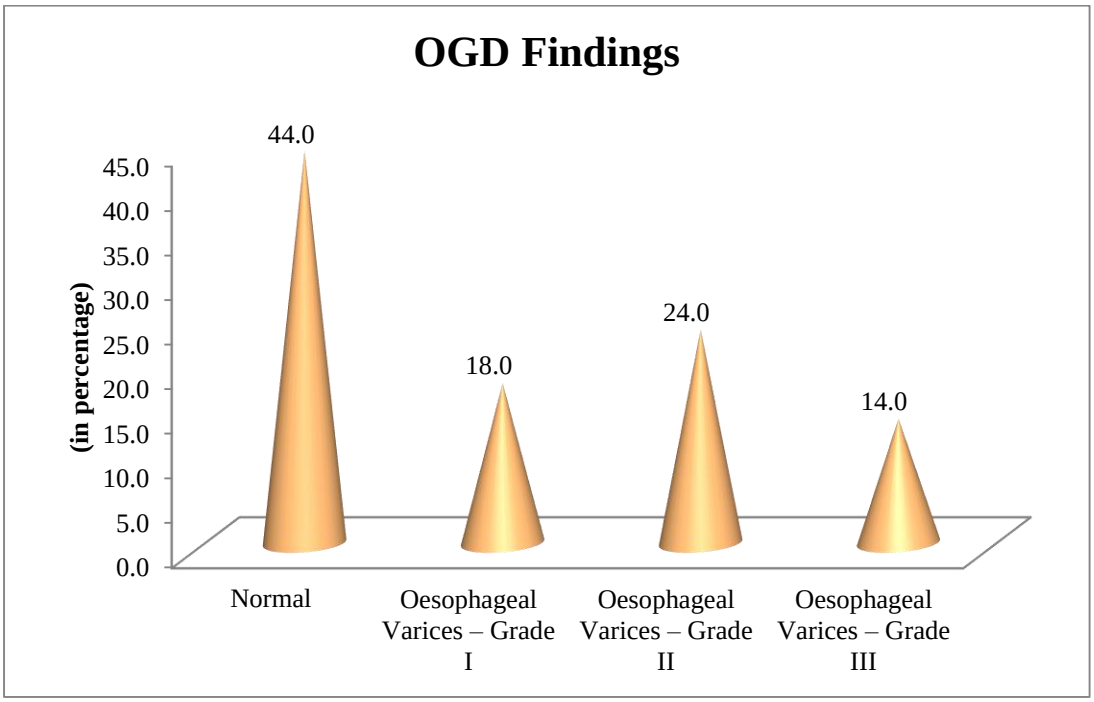


Table 4 .OGD findings of the patients

OGD Findings	No. (%)
Normal	22 (44.0)
Oesophageal Varices – Grade I	9 (18.0)
Oesophageal Varices – Grade II	12 (24.0)
Oesophageal Varices – Grade III	7 (14.0)
Total	50 (100.0)

COMMENTS:

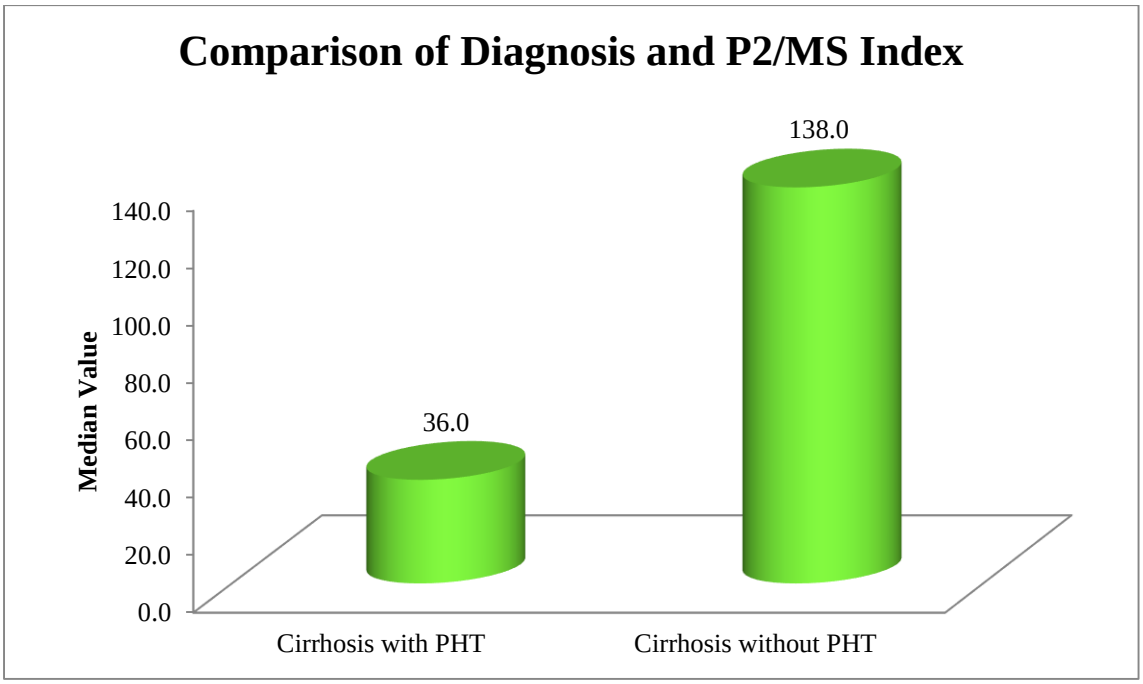
Out of 50 patients ,ogd findings were normal in 22 patients(44%) ,grade I esophageal varices in 9 patients(18%) ,grade II varices in 12 patients(24%) and grade III varices in 7 patients(14%)



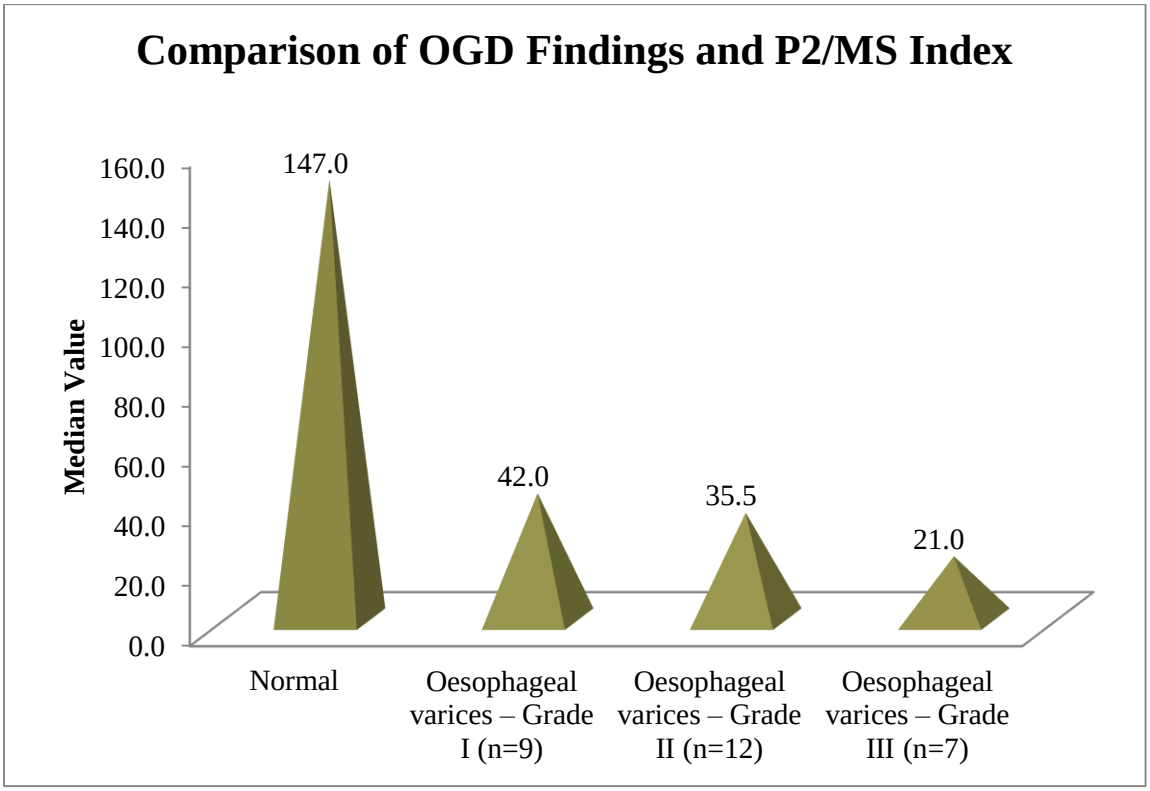
	Diagnosis	
	Cirrhosis with PHT (n=25)	Cirrhosis without PHT (n=25)
	Median (IQR)	Median (IQR)
P^2/MS Index	36.0 (27.0, 41.0)	138.0 (96.5, 160.5)
p-value	<0.001 (Significant)	

COMMENTS:

In patients with portal hypertension the median p2/ms index was 36 where as in patients without portal hypertension the median p2/ms index was 138



	OGD Findings			
	Normal (n=22)	Oesophageal varices – Grade I (n=9)	Oesophageal varices – Grade II (n=12)	Oesophageal varices – Grade III (n=7)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
P^2/MS Index	147.0 (122.5, 171.0)	42.0 (41.0, 44.0)	35.5 (32.2, 38.0)	21.0 (14.0, 25.0)
p-value	<0.001 (Significant)			



COMMENTS:

Out of 50 patients ogd findings were normal in 22 patients with median p2/ms index of 147,grade I varices in 9 patients with median p2/ms index of 42,grade II varices in 12 patients with median p2/ms index of 35.5,and grade III varices in 7 patients with median p2/ms index of 21.

ROC data for higher Oesophageal Varcies

Area under the ROC curve 0.976						**p=0.001**				
P^2/MS Index	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**95% CI**	**NPV**	**95% CI**	**+LR**	**-LR**
>32.5	100.0	59.0 – 100.0	75.0	42.8 – 94.5	70.0	46.6 – 86.1	100.0	-	4.0	0.0
>30.5	85.7	42.1 – 99.6	91.7	61.5 – 99.7	85.7	47.2 – 97.5	91.6	64.0 – 98.5	10.2	0.16
>27.0	85.7	42.1 – 99.6	100.0	73.5 – 100.0	100.0	-	92.3	66.1 – 98.6	-	0.14

DISCUSSION

DISCUSSION

Our study was conducted to assess the predictive value of p2/ms index using complete blood count in finding the esophageal varices in cirrhosis patient and to find the cut off value below which the esophagealvarices are more likely present

In this study of 50 patients 36 patients were male patients and 14 patients were female

Out of 50 patients ogd findings were normal in 22 patients with median p2/ms index of 147,grade I varices in 9 patients with median p2/ms index of 42,grade II varices in 12 patients with median p2/ms index of 35.5,and grade III varices in 7 patients with median p2/ms index of 21.

In patients with portal hypertension the median p2/ms index was 36 where as in patients without portal hypertension the median p2/ms index was 138

Among 50 cirrhosis patients ogd findings were normal in 22 patients with median p2/ms index of 147 .

In this study. above a cut-off value for P2/MS of 30.5, HREV could be excluded, with a negative predictive value [NPV] of 91.6%

The diagnosis of EV is required for patients with liver cirrhosis to detect those who will benefit from variceal bleeding primary prophylaxis. Currently, esophago-gastro-duodenoscopy (EGD) remains the gold standard test for such diagnosis.

However, EGD is limited by its invasiveness andhigh cost. A simple non-invasive widely available and cheap test would be ideal if proved to have sufficient specificity and sensitivity. Therefore, we aimed to study the diagnostic value of an index derived from the patients' complete blood count; namely the P2/MS ratio as a predictive tool for the presence of varices and if they are at high risk of bleeding.

Thus, various noninvasive tests based on biochemical and imaging studies have been proposed . This is particularly important in nations whose healthcare budget is low and the availability of endoscopic units is limited. Indeed, selective screening endoscopy becomes cost-effectivewith respect to universal screening endoscopy when non-invasive tests are sufficiently reliable to rule-in or rule-out the presence of esophageal varices.

A new index, P2/MS, based on a complete blood count, is specifically designed to predict esophageal varices in chronic liver disease. We conducted validation of the P2/MS index, and can now

suggest optimal cut-off points to predict the presence of HREVs in patients with liver cirrhosis. Our study, has shown that a combination of simple, non-invasive serum markers could avoid performing unnecessary endoscopies, with only a small number of misdiagnosed cases.

In the previous study conducted by M.A.amin et al in terms of the AUROC, P2/MS showed a high likelihood of reliably identifying patients with HREV [0.897], with values slightly lower than those seen in the other study by Beom Kyung et al . [0.941] . In predicting HREV, P2/MS showed a higher accuracy than all variables except for our new test variable. We have suggested one cut off point for detection of HREV, which differ slightly from those of Beom Kyung et al . who used two cut off values so patients may be in the zone between the two cut off values. Above a cut-off value for P2/MS of 28.85, HREV could be excluded, with a negative predictive value [NPV] of 86.3%. Based on this value, patients could avoid unnecessary endoscopy. These patients have a low risk of bleeding and periodic follow up using thisformula could be considered adequate. In contrast to other studies, our study aimed primarily to predict the presence of HREV rather than varices of any size, with the aim of selecting these patients for prophylactic endoscopic ligation. Empirical Beta blocker therapy for primary

prophylaxis can no longer be recommended for all cirrhotic patients without diagnostic endoscopy; it was not found to incur long term benefit. The formula P2/MS has several clinical advantages. First of all, one can easily calculate P2/MS at the bedside or in the outpatient clinic, as it does not require standardization and is free of intra-/interobserver variability. This make it different from other noninvasive tests that use ultrasonographic parameters such as portal vein velocity, portal vein diameter, hepatic impedance indexes, splenic impedance indexes and splenic diameter

Similar results were shown by Kim et al , who studied the validity of P2/MS in predicting esophageal varices in 318 patients with hepatitis B (HBV) related cirrhosis. They found that P2/MS<11 reliably identified 83 patients as having HEV (94 % positive predictive value), while 179 patients were reliably identified as not having HEV with P2/MS more than 25 (94.4% negative predictive value).

Overall, P2/MS reliably determined the likelihood of HEV in 262 patients (82.4%) in their study. They recommended that patients with P2/MS<11 should be considered for appropriate prophylactic treatments, while those with P2/MS>25 may avoid endoscopy reliably.

In another study, 475 patients with HBV related cirrhosis were followed prospectively for 4 years. The risk of EV bleeding was significantly higher in subgroup 1: P2/MS ≥9 than in subgroup 2: P2/MS <9 (p = 0.029). A lower P2/MS was significant predictor for EV bleeding (p = 0.04). So authors recommended that different prophylactic treatments should be considered for the subgroup with a P2/MS <9 .

The study revealed that P2/MS had the highest area under the curve (AUROC) when compared to other studied noninvasive scores in detecting the presence of EV with significant difference (AUROC= 0.987, 95% CI 0.940 - 0.998, p< 0.001). Kim *et al.* found that in predicting EV, P2/MS AUROC (0.915, 95% CI 0.881–0.949) values were comparable to those of ASPRI (p = 0.968) and SPRI (p = 0.871), and better than those of API (p <0.001), APRI (p <0.001) and AAR (p <0.001)

CONCLUSION

CONCLUSION

In patients with low p2/ms index esophageal varices are more likely present and it has emerged as significant predictors for the presence of esophageal varices in cirrhosis patient.

P2/ms index was low in patients with portal hypertension when compared to patients without portal hypertension

SUMMARY

SUMMARY

A cross sectional observational study was done at Government Rajaji Hospital, Madurai among 50 patients for assessing a noninvasive Predictor p2/ms index using complete blood count that could predict the presence of esophageal varices. P2/MS is a reliable simple non-invasive index for the detection and classification of EV in patients with cirrhosis

We believe that this index may be of help to the physicians practicing in areas where endoscopy facilities are not readily available, in helping them to initiate appropriate primary pharmacological prophylaxis in these patients. In a limited resources setting like ours,where financial constraints are a major problem ,predicting the presence and grade of varices by non-invasive methods help to avoid unnecessary upper G.I endoscopies.

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PROFORMA

PROFORMA

Name:

Age / Sex:

IP no:

Occupation:

Presenting complaints:

h/o,jaundice, ascites, oliguria, pedal edema , gastrointestinal bleed,

altered

sensorium.

Past History:

h/o Jaundice, blood transfusion, tattoing, iv drug use, sexual promiscuity

h/o CLD, DM, HT, CKD, CVD, DRUG INTAKE, THYROID

DISORDERS,EPILEPSY,HEPATITIS.

Personal history

alcoholic/ non alcoholic

smoker/ nonsmoker

Clinical Examination:

General Examination:

Consciousness, orientation, febrile/afebrile, Pallor, jaundice, Clubbing,

Lymphadenopathy, pedal edema.

Vitals:

PR

BP

RR

SpO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

Complete blood count – differential count,platelet count

Liver function test

Ultrasound abdomen

Endoscopy

Diagnosis

ABBREVIATIONS

LIST OF ABBREVIATIONS

LFT	-	liver function test
AST	-	Aspartate aminotransferase
ALT	-	Alanine aminotransferase
UGI	-	Upper Gastrointestinal
MELD	-	Model for End stage Liver Disease score
CTP	-	child turcotte pugh
PT	-	prothrombin time
TIPSS	-	Transjugular Intrahepatic Portosytemic Shunt Surgery
BRTO	-	balloon retrograde transvenous obliteration
NO	-	Nitric Oxide
GV	-	gastric varices
EVL	-	endoscopic variceal ligation
EGD	-	esophago gastroduodenoscopy

MASTER CHART

MASTER CHART

S.NO	NAME	AGE	SEX	DIAGNOSIS	PLATELET COUNT (X10^5 CELLS /CU.MM)	NEUTRO PHIL %	MONO CYTE%	P2 /MS INDEX	OGD FINDING
1	SELVARAJ	51	M	CIRRHOSIS WITH PHT	0.86	78	5	19	OESOPHAGEAL VARICES-GRADE III
2	CHINNAPPAN	58	M	CIRRHOSIS WITH PHT	1.02	75	4	35	OESOPHAGEAL VARICES-GRADE II
3	KANNAN	54	M	CIRRHOSIS	1.98	69	4	142	NORMAL STUDY
4	RAMACHANDRAN	37	M	CIRRHOSIS	2.1	71	3	207	NORMAL STUDY
5	RAMALINGAM	41	M	CIRRHOSIS WITH PHT	1.16	74	4	45	OESOPHAGEAL VARICES-GRADE I
6	RAJA	45	M	CIRRHOSIS	1.86	70	4	123	NORMAL STUDY
7	PONNATHAL	47	F	CIRRHOSIS WITH PHT	0.68	74	3	21	OESOPHAGEAL VARICES-GRADE III
8	LAXMANAN	65	M	CIRRHOSIS WITH PHT	1.02	72	4	36	OESOPHAGEAL VARICES-GRADE II
9	MOHAMED ISMAYIL	45	M	CIRRHOSIS	1.63	66	3	134	NORMAL STUDY
10	RADHAKRISHNAN	45	M	CIRRHOSIS WITH PHT	0.98	72	4	33	OESOPHAGEAL VARICES-GRADE II
11	PARVATHAM	35	F	CIRRHOSIS WITH PHT	1.08	72	4	39	OESOPHAGEAL VARICES-GRADE II
12	NATCHAMMAL	60	F	CIRRHOSIS	1.35	68	2	134	PHT GASTROPATHY
13	MANI	47	M	CIRRHOSIS WITH PHT	1.24	75	5	41	OESOPHAGEAL VARICES-GRADE I
14	PRAKASH	60	M	CIRRHOSIS	1.01	68	4	37	OESOPHAGEAL VARICES-GRADE II

15	SOUNDARAJAN	66	M	CIRRHOSIS WITH PHT	1.43	69	2	148	NORMAL STUDY
16	MANORANJITHAM	62	F	CIRRHOSIS	1.78	72	3	146	NORMAL STUDY
17	PANDIYAN	40	M	CIRRHOSIS	1.37	68	2	138	NORMAL STUDY
18	PORKODI	50	F	CIRRHOSIS WITH PHT	1.04	71	4	38	OESOPHAGEAL VARICES-GRADE II
19	MADHAVAN	31	M	CIRRHOSIS	1.5	72	2	156	NORMAL STUDY
20	GEETHA	36	F	CIRRHOSIS	1.25	76	5	41	OESOPHAGEAL VARICES-GRADE I
21	PANDIYAMMAL	43	F	CIRRHOSIS WITH PHT	0.83	71	3	32	OESOPHAGEAL VARICES-GRADE III
22	ILAYAPERUMAL	60	M	CIRRHOSIS WITH PHT	0.97	68	3	46	OESOPHAGEAL VARICES-GRADE I
23	SUNDARAM	48	M	CIRRHOSIS	1.48	71	2	154	NORMAL STUDY
24	MUTHULAKSHMI	40	F	CIRRHOSIS	1.82	68	3	162	NORMAL STUDY
25	PETCHIYAMMAL	43	F	CIRRHOSIS WITH PHT	0.54	68	2	21	OESOPHAGEAL VARICES-GRADE III
26	PANDI	55	M	CIRRHOSIS	1.23	72	5	42	OESOPHAGEAL VARICES-GRADE I
27	DESIKAN	72	M	CIRRHOSIS WITH PHT	0.92	74	3	38	OESOPHAGEAL VARICES-GRADE II
28	KRISHNAN	50	M	CIRRHOSIS	2.1	69	4	159	ESOPHAGEAL CANDIDIASIS
29	BUVANEESWARI	57	F	CIRRHOSIS WITH PHT	0.73	71	3	25	OESOPHAGEAL VARICES-GRADE III
30	RAVICHANDRAN	47	M	CIRRHOSIS	1.67	68	2	205	NORMAL STUDY
31	MAHESH	31	M	CIRRHOSIS WITH PHT	1.16	69	2	97	NORMAL STUDY
32	JEYARAJ	70	M	CIRRHOSIS	1.13	74	4	43	OESOPHAGEAL VARICES-GRADE I
33	MUTHUVELLAI	65	M	CIRRHOSIS WITH PHT	0.82	71	3	32	OESOPHAGEAL VARICES-GRADE II
34	KRISHNASAMY	57	M	CIRRHOSIS WITH PHT	0.94	69	3	43	OESOPHAGEAL VARICES-GRADE I

35	KOWSALYA	32	F	CIRRHOSIS	1.54	65	3	121	NORMAL STUDY
36	ASAIPANDI	45	M	CIRRHOSIS	2.2	70	3	230	NORMAL STUDY
37	DHANAM	65	F	CIRRHOSIS WITH PHT	0.78	71	3	29	OESOPHAGEAL VARICES-GRADE II
38	ESWARAN	42	M	CIRRHOSIS WITH PHT	0.91	70	2	39	OESOPHAGEAL VARICES-GRADE I
39	RAMASAMY	55	M	CIRRHOSIS	1.18	69	2	101	NORMAL STUDY
40	BALASUBRAMANI	37	M	CIRRHOSIS WITH PHT	0.73	70	2	38	OESOPHAGEAL VARICES-GRADE II
41	SURESH	37	M	CIRRHOSIS	1.26	67	2	118	NORMAL STUDY
42	RAJENDRAN	52	M	CIRRHOSIS WITH PHT	1.08	71	4	41	OESOPHAGEAL VARICES-GRADE I
43	RAVI	40	M	CIRRHOSIS	1.88	69	2	256	NORMAL STUDY
44	MURUGESAN	56	M	CIRRHOSIS	1.38	69	3	92	NORMAL STUDY
45	ABDUL KAREEM	42	M	CIRRHOSIS WITH PHT	0.97	74	4	32	OESOPHAGEAL VARICES-GRADE II
46	SUSEELA	60	F	CIRRHOSIS WITH PHT	0.45	70	2	14	OESOPHAGEAL VARICES-GRADE III
47	CHELLAPANDI	48	M	CIRRHOSIS	1.42	68	2	148	NORMAL STUDY
48	MEENA	35	F	CIRRHOSIS	1.13	78	5	33	OESOPHAGEAL VARICES-GRADE II
49	MURUGAN	42	M	CIRRHOSIS WITH PHT	0.53	70	3	13	OESOPHAGEAL VARICES-GRADE III
50	RAJKUMAR	50	M	CIRRHOSIS	2.6	68	5	198	NORMAL STUDY

ETHICAL COMMITTEE APPROVAL LETTER

ETHICAL COMMITTEE APPROVAL LETTER

MADURAI MEDICAL COLLEGE
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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.K.Loganathan
Course	:	PG in MD., General Medicine
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Noninvasive index P2/MS (platelet count)2/(monocyte fraction (%) x segmented neutrophil fraction (%) using complete blood counts for detecting oesophageal varices in cirrhosis
Ethical Committee as on	:	27.07.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

Madurai Medical College
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Urkund Analysis Result

Analysed Document: NONINVASIVE INDEX USING COMPLETE BLOOD COUNTS (P2MS)FOR DETECTING OESOPHAGEAL VARICES IN CIRRHOSIS.docx (D31241815)
Submitted: 10/12/2017 10:13:00 AM
Submitted By: drloghu@gmail.com
Significance: 19 %

Sources included in the report:

SrinivasanKarthikeyan.01p.docx (D30901914)
A STUDY OF HYPONATREMIA IN CIRRHOSIS LIVER.docx (D31101988)
Dr.Anandh.doc (D31122078)
prolactin in cirrhosis.docx (D31131800)
http://gi.org/guideline/prevention-and-management-of-gastroesophageal-varices-and-variceal-hemorrhage-in-cirrhosis/
http://onlinelibrary.wiley.com/doi/10.1002/hep.21907/full
5fb3239e-5c8b-4c74-8bb2-79068859b664

Instances where selected sources appear:

45

CERTIFICATE - II

This is to certify that this dissertation work titled **"NON INVASIVE INDEX USING COMPLETE BLOOD COUNTS (P2/MS) FOR DETECTING OESOPHAGEAL VARICES IN CIRRHOSIS"** of the candidate **DR. K.LOGANATHAN** with registration Number **201511114** for the award of **M.D.,** in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **19%** percentage of plagiarism in the dissertation.

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