A STUDY ON PLATELET COUNT- SPLENIC DIAMETER RATIO AS A NON-INVASIVE PREDICTOR OF OESOPHAGEAL VARICES IN CIRRHOSIS

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

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CHENNAI

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled **"A STUDY ON PLATELET COUNT SPLENIC DIAMETER RATIO AS A NON-INVASIVE PREDICTOR OF OESOPHAGEAL VARICES IN CIRRHOSIS"** is a bonafide work submitted by **Dr.R.VISHNUPRIYA ,**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 2015.

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DECLARATION

I, **Dr. R.VISHNUPRIYA,** declare that, I carried out this work on, **"A STUDY ON PLATELET COUNT SPLENIC DIAMETER RATIO AS A NON-INVASIVE PREDICTOR OF OESOPHAGEAL VARICES IN CIRRHOSIS "** at the Department of Medicine, Govt. Rajaji Hospital during the period of September 2013 to August 2014. I also declare that this bonafide work or any part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

Date : **Dr. R.VISHNUPRIYA**

Place :

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LIST OF ABBREVIATIONS

CC : CONTRACTILE CELL

CI : CONFIDENCE INTERVAL

OGD :OESOPHAGOGASTRODUODENOSCOPY

OGV : ESOPHAGOGASTRIC VARICES

ET-1 : ENDOTHELIN-1

EV : ESOPHGEAL VARICES

EVL : ENDOSCOPIC VARICEAL LIGATION

HVPG : HEPATIC VENOUS PRESSURE GRADIENT

LEV : LARGE ESOPHGEAL VARICES

MELD : MODEL FOR END STAGE LIVER DISEASE

NPV : NEGATIVE PREDICTIVE VALUE

NSAIDs : NONSTEROIDAL ANTIINFLAMMATORY AGENTS

PCV : PACKED CELL VOLUME

PC/SD : PLATELET COUNT TO SPLEEN DIAMETER RATIO

PLT : PLATELET

PPV : POSITIVE PREDICTIVE VALUE

SD :STANDARD DEVIATION

SGOT : SERUM GLUTAMATE OXALOACETATE TRANSAMINASE

SGPT : SERUM GLUTAMATE PYRUVATE TRANSAMINASE

SV : SMALL VARICES

TIPS : TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

TPO : THROMBOPOIETIN

UGIE : UPPER GASTROINTESTINAL ENDOSCOPY

US : ULTRASONOGRAPH

TABLE OF CONTENTS

ABSTRACT

BACKROUND AND OBJECTIVE

Cirrhosis is a common disease which has significant morbidity and it is one of the cause for premature mortality. The major complication of cirrhosis is portal hypertension which in turn leads to variceal bleeding which accounts for 35-40% mortality.

In patients with chronic liver disease, endoscopic screening for esophageal varices (EV) is currently recommended in all patients at the time of diagnosis of cirrhosis. In order to improve the compliance of patients and to reduce the burden on physicians and hospitals, invasive procedures to diagnose the incidence of oesophageal varices need to be avoided and replaced with simple and easily available and reproducible investigation/screening.

This study is done to analyse the predictive value in the diagnosis of Oesophageal varices in patient with Cirrhosis with a non-invasive parameter like Platelet count Splenic Diameter ratio.

METHODS

The study included 75 patients admitted in Government Rajaji Hospital, Madurai with Cirrhosis in the period between September 2013 to August 2014. Cirrhosis was diagnosed with the help of history, clinical examination and ultrasonogram. All 75 patients underwent Ultrasonogram (for splenic diameter) and platelet count was done. The following patients were included viz…1.Age

> 18 years/ Males 2.Patients undergoing screening endoscopy for varices at the time of diagnosis of cirrhosis 3.Known cirrhotic patients who have never undergone screening endoscopy for EV.Patients with

1.Active upper G.I.bleeding

2.Previous history of endoscopic sclerosis / band ligation of EV

3.Previous surgery for portal hypertension (stents)

4.Previous history of Beta Blocker treatment / prophylaxis.

5.Inabilty to abstain from alcoholism were excluded from the study.

The data and variables collected from the patients were compiled and analysed with statistical methods (Chi square).

RESULTS AND INTERPRETATION

Among the 75 patients, a total of 50 patients had esophageal varices on upper gastrointestinal endoscopy. Out of these, 48 patients had a platelet count/splenic diameter <909. The remaining 2 patients had a ratio of >909.

A total of 54 patients in the study had a ratio of <909 in the study. Varices were absent in 4 of them. The mean platelet count spleen diameter ratio of patients with out varices was 961.98 and the mean platelet count spleen diameter ratio of patients with varices was 689.62. Hence, using a ratio of 909 as cutoff, 96% of patients with varices were detected (sensitivity-96% and specificity-90.48%).

The P value <o.oo7 which is more significant than using a single parameter.

The positive predictive value is 88.% and the negative predictive value is 90.4%.

CONCLUSION

Lower the platelet count spleen size ratio, higher the incidence of varices and higher the grades. This study conclude that presence of a lower PC/SD ratio determine the presence of varices and hence identify the subset of patients who require endoscopy for the prophylactic management of esophageal varices. Apart from being noninvasive, platelet count, spleen bipolar diameter and the PC/SD ratio is a relatively inexpensive test.

KEY WORDS

Cirrhosis, oesophageal varices, platelet count-spleen diameter ratio,Upper Gastrointestinal bleeding

INTRODUCTION

Cirrhosis is a common disease which has significant morbidity and it is one of the cause for premature mortality. It can occur at any age. World-wide the most common causes are viral hepatitis and consumption of excessive alcohol.

Among the viral hepatitis the most common are hepatitis B and C viruses. 300 million people are affected by viral hepatitis B. The spectrum is from acute infection mostly asymptomatic to a chronic hepatitis B which leads to complications such as cirrhosis and hepatocellular carcinoma. Following exposure to hepatitis B 15-20% develop cirrhosis over 5-20years. The incidence of cirrhosis is directly proportional to the positivity of HBeAg. The patients infected with Hepatitis C are unaware of the disease and diagnosed only when they progress to chronic liver disease.> $3/4^{th}$ of patients succumb to chronic infection and later leads to inadequate clearance of virus.

The next most common cause is chronic liver disease is Alcohol. The death due to alcoholic liver disease is on raising trend with over 3000deaths/year. The mean age at presentation is also falling. When the alcohol consumption is > 160g/day for 8 years they are more to develop cirrhosis.

The 3rd most common cause of chronic liver disease is Non-alcoholic fatty liver disease (NAFLD). It mostly affects the affluent societies. The prevalence increases with raise of obesity. The patients with Diabetes and Metabolic syndrome are more prone to develop NASH.

The major complication of cirrhosis is portal hypertension which in turn leads to variceal bleeding which accounts for 35-40% mortality.

In patients with chronic liver disease, endoscopic screening for esophageal varices (EV) is currently recommended in all patients at the time of diagnosis of cirrhosis. As far as patients with no varices at screening endoscopy are concerned, surveillance should be performed every 2 years on patients with stable liver function and every year on those who show signs of liver function deterioration.

Finally, endoscopy should be repeated every year when screening endoscopy reveals small varices. These practices are recommended because if high-risk EV are detected, then either pharmacologic or endoscopic treatment aimed at preventing first bleeding can be started .

. Nevertheless, although criteria for this surveillance practice are part of well-established guidelines, they stem from the opinions of

experts rather than being evidence based. Furthermore, such policy eventually places a strong burden on medical resources, and may be hampered by the lack of compliance with both screening and surveillance. Indeed, one recent study compared universal endoscopic screening and treatment of high-risk varices with treating all cirrhotic patients with β-blockers, and the latter approach proved to be more cost-effective. In another similar study, screening endoscopy proved to be cost-effective in patients with decompensated disease alone. Lastly, although administering timolol to cirrhotic patients without EV proved to be ineffective at preventing the formation of varices and propranolol seemed to be ineffective in the prevention of the development of large varices.

Taking into account the above mentioned considerations, the cost- effectiveness of universal empirical β-blocker treatment should be even greater, although in some patients it would be useless. In fact, the average prevalence of EV in cirrhotic patients ranges from 60% to 80%, depending on severity and etiology of liver disease, and empirical treatment of all cirrhotic patients would expose a significant proportion of treated patients to unnecessary and potentially harmful side effects.

Therefore, the use of accurate and specific methods that could noninvasively diagnose EV would likely increase the cost-benefit of

empirical treatment by decreasing the number of patients who are administered avoidable treatment and by increasing the number of properly screened and treated patients. Such a noninvasive means should have a confident safety profile (i.e., a negative predictive value approaching 100%) so as to avoid missing the diagnosis in patients at risk, and a relevant cost-benefit profile so as avoid unnecessary endoscopy and/or treatment of patients who would not benefit from therapy (i.e., high positive predictive value). In this scenario, we previously showed that the use of the platelet count/spleen diameter ratio for the noninvasive assessment of EV seems to fulfill these requirements and is based on pathophysiological criteria as well.

Furthermore, we validated the diagnostic accuracy of this parameter in the follow-up of patients free from EV at screening endoscopy. Lastly, preliminary results obtained by other authors demonstrated that the diagnostic accuracy of the platelet count/spleen diameter ratio is maintained in subsets of patients with different etiologies of liver disease and by applying different methodologies, thus suggesting the generalizability of the diagnostic method.

In this prospective study, our aim is to assess the validity of using the platelet count/spleen diameter ratio for the noninvasive diagnosis of EV in patients with cirrhosis. In this study, we also aim to

assess the validity of this diagnostic tool in patients with various degrees of liver function impairment and in patients with various etiologies of liver disease.

Splanchnic blood flow due to vasodilatation and greater resistance to the flow of blood through cirrhotic tissue causes portal hypertension.The major complication of portal hypertension is formation of oesophageal varices the prevalence of which is about 50%.About 33% of patients die from bleeding varices after its development.Incidence of bleeding from varices in the subsequent years especially in the 1st two years of detection increases by about thirty percentage.The mortality is high (about 40-70%) from the 1st episode of bleeding.Thereafter the morbidity increases by five percent per year and the development of large varices is about 5-10% in the subsequent year and the rupture of those varices is more in the 2years following diagnosis.

But the method has two problems viz…1.Invasiveness of the endoscopic procedure 2.Financial burden to the patient.These problems can be solved by using other biochemical,clinical and sonographic parameters which when put together have positive predictive value for noninvasive detection of varices.So that the invasive upper and lower G.I scopy will be done in only a group of patients thereby

preventing needless intervention and at the same time finding out the patients with varices.

In order to reduce the workload on the endoscopic units and financial constrain to the patients, many non invasive procedures have been developed. One of the parameters related to portal hypertension is increased spleen size and thrombocytopenia which can be used as a better predictor to identify the engorgement of veins in portal hypertension.

But shortcomings in this study incorporating platelet count as noninvasive predictor is that in patients with cirrhosis, the presence of thrombocytopenia may be due to 1.Reduced average platelet survival 2.suppressed thrombopoitein levels 3.bone marrow suppressive effects of viruses and alcohol whereas spleenomegaly in cirrhosis is mainly due to disturbances in the vasculature correlated to portal hypertension.

AIMS AND OBJECTIVES :

- To assess the validity of Platelet count / Splenic diameter ratio as a non-invasive predictor of Oesophageal Varices in Cirrhosis

REVIEW OF LITERATURE

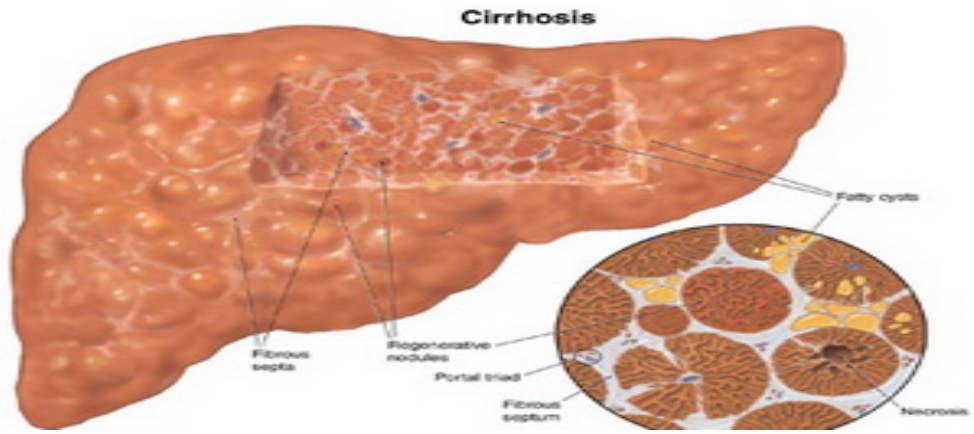
Cirrhosis is an irreversible liver disease with definable pathological change and a spectrum of clinical features.The hallmark pathological events are 1.Chronic damage of the hepatocytes which is not reversible 2.fibrosis of the liver distorting the architecture 3.reactive nodular regeneration.

Cirrhosis is defined “anatomically as a diffuse process with fibrosis and nodule formation”.The hall mark pathological feature chronic extreme damage to the hepatocyte followed by replacement of normal liver tissue by fibrosis which is extensive with nodule formation. This is mainly due to necrosis of hepatocytes, loss of reticular network &regeneration of remaining liver tissue by nodules.Whatever may be etiology the end result is the same..

Pathogenesis.

The liver damage leads to activation of stellate cells in the space of disse. The stellate cells are activated cytokines which are primarily produced by hepatocytes, tissue macrophages(kupffer cells), lymphocytes and megakaryocytes. The cascade of events following stellate cell activation mainly by self stimulation leading to synthesis of platelet derived growth factor, transforming growth factor beta 1.these

stellate cells produce collagen matrix and substance that inhibit the break down of collagen. The substance that inhibit collagen break down are metalloproteinases 2 and 9 are inturn stimulated by TIMP 1and TIMP2, the other cytokines produced are T helper 2 lymphocytes – IL 6 and 13.

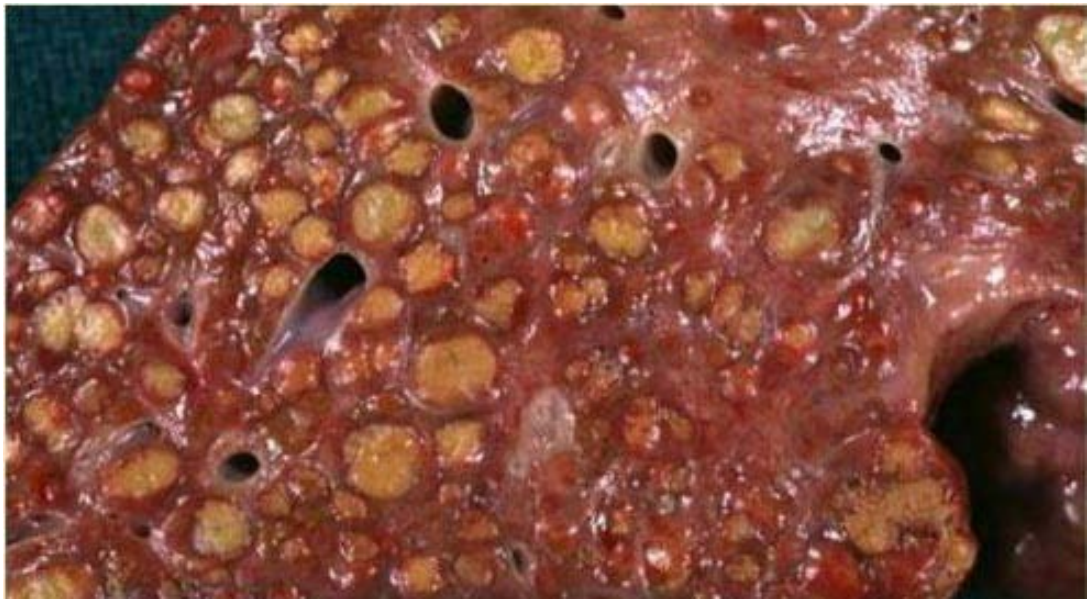


Similarly clinical manifestation often are due to alteration in the morphology and this correlates with severity of damage to the hepatocyte rather with the etiology of the liver disease.

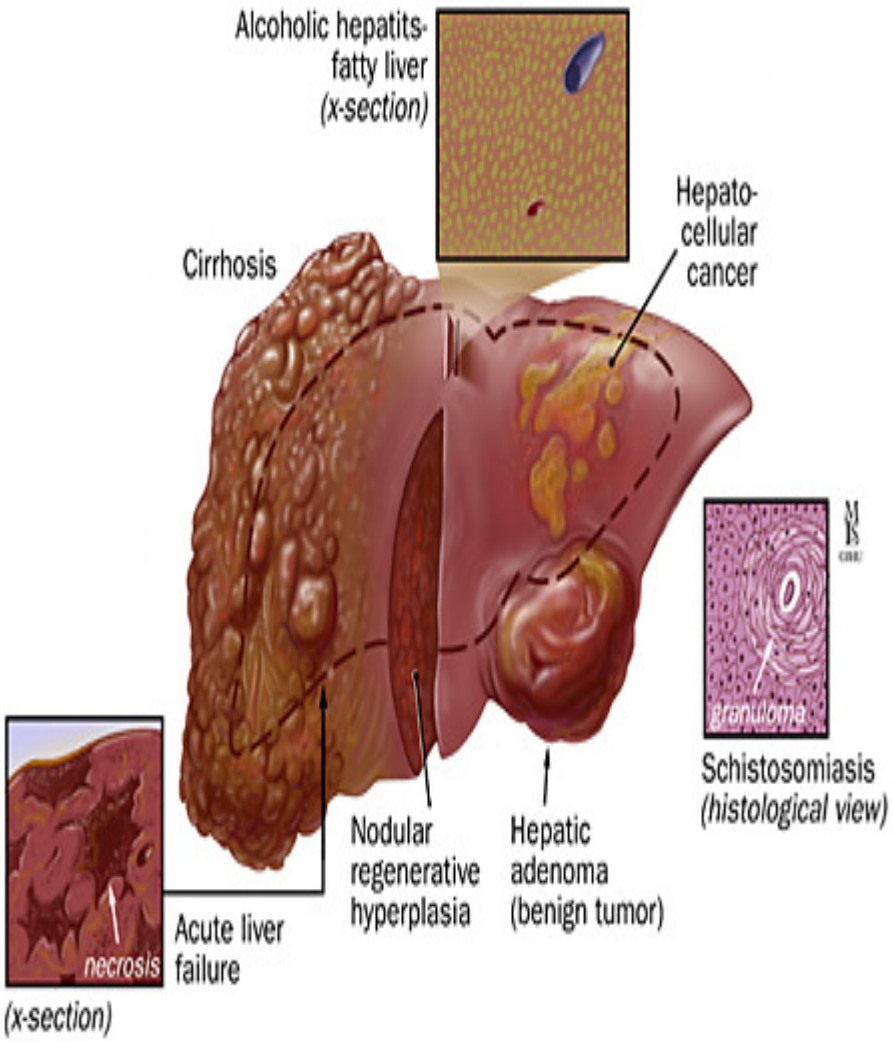
Distortion of functional hepatocyte may cause icterus, coagulation abnormalities,onasarca,vascular disturbances due to fibrosis (portal hypertension) and its complications – oesophageal varies and splenomegaly.Both portal hypertension and hepatocellular damage cause ascites and hepatic encephalopathy.

Micronodular cirrhosis is characterized by " thick ,regular septa, with regenerating small nodules varying little in size, and involvement of every lobule.May represent impaired capacity for regrowth as in alcoholism, malnutrition ,old age and anaemia

Macronodular cirrhosis is characterized by "septae and nodules of variable sizes and by normal lobules in larger nodules.Previous collapse is shown by juxtaposition of three or more portal tracts in the fibrous scars. Regeneration is reflected by large cells with large nuclei and by cell plates of varying thickness.With time macronodular converts to micronodular"

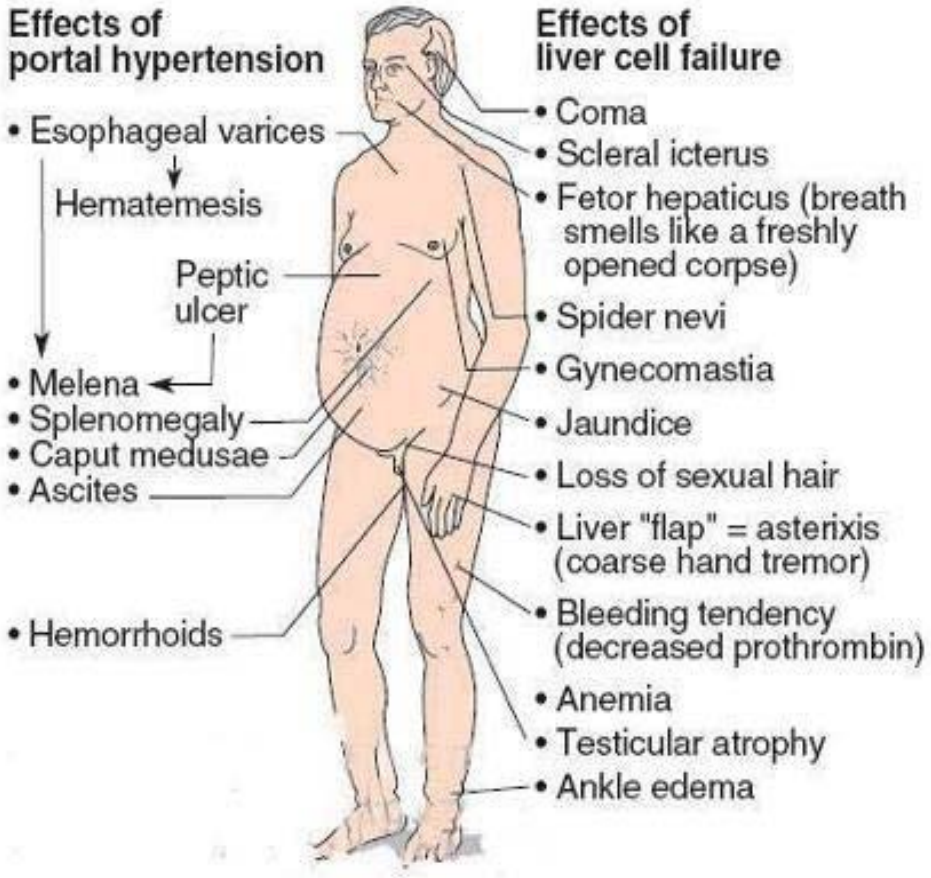


MACRONODULAR CIRRHOSIS.



EVOLUTION OF LIVER CELL DAMAGE.

Symptoms and Signs of Liver Cell Failure



The clinical features of cirrhosis are….

1.Liver enlargement (initially)

2.Icterus

3.Free fluid in abdomen (ascitis)

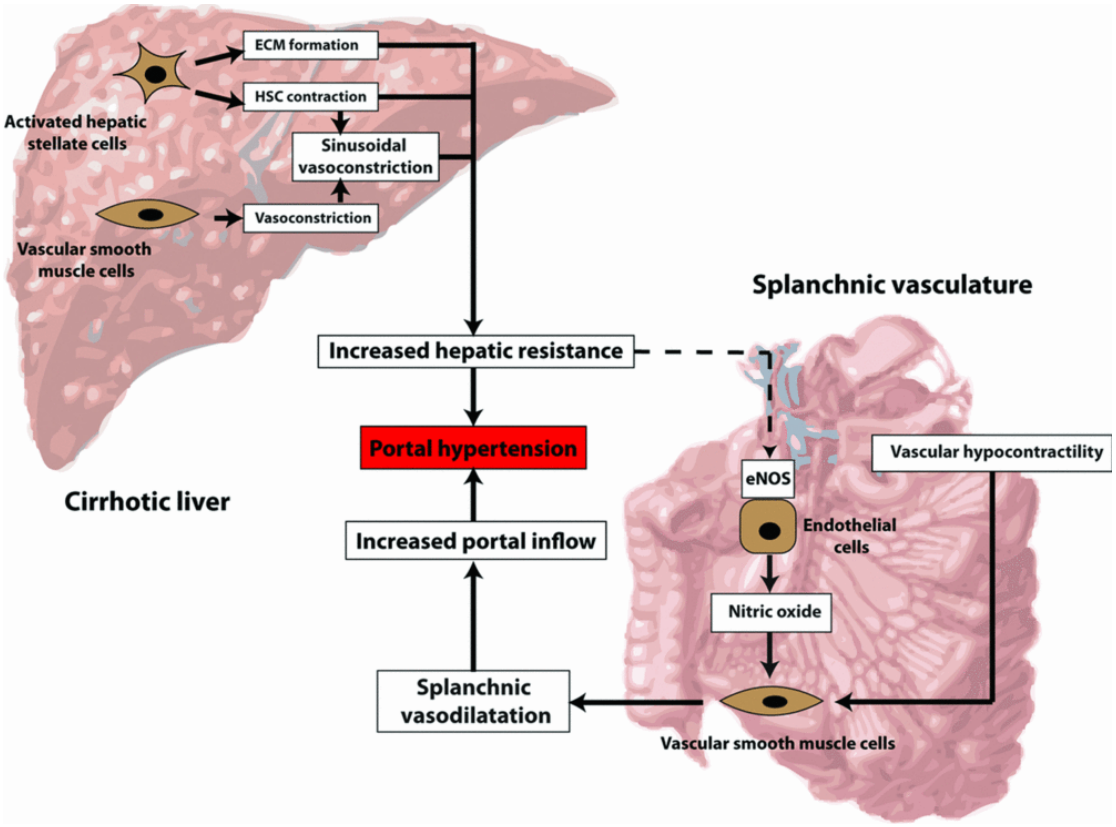
4.Endocrine abnormalities – loss of erection and sparse pubic and axillary hair with gynaecomastia,atrophy of testis and impotence in malesand atrophy of breast secondary amenorrhea and menstrual disturbances in females.

5. Palmar erythema,Spider naevi,Dupuytren contracture

6.Hemorrhagic – bruises,purpura,menorrhagia & gum bleeding

7.Portal hypertension – splenomegaly, G.I bleed.

8.Hepatic encephalopathy and fetor hepatis.



Aetiology of Cirrhosis :

1. Alcohol.
2. Viral hepatitis types B ± delta; type C.
3. Non alcoholic steatohepatitis.
4. Metabolic, e.g. haemochromatosis, Wilson's disease, α1 antitrypsin deficiency, type IV glycogenosis, galactosaemia, congenital tyrosinosis.
5. Prolonged cholestasis, intra-and extra-hepatic.
6. Hepatic venous outflow obstruction, e.g. venoocclusive disease, Budd-

Chiari syndrome, constrictive pericarditis.

7. Disturbed immunity (autoimmune hepatitis).

8. Toxins and therapeutic agents, e.g. methotrexate, amiodarone.

9. Indian childhood cirrhosis.

10. Others: Malnutrition, infections, granulomatous lesions, cryptogenic cirrhosis.

CHILD-PUGH CLASSIFICATION

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
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
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<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)			

This classification is used to assess prognosis, especially to predict the mortality risk after shunt surgery.This is equally efficient similar to that of liver function test in ascessing the prognosis in patients waiting for liver transplantation.

Now the system has been replaced by MELD score (Model For End Stage Liver Disease) for risk stratification in Liver transplant recipients.It is a prospective scoring system useful in assessing the prognostic outcome in patients with liver disease and portal hypertension.

Parameters included in MELD score are prothrombin time expressed as international standardized ratio, serum bilirubin and serum creatinine.

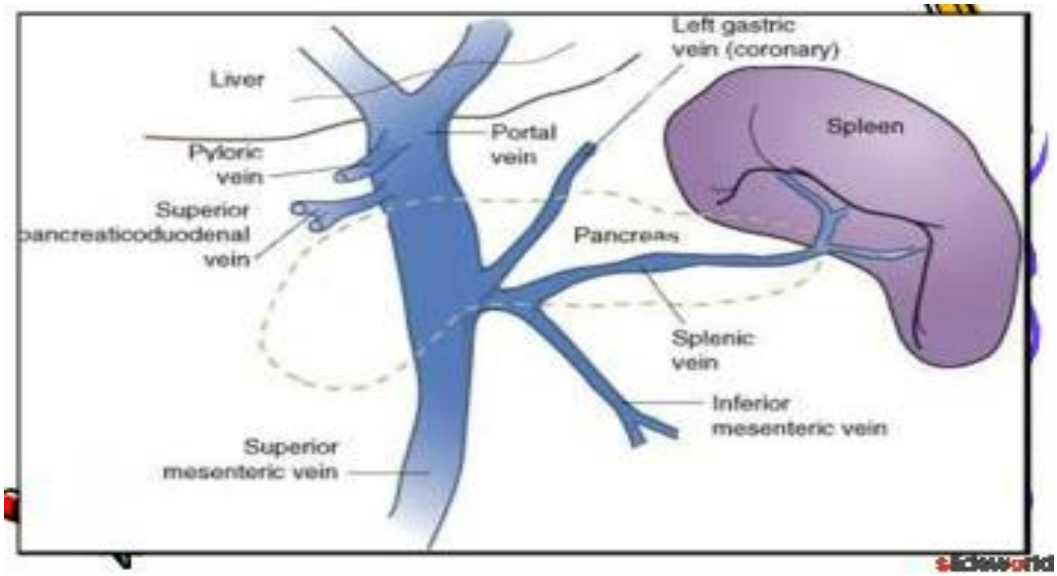
Prognosis:

Cirrhosis as such has a poor prognosis.In case of one or more life threatening complications and in chronic decompensated disease, it has a very high death rate. About one fourth of patients have a survival rate of five years when is there is functioning hepatotocytes. Only one fourth has ten year survival. Prognosis mainly depends upon the etiology of cirrhosis especially when there is treatable conditions like alcoholics – have better prognosis.

Portal Hypertension :

The term portal hypertension was coined by Gilbert in 1902. However, it was not until 1937 when Thompson could verify the increase in portal pressure directly during laparotomy that portal hypertension was confirmed. It was way back in 1650 that Glisson at a dissection in London, established the portal vein as the vessel by which blood was collected from the gastrointestinal tract and returned to the systemic circulation. As early as 1543, Vesalius drew an anatomical picture of the portal venous system.

The blood from the G.I tract mainly pancreas, spleen, gall bladder drain venous blood in to the portal vein, from there it enters the liver. At the level of L2 superior mesenteric vein joins with splenic vein to form portal vein. Portal venous system is a high flow, low pressure system. Portal pressure is related to Hepatic venous pressure gradient. HVPG is the difference in pressure between inferior vena cava and portal vein – it is <6mm Hg.



FORMATION OF PORTAL VEIN.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension is one of the prime complications of cirrhosis. Patients developing clinical features or complications of cirrhosis usually have portal venous pressures above 12 mmHg.

NORMAL PHYSIOLOGY

The movement of portal blood across the liver is dependent on the pressure gradient between the portal and hepatic veins. Hepatic venous pressure in part reflects the state of central venous filling pressure. Portal pressure is determined by the product of portal venous inflow and the vascular resistance to this flow:

Portal pressure = portal flow x vascular resistance.

Normally, the difference between portal venous pressure and hepatic venous pressure is never greater than 4mm Hg. A compliant liver acts as a blood reservoir to maintain a normal hepatic pressure gradient.

When outflow pressure increases, an increasing number of sinusoids are recruited to accommodate these changes. Thus, elevations of hepatic venous pressures do not result in similar increases in portal pressure.

The main site of portal vascular resistance in humans appears to reside at the level of the hepatic sinusoids. Portal venous inflow is the sum of the flow from the 3 main splanchnic tributaries. The splenic vein joins the inferior mesenteric vein at the level of the pancreatic body and tail, where pancreatico duodenal vessels also enter. Superior mesenteric venous drainage from the small and proximal large intestine joins the splenic vein at a site superior to the pancreatic head, forming the portal vein trunk.

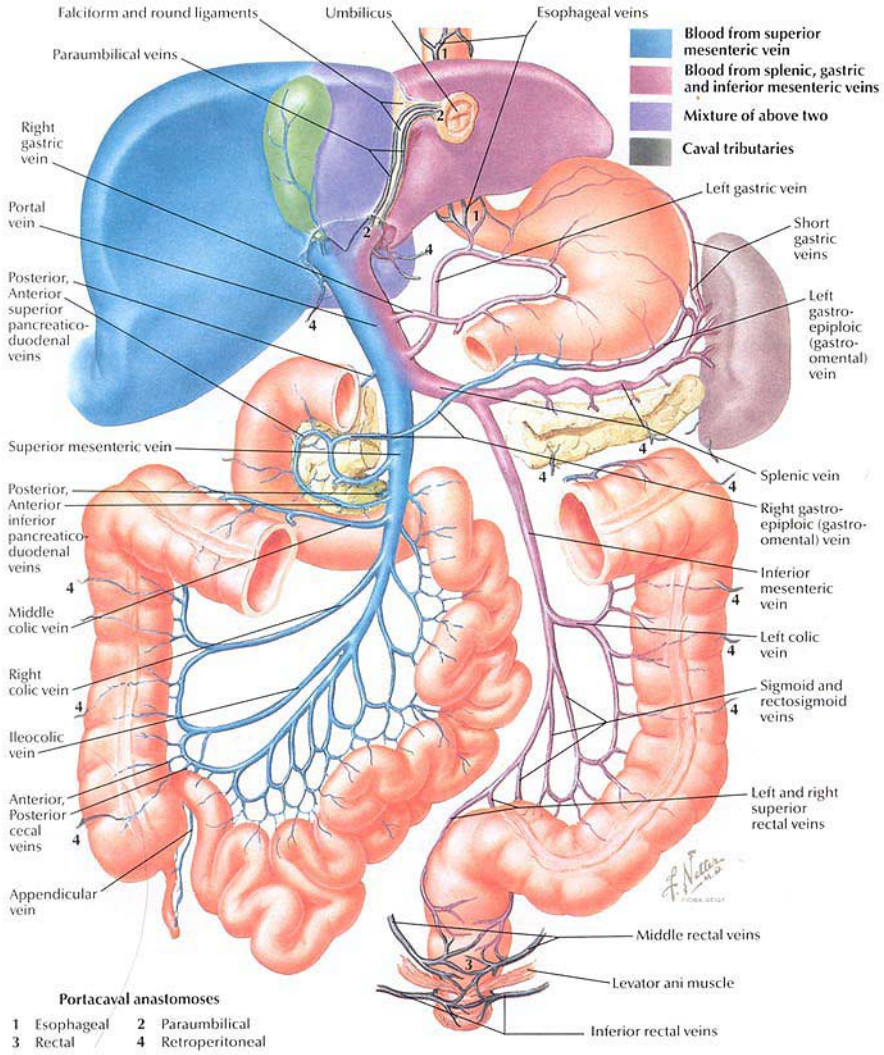
The coronary vein drains the venous circulation of the lesser gastric curvature into the proximal portal vein. The gastroduodenal vein collects drainage from the area of the pancreatic head.

Total portal venous flow in a normal man ranges between 600 and1200ml/min, as measured intra operatively and by Doppler flowmetry. The volume of portal flow is regulated by the vascular resistance of the splanchnic arteries.

Changes in portal inflow result from modifications in splanchnic arteriolar resistance, as seen with physiologic events such as a change in posture or in the postprandial state. The increase in portal blood flow after a meal can be prevented by pre-administration of somatostatin, an inhibitor of the release of several gastrointestinal

hormones that may mediate the arteriolar vasodilatation that occurs after feeding.

Portal venous oxygen content decreases after a meal because of increased intestinal arteriovenous extraction of oxygen.



The sites of porto - systemic collaterals in patients with cirrhosis of liver.The most common of site of bleeding among patients with portal hypertension is from the gastro-esophageal varices.

HEMODYNAMICS IN PORTAL HYPERTENSION

Vascular Resistance

Theoretically, a rise in portal pressure could stemfrom an increase in either portal flow or vascular resistance. Under normal conditions, a rise in portal flow can be accommodated by the compliant hepatic sinusoidal bed so that portal pressure increases only in extreme conditions.

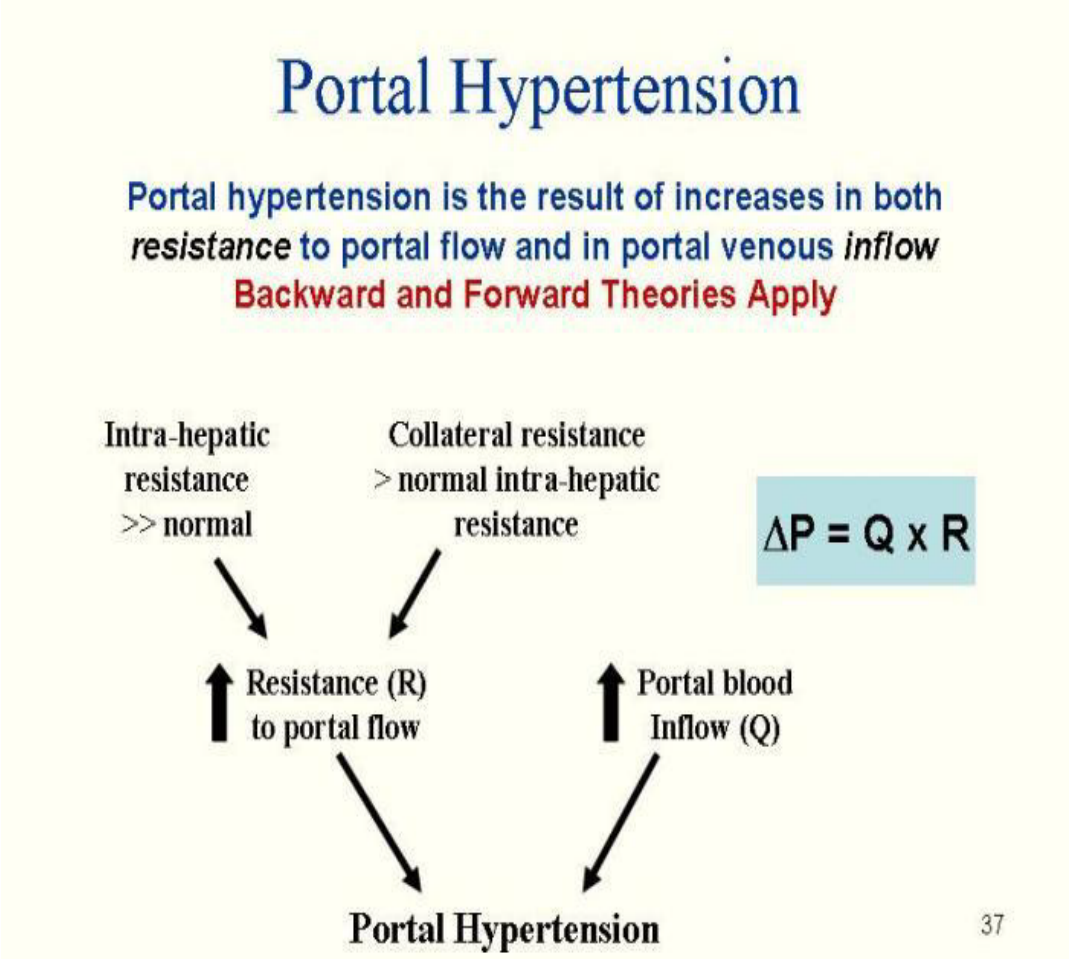
For example, although splenic flow increases markedly in the presence of massive splenomegaly, the critical threshold in the portal flow-pressure relationship is not reached and portal hypertension does not develop unless increased vascular resistance is also present.

This hemodynamic combination can be seen in conditions with splenomegaly, such as Felty's syndrome, sarcoidosis, or lymphomas. An exception is portal hypertension caused by a high portal flow from an arterio- venous fistula, as with splenic artery splenic vein communications, where the flow-volume relation exceeds a critical threshold.

The genesis of portal hypertension involves an increase in portal vascular resistance and is the basis for its classification. Insight into the location of vascular resistance in human cirrhosis has been provided by combined hepatic vein and portal pressure measurements.

Most measurements in non-alcoholic cirrhosis show a higher portal venous pressure than hepatic venous wedge pressure, which is an estimate of sinusoidal pressure. This indicates the presence of a pre sinusoidal component, probably related to inflammatory activity or fibrotic changes in the portal triads.

In alcoholic cirrhosis, the vascular resistance must reside at the level of the sinusoids because portal and hepatic venous wedge pressures are similar



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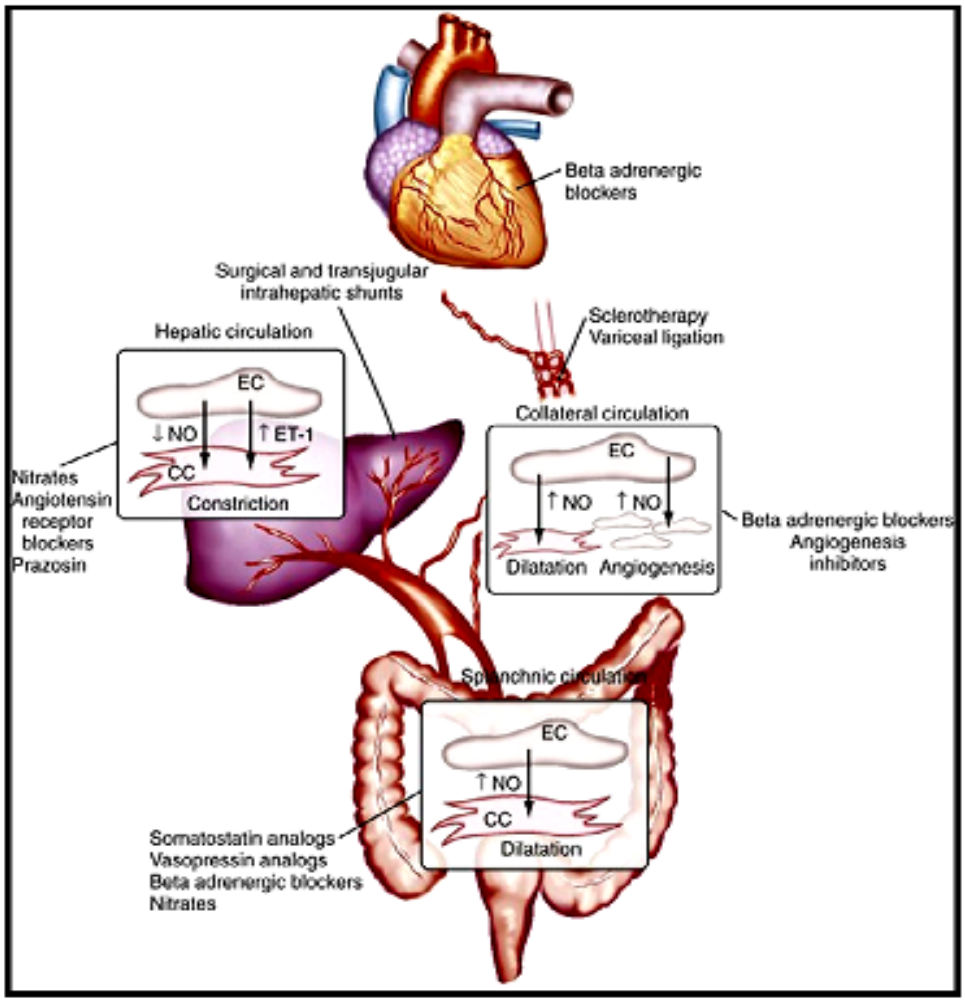
The pathogenesis of the increased sinusoidal resistance in alcoholic cirrhosis is controversial. The concept of a pathogenic role for the architectural rearrangement and development of fibrotic septa in cirrhosis has been replaced by an emphasis on sinusoidal events. Hepatocyte enlargement, resulting from an alcohol-induced accumulation of fat and protein, may compress the liver sinusoids and obstruct portal flow.

Studies of pre cirrhotic portal hypertension in baboons chronically fed with alcohol have suggested that the degree of perivenular and pericellular fibrosis induced by alcohol correlates with in vivo measurements of portal pressure.

This further implicates the hepatic sinusoids as the site of increased vascular resistance in alcoholic cirrhosis. Capillarization of these low-resistance channels, with loss of sinusoidal fenestrae, appearance of collagen in the space of Disse, and the presence of contractile myofibroblasts, may contribute to the development of increased sinusoidal resistance.

A relation between hepatocyte size and intrahepatic pressure in alcoholic liver disease was found for only mild to moderate pressure elevations, although the accuracy of intrahepatic pressure measurements has not been confirmed by others. In non-alcoholic cirrhosis, a more complex relation exists between these parameters.



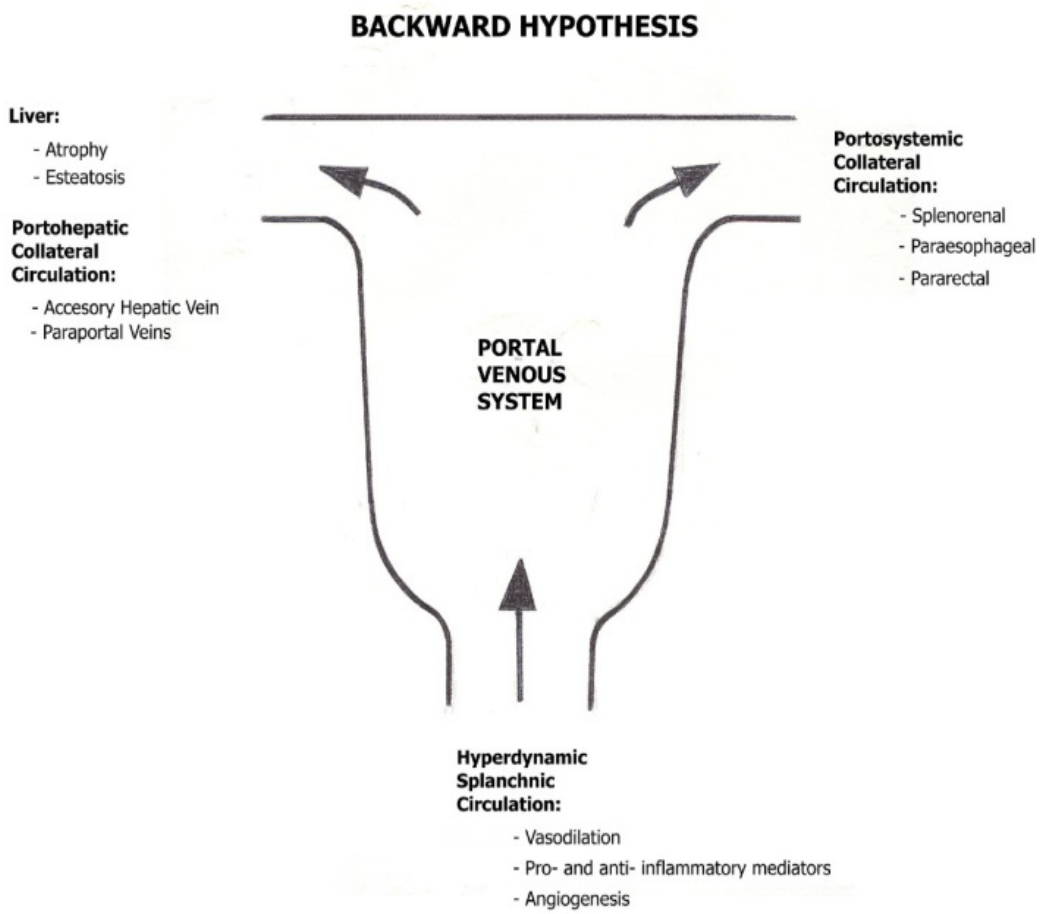
Vascular disturbances in portal hypertension and sites of action of portal pressure-reducing therapies. CC, contractilecell; EC, endothelial cell.

PORTAL BLOOD FLOW AND THE SYSTEMIC CIRCULATION

Two models have been proposed to explain the alternations of portal flow in response to portal hypertension:

1.Forward hypothesis

2.Backward hypothesis



"

FORWARD HYPOTHESIS

The first is based on a rise in portal venous pressure triggering a myogenic response that reduces splanchnic arterial inflow. As a net result, portal pressure values drift back toward normal. If the splanchnic circulation is considered as 2 organs in series (the gastrointestinal tree and the liver), the backward flow hypothesis predicts that inflow into the gastrointestinal tree would be reduced as a result of this rise in portal venous pressure.

Even when portal hypertension is fully established, the backward component contributes to its maintenance. The forward flow hypothesis, in which portal venous inflow is increased, is based on observations in several experimental models and patients.

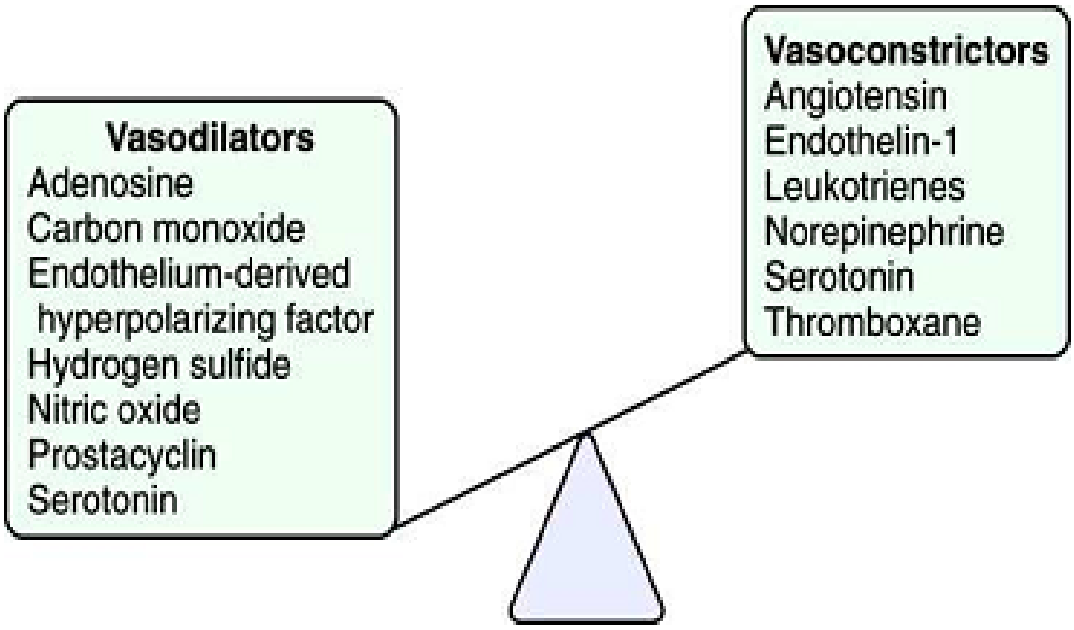
This paradoxical increase in portal venous inflow contributes to the maintenance of portal hypertension. As a hemodynamic syndrome, portal hypertension is unique in exhibiting both increased inflow and increased resistance.

The increase in portal inflow occurs as part of a more generalised hemodynamic disturbance, the `hyperdynamic" circulation. This is characterized by peripheral vasodilatation, a

reduction in peripheral vascular resistance, and an increase in plasma volume. As a result, cardiac output and heart rate increase.

Decreases in splanchnic and muscular arterial resistance are the main factors contributing to the decrease in systemic vascular resistance. Variable effects are seen on the renal circulation, in which compensatory mechanisms such as renal sympathetic nervous system activity, renin-angiotensin, and circulating catecholamines may induce renal vasoconstriction in spite of a decreased peripheral vascular resistance.

The hyperdynamic circulatory state is seen in many forms of portal hypertension. Humoral factors may be responsible for the development of peripheral vasodilatation. Glucagon levels are elevated in the presence of portal hypertension and porto systemic shunts. Other postulated humoral factors include prostacyclin, prostaglandins, bile salts and endotoxin mediated activation of nitric oxide.



Representative vasodilator and vasoconstrictor molecules implicated in the vascular abnormalities in portal hypertension.

PORTAL HYPERTENSION AS A HEMODYNAMIC SYNDROME

Splanchnic hemodynamics

* Increased portal vascular resistance
* Increased portal venous inflow
* Portosystemic shunting

Systemic hemodynamics

* Arterial vasodilatation
* Increased plasma volume.
* Variable renal blood flow.

A sequence of events that leads to the hyperdynamic state has been proposed. Although the primary pathophysiologic event is arterial vasodilation, a hyperdynamic state would not develop unless sodium was retained by the kidney, a process mediated by the activation of compensatory mechanisms triggered by the same vasodilatation. Plasma volume is then expanded, which triggers a further decrease in peripheral vascular resistance.

Influences of Portal Hypertension on Other organs :

Hypersplenism may occur in the absence of splenomegaly. Alterations of the splenic microcirculation, with fibrotic changes in the splenic sinusoids, favour entrapment of red cells, white cells (especially polymorphonuclear leukocytes), and platelets. However, the bone marrow remains active and infection or bleeding seldom results from leukopenia or thrombocytopenia, respectively. In the absence of other factors that affect the platelet count (alcohol, medications), thrombocytopenia between 50,000 and 125,000 platelets/mm is an indicator of portal hypertension in cirrhosis.

Hypoxemia, with an arterial partial pressure of oxygen between 60 and 80 mmHg, is a common finding in established portal hypertension. Administration of 100% oxygen does not correct the hypoxemia, suggesting that functional pulmonary arteriovenous shunting is the basic defect. Anatomic connections have been demonstrated on the pleural surface and termed lung "spiders". Vasodilatation of pulmonary capillaries, as part of the generalised process of systemic vasodilatation may increase the distance for oxygen diffusion between the blood and alveolus, resulting in functional shunt. The degree of hypoxemia can be severe.

Pulmonary hypertension develops in a few patients, regardless of the etiology of portal hypertension. The pathophysiology is unclear. Histologic studies do not suggest microscopic pulmonary embolism as a possibility. Rather, vasoactive substances arising from the splanchnic territory, which now by pass the liver, may induce permanent changes in the pulmonary vasculature. Serotonin, thought to be elevated in these patients, is of particular interest as it has been implicated in the pathogenesis of pulmonary hypertension associated with the carcinoid syndrome.

CLASSIFICATION OF PORTAL HYPERTENSION

A logical classification of portal hypertension is based on the site of increased resistance to portal flow. Five main groups can be delineated according to pre sinusoidal, sinusoidal, or post sinusoidal block. Pre sinusoidal and post sinusoidal portal hypertension can be further subdivided into intra-or extrahepatic causes.

Pre sinusoidal Pre hepatic :

Presinusoidal extra hepatic portal hypertension is most commonly due to portal vein thrombosis. A blood clot in the portal vein can have several causes; however, a definitive diagnosis cannot be made

for many patients. Many of these idiopathic cases may represent an early manifestation of a myeloproliferative syndrome. When the colony-forming units were quantitated after bone marrow culture - a diagnostic criterion for myeloproliferative syndrome, many patients with idiopathic portal hypertension met criteria for the diagnosis of this hematologic disorder. Catheterization of the umbilical vein in newborns has been associated with the developmentof omphalitis with secondary portal vein thrombosis. Over the years, bridging collaterals develop toward the liver, resulting in a "cavernous" appearance of the portal vein. The prognosis is relatively good because these patients have normal liver function, variceal hemorrhage is better tolerated, and the incidence of bleeding decreases after the second decade.

Disorders of the coagulation system may present as portal vein thrombosis. These include congenital deficiencies of natural anticoagulants such as deficiency of antithrombin III, protein C, protein S, and plasminogen activator. An acquired lupus anticoagulant may also predispose patients to this thrombotic event.

Diseases of the adjacent organs may also cause portal vein thrombi. Invasion into the portal vein by carcinoma of the head of the pancreas or common bile duct denotes inoperability; carcinomas of the

pancreatic body and tail affect the splenic vein. Cirrhosis has been viewed as predisposing to portal vein thrombosis because of stasis.

Pre sinusoidal portal hypertension

Extrahepatic

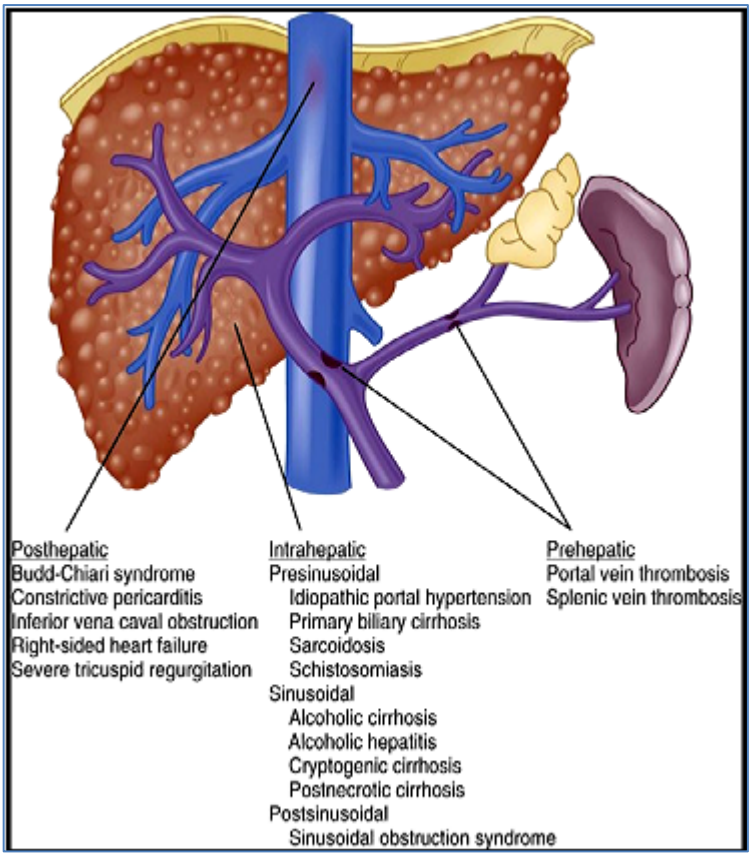
- Portal vein thrombosis

Intrahepatic

- Schistosomiasis (S.mansoni, S.japonica)
- Sarcoidosis
- Felty's syndrome
- Arsenic poisoning
- Idiopathic portal hypertension
- Congenital hepatic fibrosis
- Primary biliary cirrhosis(early stages)

Sinusoidal portal hypertension

- Alcoholic cirrhosis
- Vitamin A intoxication
- Nodular regenerative hyperplasia



Post sinusoidal portal hypertension

Intrahepatic :

- Veno-occulsive disease
- Senecio alkaloids
- Alcoholic hepatitis (venular sclerosis type)

Extrahepatic :

- Budd-Chiari syndrome
- Congenital web

Splenic vein thrombosis may give rise to gastric varices with hemorrhage. If the liver is normal, the gastric varices drain toward the liver through the coronary vein and esophageal varices may be absent. Chronic pancreatitis and many of the previously discerned disorders that cause portal vein thrombosis may also give rise to this segmental abnormality.

Pre sinusoidal intrahepatic

A wide range of disorders are included in this category, but portal venule obstruction is the common link. It can occur as a result of vascular obliteration (non cirrhotic portal fibrosis) or as a result of inflammatory activity in the portal triad (early stage of primary biliary cirrhosis, lymphoma) that impinges on the portal venous system.

Schistosomiasis is the most common entity in this group. Eggs shed by the parasite into the splanchnic venous tributaries lodge in the portal vein radicles within the liver. A granulomatous, fibrotic reaction develops around the eggs of eitherSchistosoma mansoni or Schistosoma japonicum, obstructing portal venous flow. As a result, prominent hepatomegaly can be detected. Splenomegaly and portosystemic collaterals arise as a consequence of portal hypertension. With progression of the disease, cirrhotic changes may

develop, resulting in an additional component of sinusoidal resistance to portal flow.

Non cirrhotic portal fibrosis (idiopathic portal hypertension) is a common cause of portal hypertension in Asia. Obliteration of small portal venules is its characteristic feature and liver function is preserved. Non cirrhotic portal fibrosis can be reproduced in experimental animals by injection of inactivated Escherichia coli into the portal vein. This implies that enteric infection is a possible cause. Arsenic poisoning may also present with pre sinusoidal features.

Inflammatory infiltration of the portal triads coexists with splenomegaly in another group of disorders. Examples include Felty's syndrome, lymphoma, and sarcoidosis. Several chronic hepatic disorders have a pre sinusoidal component of portal hypertension; these include non alcoholic cirrhosis and primary biliary cirrhosis. Congenital hepatic fibrosis may appear with portal hypertension as its initial manifestation.

Sinusoidal

Sinusoidal portal hypertension is the characteristic feature of alcoholic liver disease. Hepatitis B-related cirrhosis has also been reported to involve a sinusoidal resistance site. Peri sinusoidal fibrosis with portal hypertension can be seen with vitamin A intoxication

and after renal transplantation. In the latter, azathioprine may be involved in its genesis. Endothelial damage can also be caused by other compounds with thiol groups.

Classified within this group is nodular regenerative hyperplasia. The nodules in this entity are delineated not by fibrous tissue but by collapsed liver parenchymal cells. Mainly reported in patients with rheumatoid arthritis, it has been described in a wide variety of disorders, including myeloproliferative disorders, lymphoma, macroglobulinemia, and myeloma. Occlusion of small portal venules may be the primary disorder that leads to collapse of the reticulin framework and the appearance of nodules not surrounded by fibrous tissue. Partial nodular transformation, with nodularity confined to the area of the hepatic hilum, may be a variant of this disorder.

Postsinusoidal

This can occur within or outside the liver. Most of these entities present with ascites as the main manifestation of portal hypertension. The causes include

- Alcoholic hepatitis.
- Veno occlusive insufficiency.
- Hepatic vein thrombosis.

The high pressure portal venous system is decompressed by extensive portosystemic communications resulting in formation of collaterals.

SITES OF COLLATERALS:

1.Cardia of the stomach.

Oesophageal and gastric varices (Left gastric vein,short gastric vein (portal system) join with intercostal, diaphragmatic, oesophageal and azygous veins of the caval system leading to oesophagogastric varices.

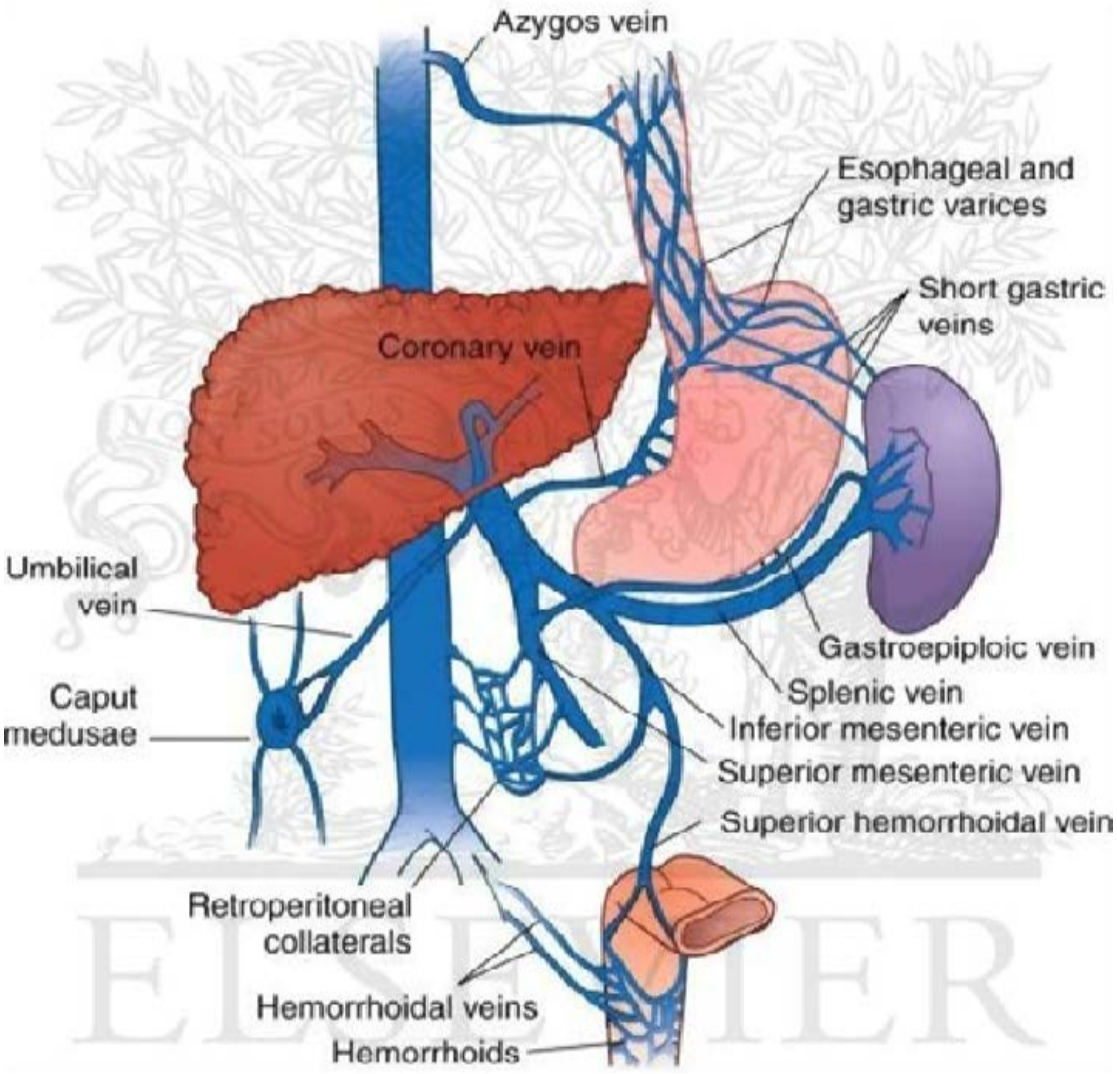
2.At the anal canal

Middle and inferior haemorrhoidal veins of the caval system joins with the superior haemorrhoidal vein of the portal system leading to rectal varices.

3.Umbilicus.

Remnants of the umbilical circulation of the foetus present in the falciform ligament form a large paraumbilical vein – Caput medusa.

4.Other sites of anastomoses are retroperitoneal vein, lumbar vein, omental vein and veins over bare area of the liver.

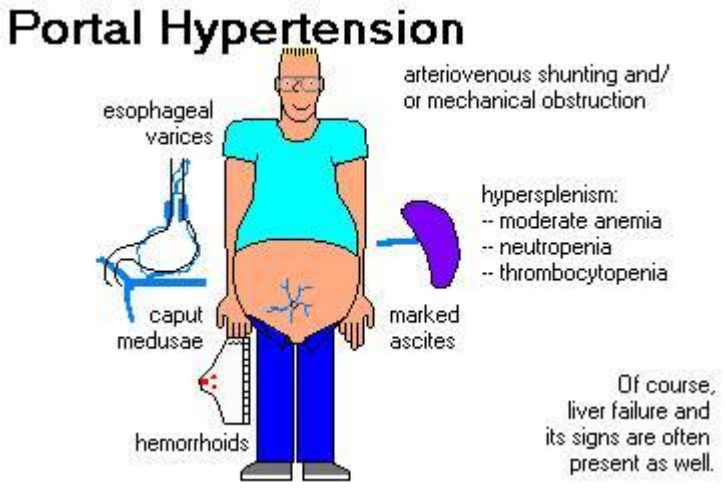


SITES OF COLLATERALS FORMATION IN PORTAL HYPERTENSION –At each of these sites, tributaries of the portal venous system anastomose with tributaries of the caval system and provide a means to by pass the liver.

INVESTIGATION OF THE PORTAL HYPERTENSIVE STATE

Physical Examination

A full clinical evaluation of patients with portal hypertension should include elucidation of the cause, evaluation of hepatic function, and screening for complications. The physical examination may provide special clues to the differential diagnosis.



When patients present with variceal bleeding, cirrhosis should not be assumed and pre sinusoidal causes should be considered. However, when patients with portal hypertension also exhibit ascites, a pre sinusoidal etiology is unlikely unless severe hypoalbuminemia alters the relation between hydrostatic and oncotic pressure in the intestinal capillaries. Cirrhosis may eventually develop in schistosomiasis, and ascites may result from sinusoidal portal hypertension.

Clinical features of Portal hypertension.

- Collateral circulation and varices.
- Ascites.
- Congestive splenomegaly, hypersplenism.
- Encephalopathy.
- Congestive gastropathy.

Liver size may offer clinical clues. A small liver in the presence of portal hypertension is suggestive of cirrhosis. The consistency of the liver edge can provide additional information, because a normal edge argues against a sinusoidal etiology.

The detection of a hepatic bruit may suggest primary carcinoma presenting with variceal bleeding as its initial manifestation. A venous hum in the periumbilical area indicates high flow through a patent umbilical vein, excluding portal vein thrombosis as a cause.

The appearance of a common ailment such as hemorrhoids can seldom be interpreted as an initial sign of portal hypertension. However, proctoscopic examination may reveal additional signs, such as the presence of rectal varies.

IMAGING OF THE PORTAL VENOUS SYSTEM.

1. Ultrasound:

On examination when the portal vein > 11mm in diameter then it is reported to be dilated portal vein which is indicative of portal hypertension.

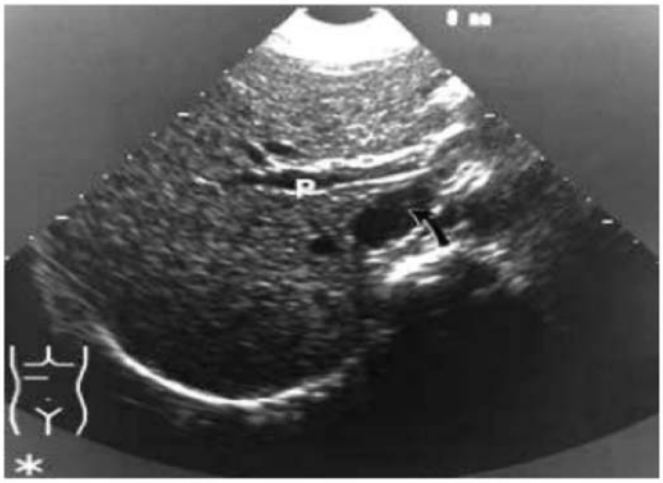


Figure 6: Transverse US shows a patent portal vein (P); the arrow indicates the inferior vena cava.

It is useful in evaluating size and any altered echo pattern of the liver, free fluid in the abdomen, biliary tract obstruction. In normal individuals parenchyma of liver is homogenous and have consistent mid level echoes whereas in cirrhosis with progressive fibrosis and nodularity there is diffuse attenuation in echo pattern that ranges from imperceptible coarsening of the echo to gross nodularity.

Cirrhotic liver differentiated from Non cirrhotic liver by using a ratio of caudate to right lobe width (C/RL)

C/RL = Transverse diameter of the Caudate lobe divided by

Transverse diameter of Right lobe.

C/RL > 0.65 in cirrhosis. With this ratio cirrhosis can be diagnosed with 96% confidence, if it is < 0.65 cirrhosis is unlikely.

Measurement of Spleen size:

Normal spleen size in adults - Males < 13 cm

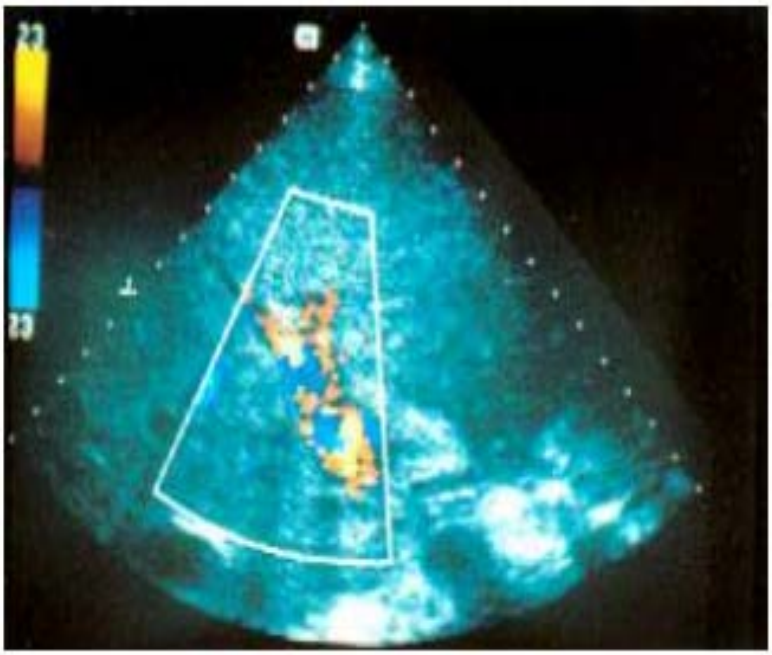
Females < 12cm.

Usually measured by taking the measurement along the long axis of the spleen in the mid axillary line. Other methods are

1. Splenic index (SI) = a * b
   a- transverse diameter(cm)
   b- vertical diameter(cm)
2. Splenic volumetric index.

2.Doppler ultrasound

Doppler US demonstrates the anatomy of the portal veins and hepatic artery. Doppler US shows spontaneous hepato-fugal flow in portal, splenic and superior mesenteric veins in patients with cirrhosis. Variceal bleeding is more likely if the flow is hepato-petal. Colour Doppler is a good way of demonstrating portal systemic shunts and the direction of flow in them. Duplex Doppler has-been used to measure portal blood flow. In cirrhosis, the portal vein velocity tends to fall and when less than 6cm/s portal hypertension is likely.



Colour Doppler Ultraound of Porta Hepatis

3.C.T scan

After contrast, portal vein patency can be established and esophageal varices may be shown as intraluminal protrusions enhancing after contrast. Gastric varices show as rounded structures, indistinguishable from the gastric wall. In cirrhosis, the venogram varies widely. It may be completely normalor may show filling of large numbers of collateral vessels with gross distortionof the intra-hepatic pattern ('tree in winter appearance).

4.X ray chest

A chest radiography may show an enlarged azygos vein appearing as a mass in the right hilar region or enlarged pulmonary arteries when pulmonary hypertension is associated with portal hypertension.

Fundico antral varices may be misinterpreted as mass lesions on upper gastrointestinal radiographs. Angiography of mesenteric vessels provides anatomical information and some functional data.

5. Splenoportography.

It offers the best anatomic detail but has seldom been used because of concern about splenic puncture. Small-gauge needles may be safe when optimal imaging is needed.

Venous phases of arterial injections can be enhanced with subtraction techniques, giving better anatomic detail.

MEASUREMENT OF PORTAL PRESSURE

a. Direct measurements of portal venous pressure can be obtained by direct puncture of portal tributaries or of venules within the liver.

b. Splenic pulp pressure, measured at the time of splenoportography, may accurately reflect portal venous pressure but is associated with risk of hemorrhage from the puncture site.

c. Catheterization of the umbilical vein, has been re-evaluated with use of the Doppler technique.

d. Percutaneous transhepatic measurements of portal pressure can be obtained at the time of portography.

e. Direct measurements in portal tributaries can also be made at the time of surgery. All these techniques require an additional measurement of hepatic venous pressure to evaluate the pressure gradient across the liver. Also, organ puncture can occur in patients with liver disease and coagulopathy.

f. The alternative is to approach the liver by way of the hepatic vein. During hepatic venous catheterization, the catheter is maximally advanced and the vein occluded so that a sinusoidal pattern can be seen during injection of dye. The pressure value at this point reflect hepatic venous wedge pressure under normal conditions. Withdrawal of the catheter into the hepatic vein allows estimation of hepatic venous free pressure.

Use of the balloon catheter allows measurements of free and wedge pressure from one position in the hepatic vein. Accurate measurements require adequate calibration of pressure transducers because the range of normal venous pressure values is narrow. An accurate tracing can be identified by its normal respiratory variation and stable values; digital readout of pressure value is unacceptable. Permanent records of such tracings should be incorporated in the patient's chart.

When the etiology of portal hypertension is unclear, pressure measured by hepatic venous catheterization can provide useful clinical information. A low hepatic venous pressure gradient in the presence of oesophageal varices, strongly argues for a pre sinusoidal etiology. This is the hemodynamic pattern in early hepatic schistosomiasis. A high pressure gradient confirms the presence of

parenchymal liver disease, but diagnosing its etiology requires additional testing.

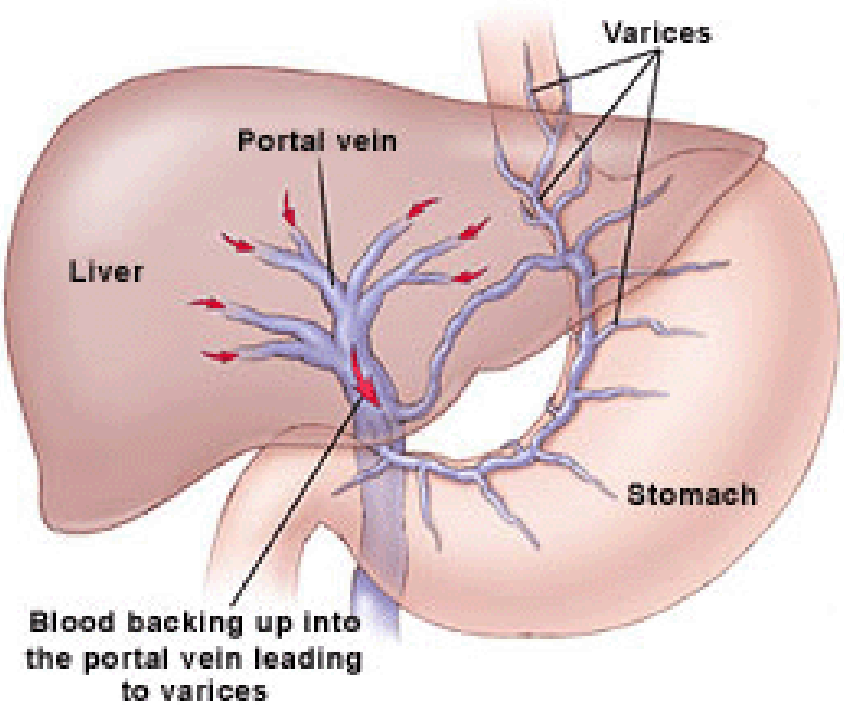
Percutaneous transhepatic measurements are useful in the diagnosis of the Budd - Chiari syndrome.

Measurements of pressure are important when therapeutic measures are planned. During surgery to relieve portal hypertension, evidence of adequate decompression is provided by intraoperative pressure measurements. The success of transjugular intrahepatic portosystemic shunt (TIPSS), a nonsurgical technique in which a metallic stent is placed between the portal and hepatic veins, can be measured by the reduction of portal pressure. When considering pharmacologic therapy with beta - adrenergic blockers, reduction of the portal venous pressure gradient to critical levels decreases the occurrence of gastrointestinal haemorrhage.

MEASUREMENT OF VARICEAL PRESSURE

Measurement of intravariceal pressure by puncture of esophagal varices before sclerotherapy has been reported. Although initial reports suggested identical values for intravariceal pressure and portal pressure, more accurate measurements indicated a lower value for the former, because pressure is dissipated over a larger vascular bed. When the sclerotherapy needle is introduced into the varix, it can cross the varix and its tip lies in the muscle layer. A manometric capsule has been used to measure variceal pressure indirectly. It is mounted on an endoscope and positioned over a variceal column. The pressure that obliterates the varix is equivalent to the intraluminal pressure and is recorded with its respiratory variation. This technique has been used to measure variceal wall tension by multiplying the apparent diameter of the varix by the recorded variceal pressure. With these parameters, wall tension was considerably higher in patients who had bled from varices than in non-bleeders.

Variceal Bleeding.



It is the most life threatening complication of portal hypertension. Most commonly bleeding arises from the oesophagogastric junction or from the cardia of the stomach. Bleeding from the varices to be treated in acute setting by supportive measures followed by a definitive procedure.

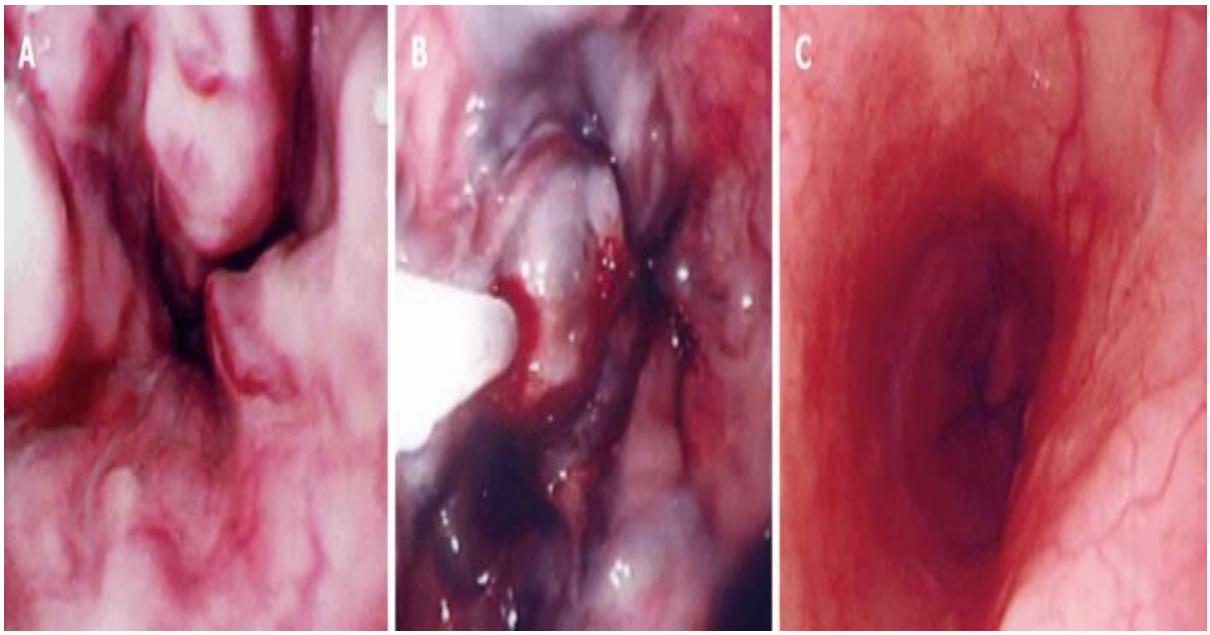
Factors predisposing to Bleeding:

1. Large varices.
2. Endoscopic variceal stigma(red spots, red stripes)
3. Elevated portal pressure.
4. Drugs like Nonsteroidal anti-inflammatory agents.
5. Tense ascites.

More than 2/3 will not bleed usually in the 1st year of diagnosis. Half of the patients will lose their life with 1st episode of haemorrhage. Size of varices is directly proportional to the risk of bleeding assessed by endoscopy.The other predictor being the portal pressure that is HVPG > 6 mm Hg is more definitive.

The best markers of bleeding are

1. Endoscopic red wales, red stripes.
2. Size of the varices.
3. Function of hepatocytes assessed by childpughs grading.



Cirrhosis due to alcoholic etiology have more risk of bleeding. This is predicted by Doppler sonography based on portal vein diameter, size of the spleen and the presence of collaterals.

Preventive methods for Bleeding:

1.Abstinence from alcohol.

2. Predisposing drugs to be avoided.

Management includes

1. Pharmacologic therapy.
2. Endoscopic therapy.

Acute variceal bleeding can be life threatening. This is defined clinically as systolic BP < 90 mm Hg, tachycardia, urine output < 30ml/hr requiring blood transfusion. All patients with cirrhosis and GI bleed should receive broad spectrum antibiotics such as Ciprofloxacin.

1. Replacement of blood, coagulation factors by fresh frozen plasma(coagulopathy).
2. Monitor CVP, PCWP, urine output and mental status.Treatment of sequelae of portal hypertension especially variceal bleeding is titrated to reduce the hepatic venous pressure gradient(HVPG) to < 12 mm Hg or 20% from the baseline.When the HVPG measurement is not feasible or available, reduction of resting heart rate by 25% - using beta blockers is reasonable.

3. Vasoconstrictors:

    a. Vasopressin.

        - 0.1to 0.5units/minute for 4to12hours
        - Then taper the dose and continue up to 48hours.
        - It reduces blood flow in the portal venous system.
        - Side effects are coronary, bowel and peripheral ischaemia, AKI, hyponatraemia.
        - Concurrent use of venodilators like nitroglycerine IV infusion, sublingual isosorbide dinitrate may enhance the effectiveness of vasopressin and reduce complications.

    b. Terlipressin. is a better alternative to vasopressin in the control of bleeding because of the beneficial effects in patients with hepatorenal syndrome.

    c. Somatostatin - direct splanchnic vasoconstrictor given as 250microgram iv stat followed by

d. infusion of 250microgram/hr for a period of 3to 5 days.

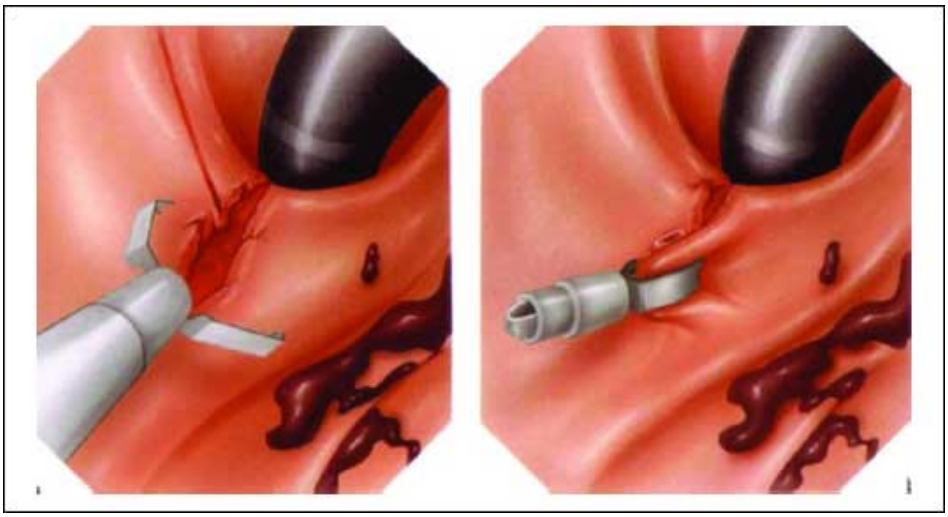
e. Octreotide- synthetic somatostatin analogue in a dose of 50microgram IV bolus followed by 50microgram/hr. These drugs can be repeated if the bleeding is severe.

f. Short acting nitrates via transdermal(10mg every 12 hours), sublingual(0.6mg every 30 minutes) or IV(40-400mirogram/minute to maintain systolic BP > 90mm Hg) routes can be tried.They reduce the peripheral vasospastic effects of vasopressin and lower the portal pressure via direct vasodilatation of porto-systemic collaterals.

g. Non selective beta blockers eg propranolol, nadolol are used prophylactically there by reducing the risk of first bleeding by 30%. They act by the unopposed alpha action by its vasoconstrictor effect.

4.Sclerotherapy:

Mechanism- the sclerosant acts by causing vessel thrombosis due to inflammatory reaction of the adjacent tissues and thereby obliterating the varix. The agents used are sodium morrhuate(5%), sodium tetradecyl sulphate(1-2%) ,ethanolamine oleate(5%), polidacanol(1-3%).



Complications:

Local effects. Ulcers , bleeding, pain, odynophagia lacerations, oesophageal dysmotility.

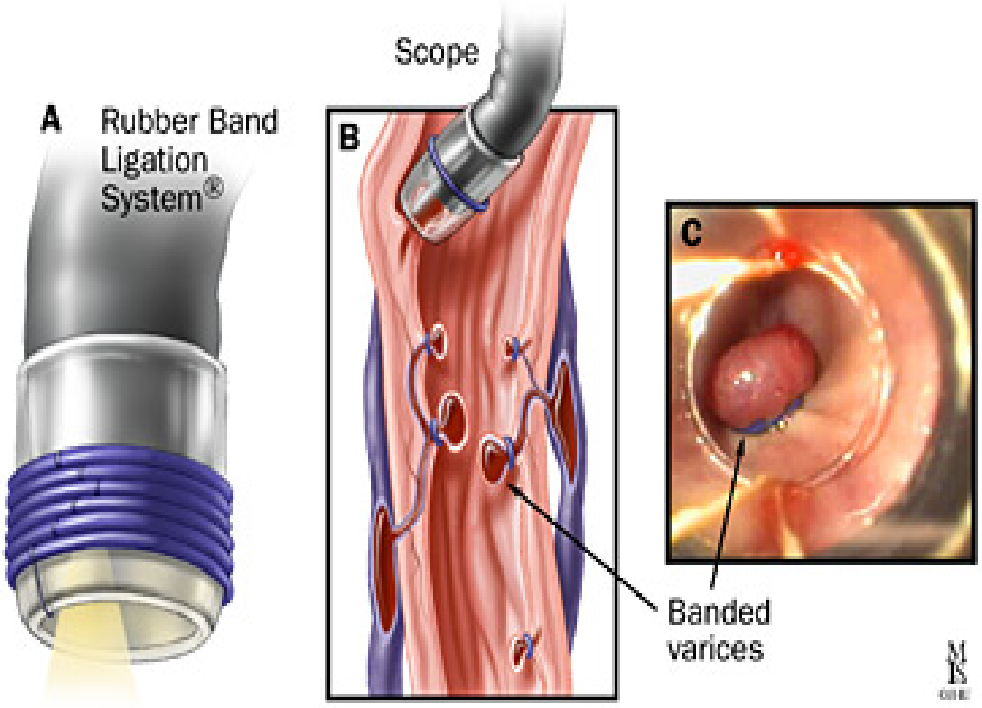
Regional. Perforation of oesophagus, inflammation of mediastinum, pleural effusion, dilatation of stomach.

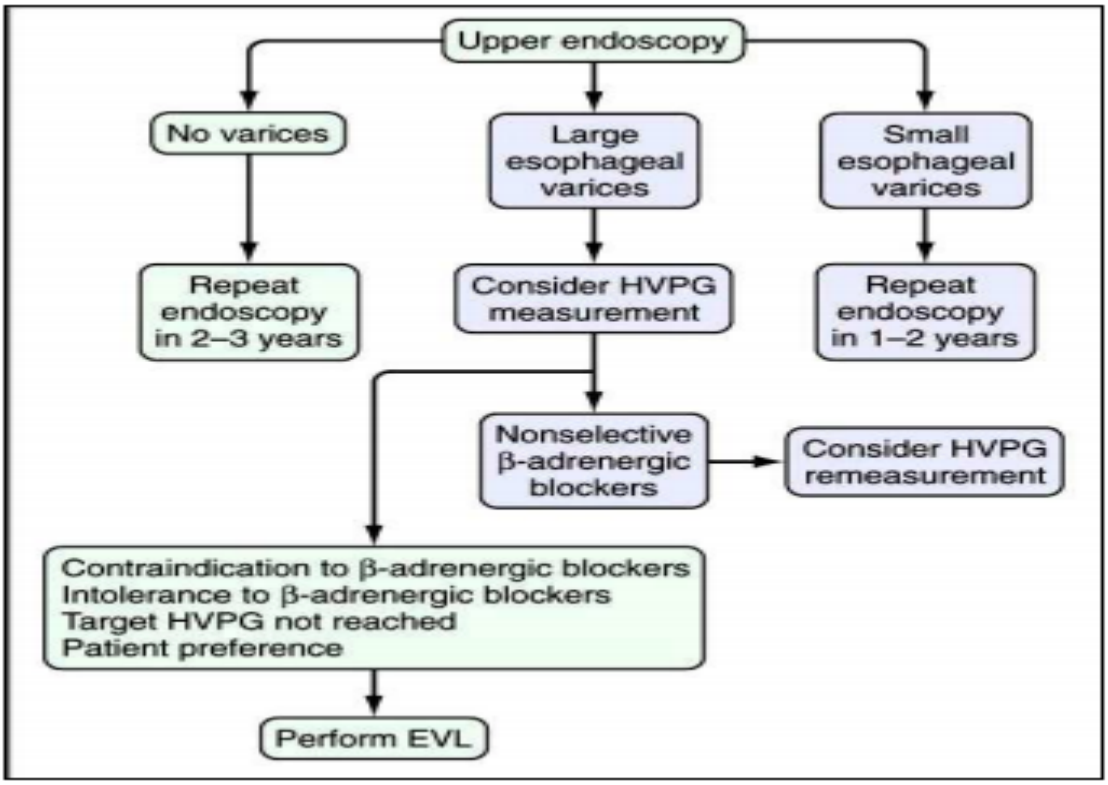
Systemic. Septicaemia, spontaneous bacterial peritonitis, ventilation perfusion mismatch, ARDS, portal vein thrombosis, aspiration.

5.Banding:

It is the procedure of choice in nonbleeding varices.

Rubber rings attached to a hollow cylinder in the tip of the scope are placed over the varices.



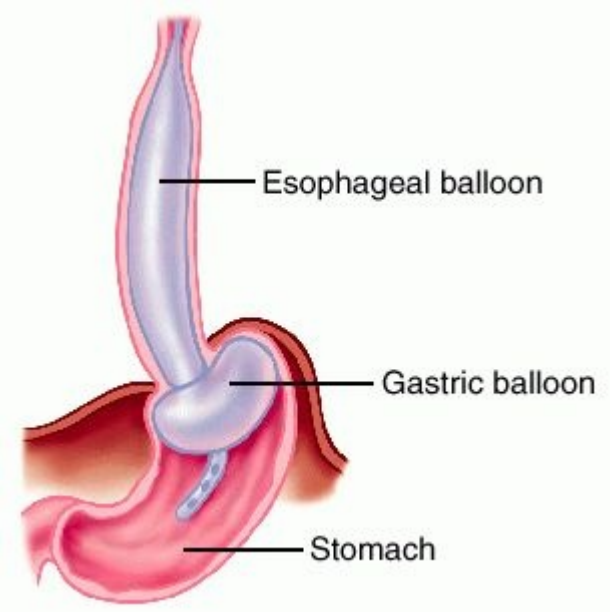


Banding leads to ischemia and necrosis of the mucosa and submucosa by interrupting the flow followed by granulation tissue formation and other tissues are sloughed off leaving a shallow ulcer in 2-3 weeks.

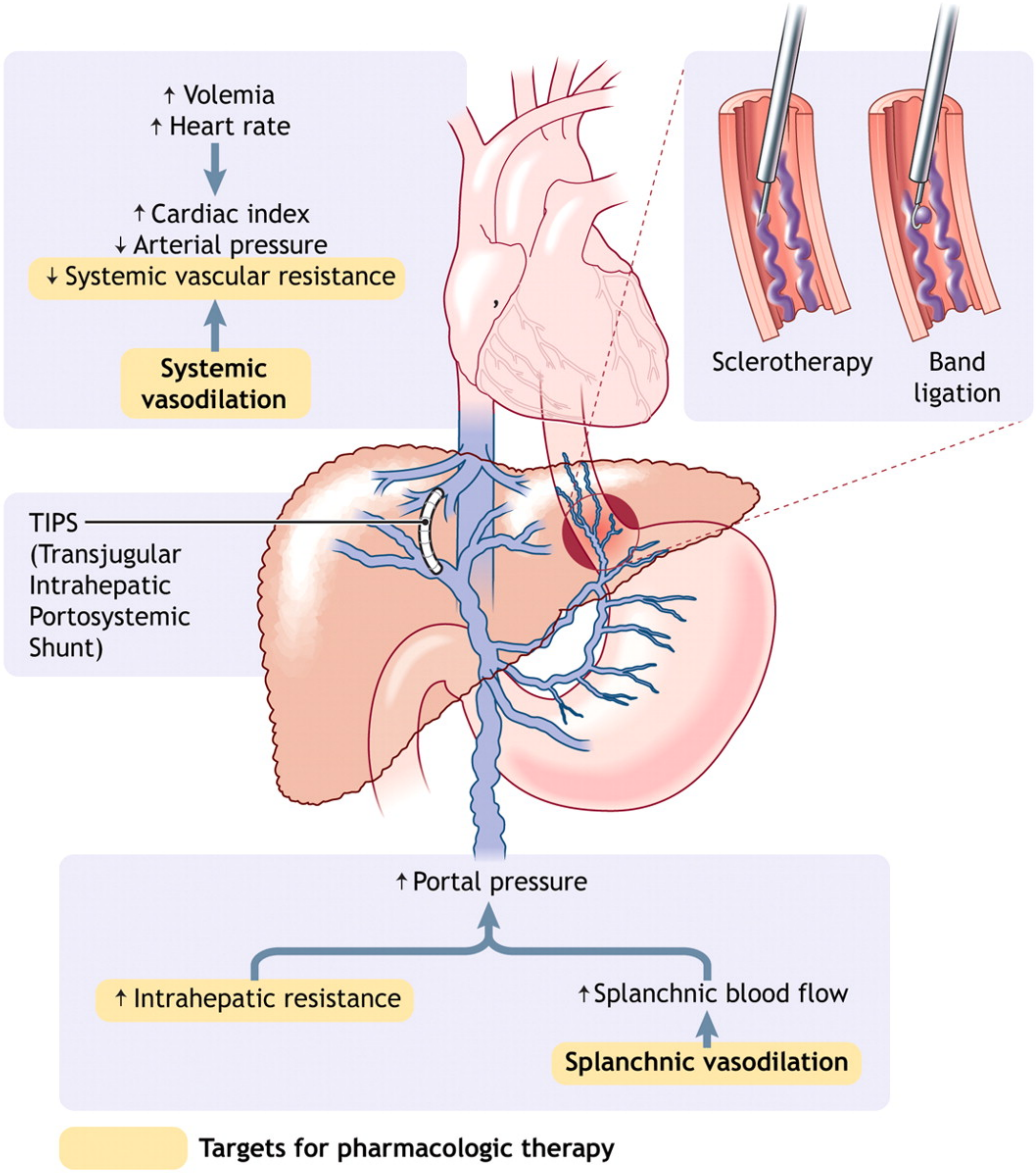
Complications. Superficial ulceration, stricture, dysphagia.

6. Balloon tamponade

It is done by a triple or four lumen Sengstaken – Blackemores tube with two balloons (gastric/ oesophageal).



Complications: Aspiration pneumonitis, oesophageal rupture depending on the length of time the balloon is inflated. Hence it has to be deflated after 24 hours. If bleeding has stopped, the tube may be removed in another 24 hours



Bleeding varices can be tackled mechanically or pharmacologically. Medical measures include drugs which reduce the portal pressure.Mechanical measures include compression of the varices by sengstaken Blakemore tube and sclerotherapy, banding.

7. Transjugular intrahepatic portosystemic stent shunting.(TIPSS)

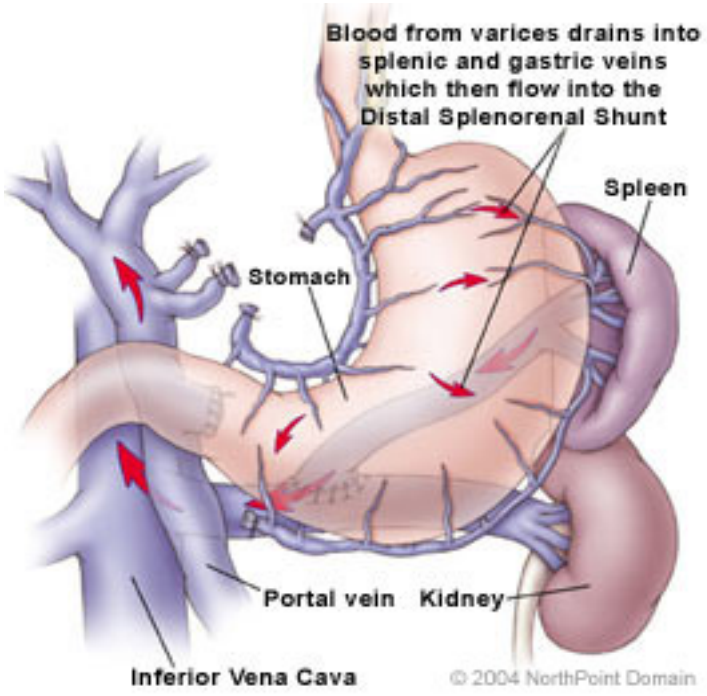
The stent is passed through the internal jugular vein under radio imaging. By angiography patency of portal vein is determined. Then the stent is kept between portal vein and hepatic vein which there by causes reduction of portal pressure.

Complications include

1. Bleeding associated with shunt occlusion or narrowing.
2. Hepatic encephalopathy. This is managed by reducing the shunt diameter.

8.Portosystemic shunt surgery:

a. Non selective shunts to decompress entire portal system. Eg side to side / end to end portocaval and proximal splenorenal anastomosis.Portosystemic



encephalopathy common.

b. Selective shunts that decompress only the varices allowing blood flow to the liver.

Eg Distal splenorenal shunt.

c. Splenectomy. – for isolated fundal varices caused by splenic vein thrombosis.

The two major complications of portal hypertension are

1.Variceal Haemorrhage.

2.Ascites.

Due to increase in the pressure of the portal venous system – it leads to formation of oesophagogastric varices, return of blood in to superior vena cava through azygos vein. The risk of bleeding from varices increases when HVPG > 12 mm Hg.

Uses of Endoscopy.

1.To detect the presence of varices and to asses high risk features related to increased bleeding risk.

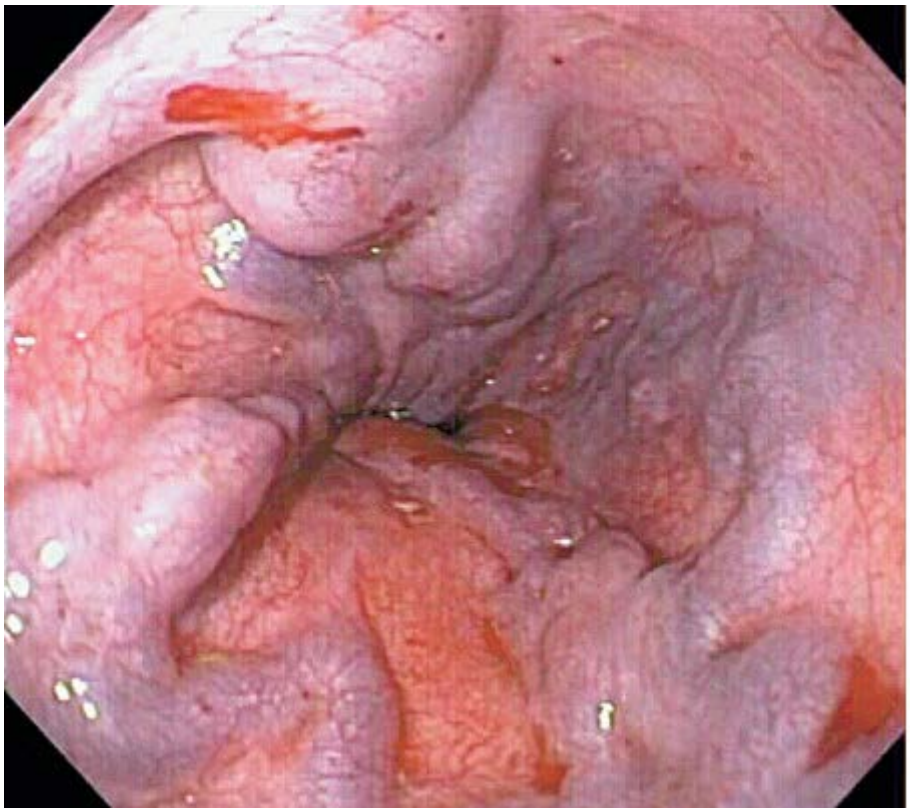
2.To intervene therapeutically in case of acute bleeding.

The risk of bleeding can be assessed by

1.Childs criteria.

2.Presence of red wales.

3.Size of varices.



Oesophageal varices

Grade 1 disappears completely with insufflation.

Grade 2 Occlusion < 2/3 of the lumen.

Grade 3 Complete occluson of the lumen.

Another classification is

1. Gastooesophageal varices (GOVs)

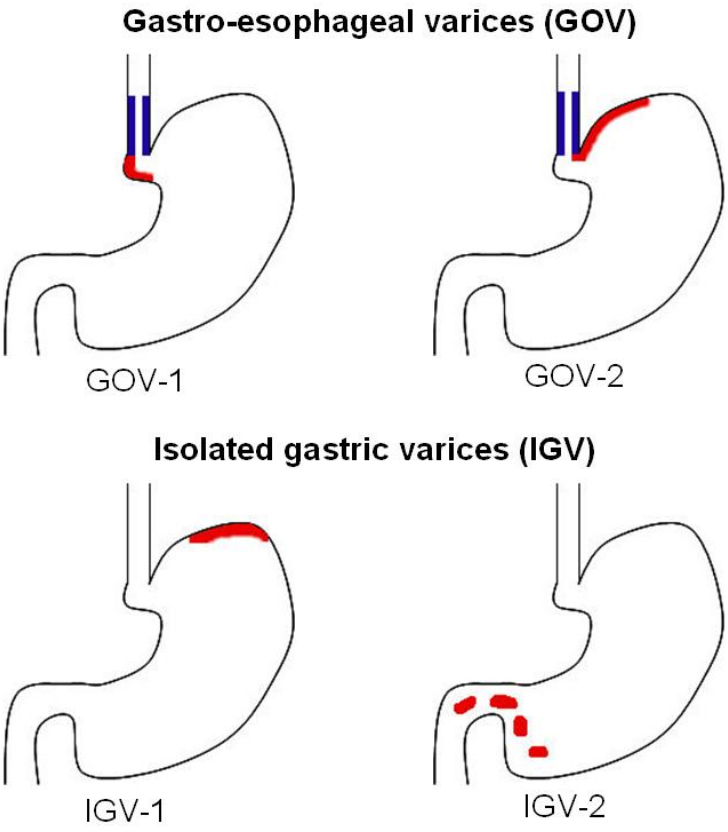
   GOV Type 1 – along the lesser curvature of the stomach.

GOV Type 2 – along the greater curvature up to the fundus of the stomach

2.Isolated gastric varices (IGV)

Type 1 IGV – Variceal clustering along the fundus of the stomach.

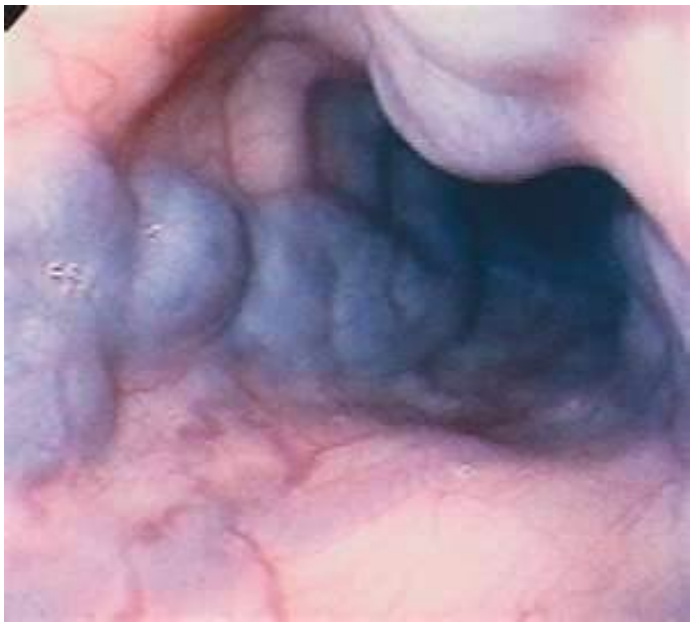
Type 2 IGV – Presence of varices in other parts of the stomach.



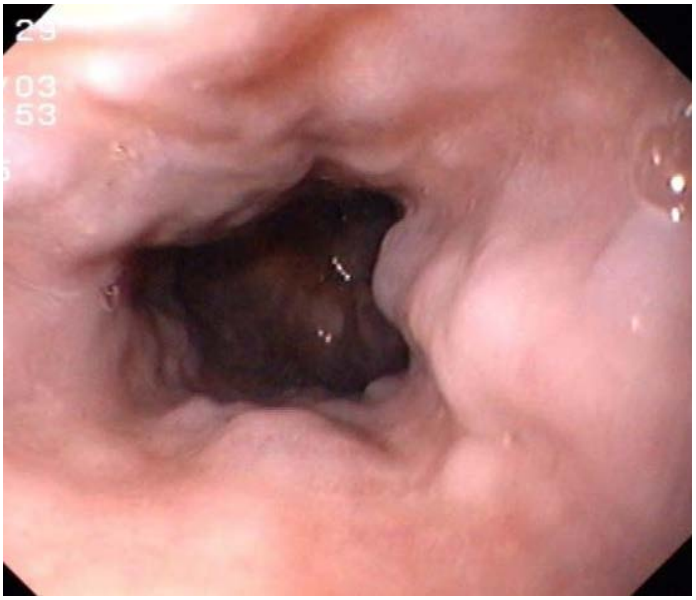
ENDOSCOPIC SCREENING FOR OESOPHAGEAL VARICES

Endoscopic grading of varices

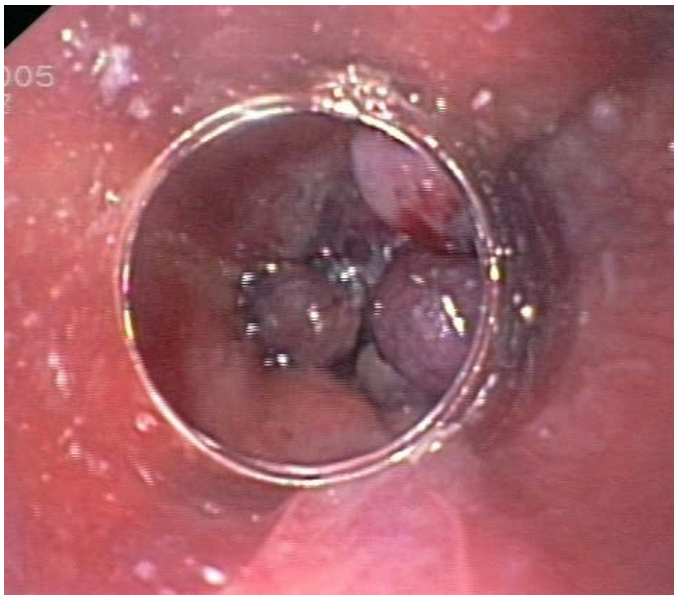
Grade I: Small varices without luminal prolapse



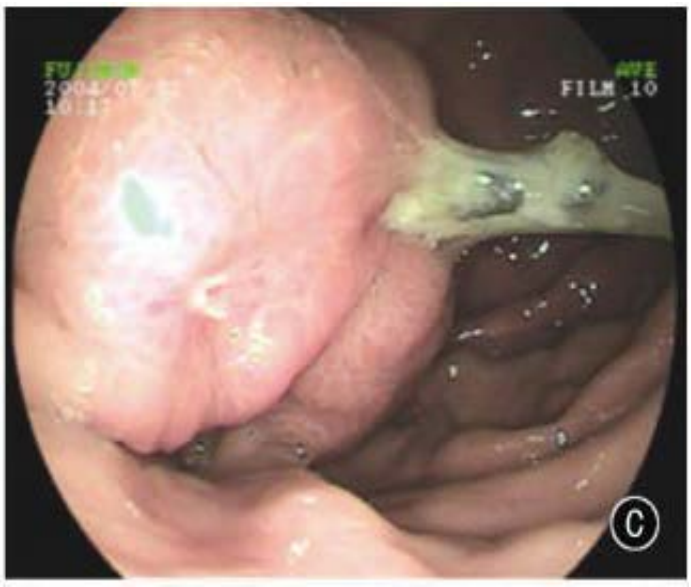
Grade II : Moderate-sized varices showing luminal prolapse with minimal obscuring of the gastro-oesophageal junction.



Grade III : Large varices showing luminal prolapse substantially obscuring the gastro oe sophageal junction

. 

Grade IV : Very large varices completely obscuring the gastroesophageal junction

. 

. MATERIALS AND METHODS

STUDY POPULATION :

The study will be conducted among 75 patients admitted in Medical ward, Government Rajaji Hospital, Madurai with history and clinical features of Cirrhosis.

INCLUSION CRITERIA:

- ☐ Age > 18 years/ Males
- ☐ Patients undergoing screening endoscopy for varices at the time of diagnosis of cirrhosis.
- ☐ Known cirrhotic patients who have never undergone screening endoscopy for EV.

EXCLUSION CRITERIA:

Patients with

- ☐ Active upper G.I.bleeding
- ☐ Previous history of endoscopic sclerosis / band ligation of EV
- ☐ Previous surgery for portal hypertension (stents)

☐ Previous history of Beta Blocker treatment / prophylaxis.

☐ Inabilty to abstain from alcoholism

ANTICIPATED OUTCOME

Platelet count/spleen diameter ratio is a predictable indicator for noninvasive diagnosis of esophageal varices in cirrhotic patients.

DATA COLLECTION :

The following information will be collected for each patient: age, gender, etiology of cirrhosis, biochemical parameters (aspartate aminotransferase [AST] , alanine aminotransferase [ALT], total bilirubin, serum albumin, prothrombin activity (%), serum creatinine, platelet count, presence and degree of ascites and encephalopathy assessed according to ChildPugh criteria, treatment with diuretics, and presence of contraindications to the use of nonselective β-blockers. The presence and size of EV will be determined and recorded for each patient. The size of varices is subdivided into two classes—small to screen and large to treat—according to the criteria proposed at the Baveno I Consensus Conference. Small EV is defined as varices that flatten with insufflation or minimally protrude into the esophageal lumen, while large EV is defined as varices that protrude into the

esophageal lumen and touch each other (presence of confluence), or that fill at least 50% of the esophageal lumen. This semiquantitative approach is chosen because it provides better interobserver agreement as compared with quantitative grading.

All patients will undergo ultrasonographic examination of the upper abdomen including spleen bipolar diameter measurement. Ultrasonographic measurement of spleen bipolar diameter is technically feasible in all patients. Both endoscopy and abdomen ultrasonography operators will be blinded to the others' instrumental results and to the patients biochemical data.

Platelet count/spleen diameter ratio is calculated in all patients as platelet platelet count/spleen diameter ratio will be evaluated in the whole cohort of patients as well as in two subanalyses carried out by considering groups of patients with various degrees of liver function impairment (Child-Pugh classes) and patients with various etiologies of liver disease.

A previously designed profoma will be used to collect the demographic and clinical details of the patients.A detailed history will be taken and a clinical examination will be performed.

LABORATORY INVESTIGATIONS:

Hb.

Total Bilirubin: Direct & Indirect

Total Protein Albumin Globulin

SGOT(AST) SGPT(ALT)

Prothromin time , Platelet count

Peripheral blood smear.

Ultrasonagram abdomen for splenic diameter

DESIGN OF STUDY : Prospective analytical study

PERIOD OF STUDY : July 2013 to August 2014

COLLABORATING DEPARTMENTS : Department of General Medicine, Department of Medical Gastroenterology, Deprtment of Radiology and Department of Biochemistry.

ETHICAL CLEARANCE : Obtained

CONSENT : Individual written and informed consent

ANALYSIS : Statistical analysis- chi square

CONFLICT OF INTEREST : NIL

FINANCIAL SUPPORT : NIL

PARTICIPANTS : Patients with history and clinical features of Cirrhosis admitted in Medical ward, Govt. Rajaji Hospital.

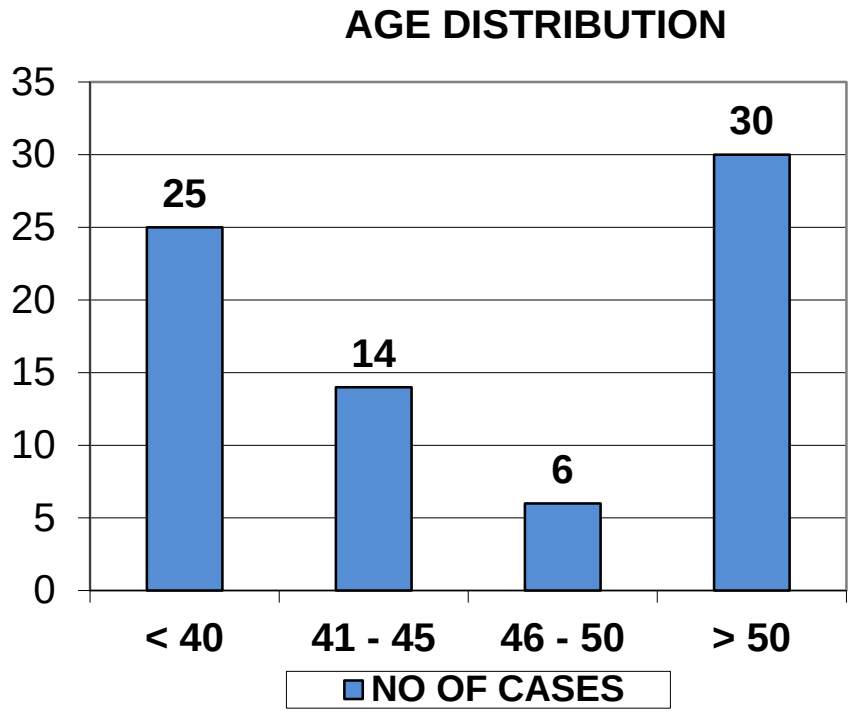
STATISTICAL METHODS:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

All the data was entered onto Microsoft excel sheet 2010 version. The statistical analysis was done using SPSS software. The statistical tools applied were mean, standard deviation, and chi – square test with Yates' correction. The results were considered very significant with p value < 0.01 and significant with p value <0.05 Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Age distribution in our study.

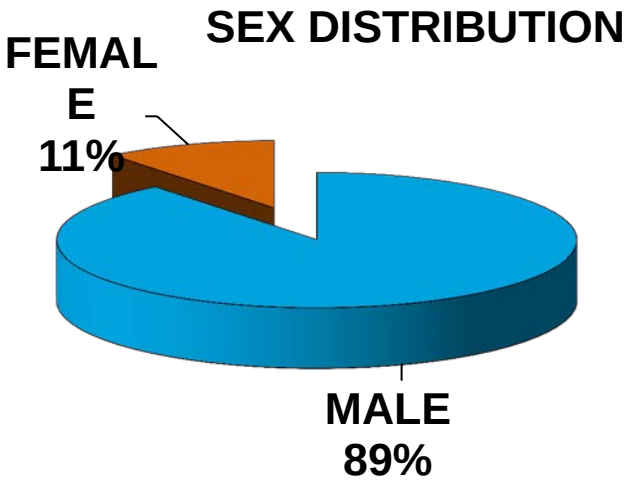
AGE	NO OF CASES	PERCENTAGE
≤ 40	25	33.33
41 - 45	14	18.67
46 - 50	6	8.00
> 50	30	40.00
TOTAL	75	100



In our study majority of the patients were between 50-60 years. The youngest patient in our study was 31 years old and the oldest was 58 years.

Sex distribution in our study.

SEX	NO OF CASES	PERCENTAGE
MALE	67	89.33
FEMALE	8	10.67
TOTAL	75	100.00

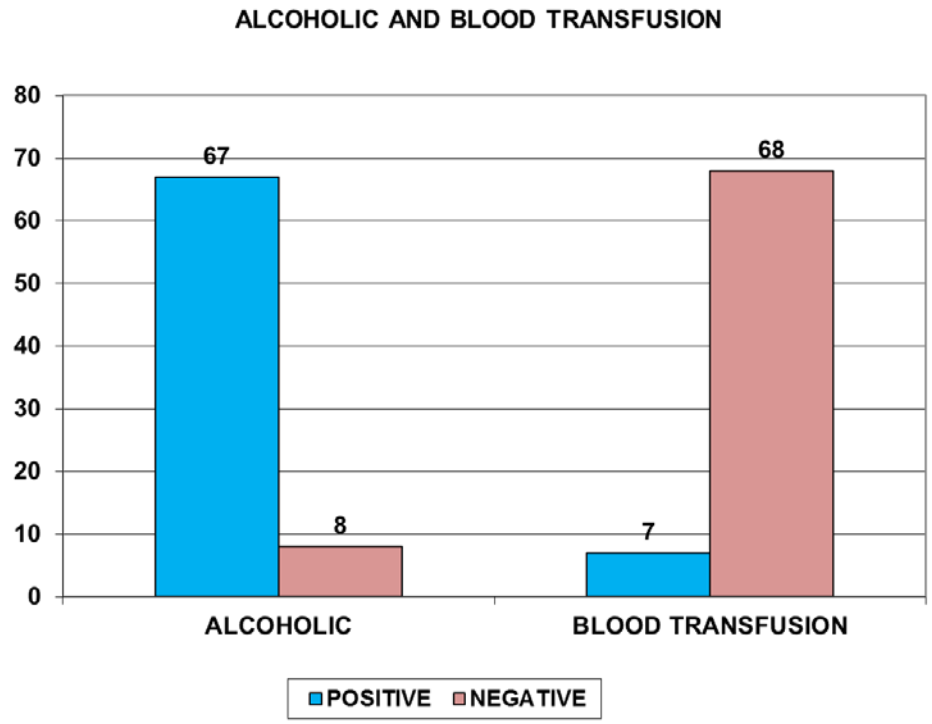


Comment :

In our study males constituted >89% and females constituted 10.67%. In our population males predominated the study.

Distribution of alcoholism in our study

	NO OF CASES	PERCENTAGE
ALCOHOLIC	67	89.33
NON-ALCOHOLIC	8	10.67
TOTAL	75	100.00

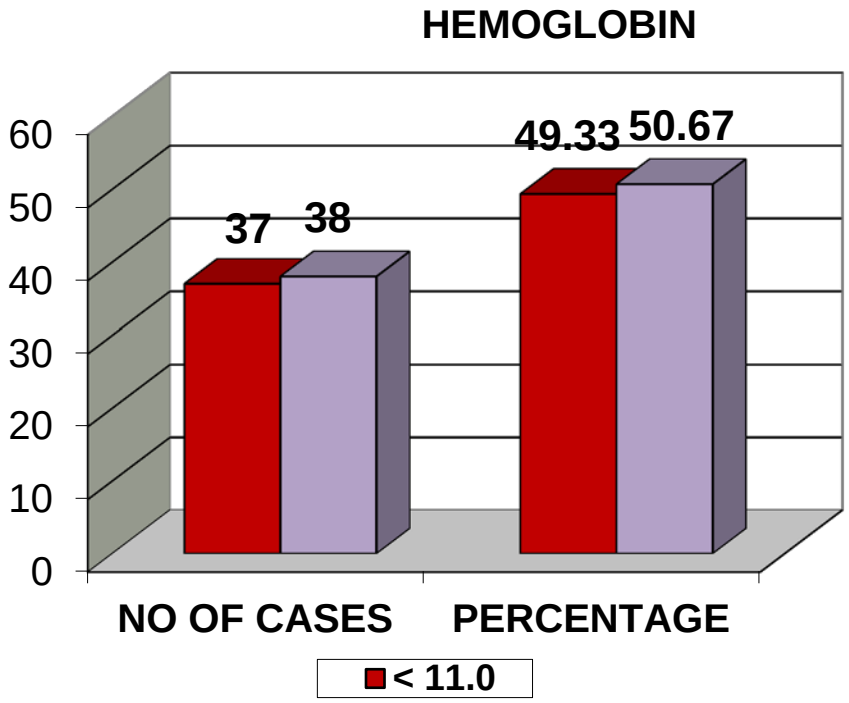


Comment :

In our study out of 75 patients, 67 patients gave a history of intake of alcohol > 180 ml/day. The remaining gave a history of blood transfusion. Thus alcoholics constitute >89.22% and blood transfusion constitutes 10.67%.

Hemoglobin distribution in our study

Hb	NO. OF CASES	PERCENTAGE
< 11.0	37	49.33
> 11.0	38	50.67
Total	75	100

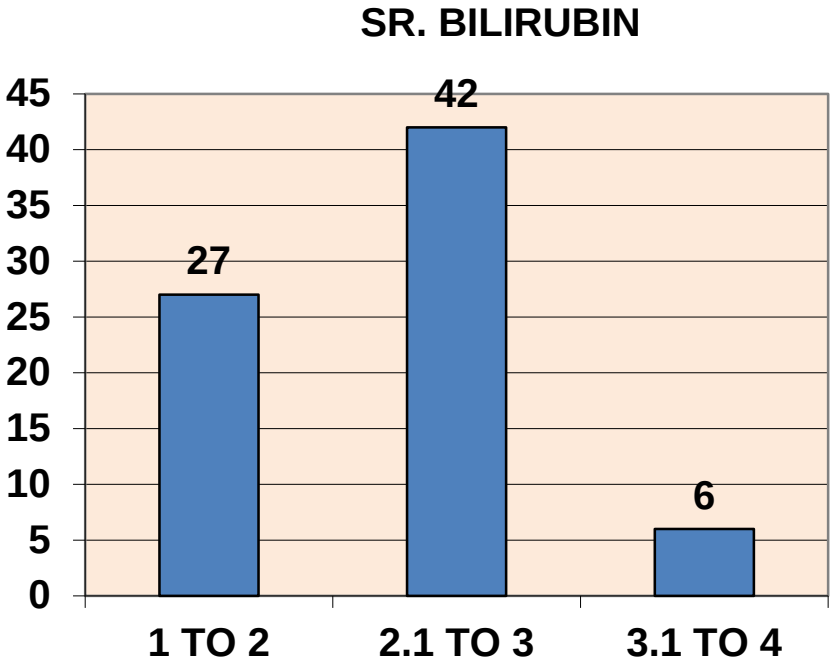


Comment :

In our study 37 patients had Hemoglobin < 11gm%.This constitutes 49.33% of the population and patients with Hb>11gm% constitutes 50.67% of the population. Chronic liver disease causes anaemia of chronic disease due to direct suppression of bone marrow.

Distribution of Serum Bilirubin among patients in our study

SR.BILLRUBIN	NO OF CASES	PERCENTAGE
1 TO 2	27	36.00
2.1 TO 3	42	56.00
3.1 TO 4	6	8.00
TOTAL	75	100.00

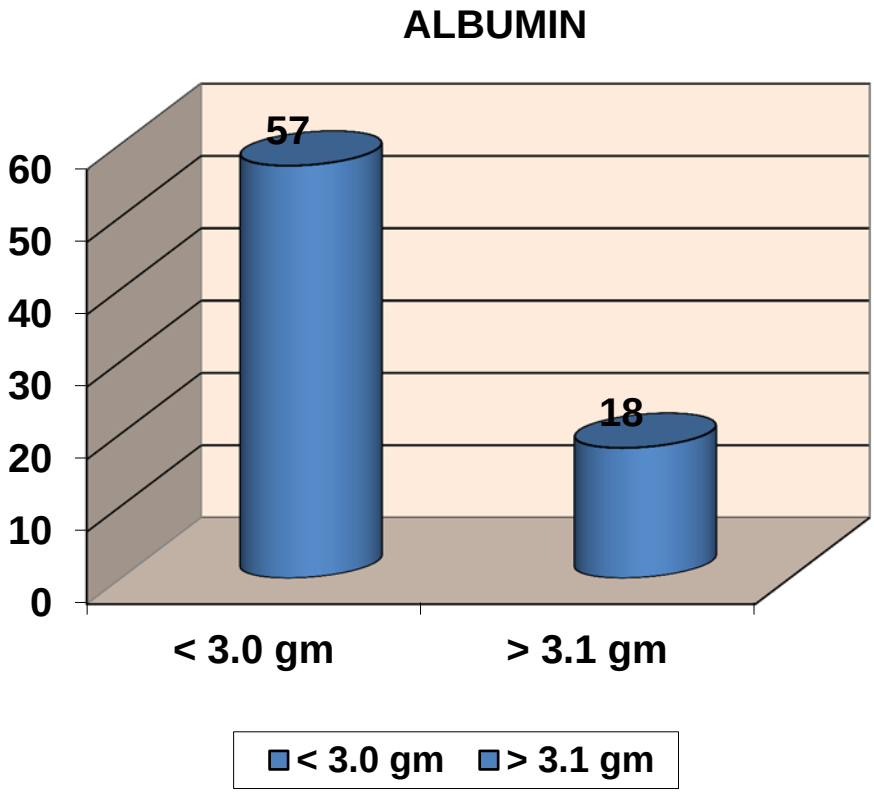


Comment.:

In our study, 42 patients had serum bilirubin between 2.1-3mg/dl. Majority of patients with cirrhosis presented with jaundice.

Serum Albumin distribution in our study

ALBUMIN	NO OF CASES	PERCENTAGE
< 3.0 gm	57	76.00
> 3.1 gm	18	24.00
TOTAL	75	100.00



Comment :

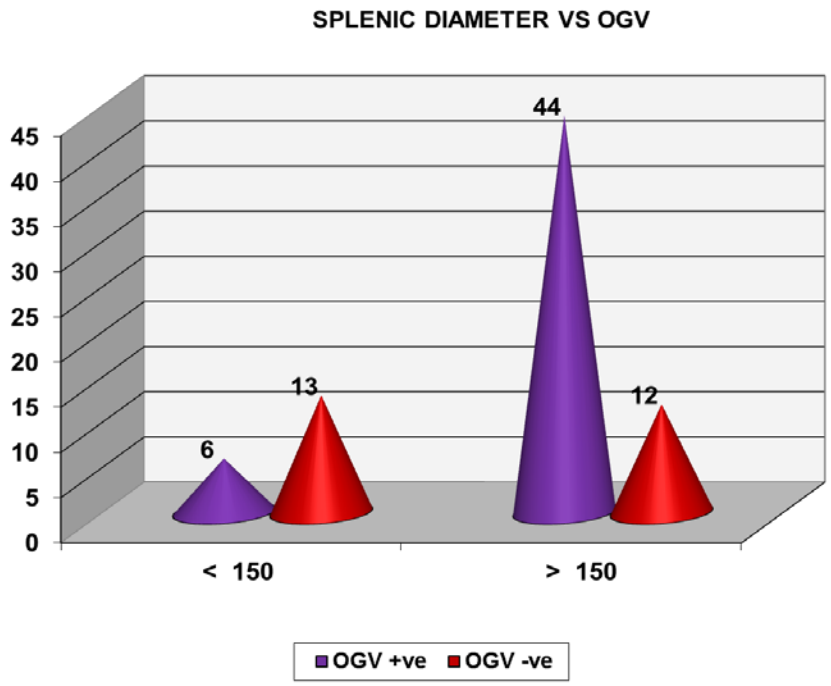
In our study out of 75 patient, 57patients presented with serum bilirubin of <3gm% that is it constitutes 76%. In chronic liver disease patient there is Albumin Globulin ratio reversal since liver is the major site of albumin production whereas the gamma globulin production occurs in the reticuloendothelial system.

Correlation of Spleen diameter with oesophageal varices

SPLEEN DIAMETER(mm)	OGV +ve	OGV -ve
< 150	6	13
> 150	44	12
TOTAL	50	25

Chi square test was applied. Degree of freedom is 1.

P value < 0.012.This is statistically significant.



Comment.:

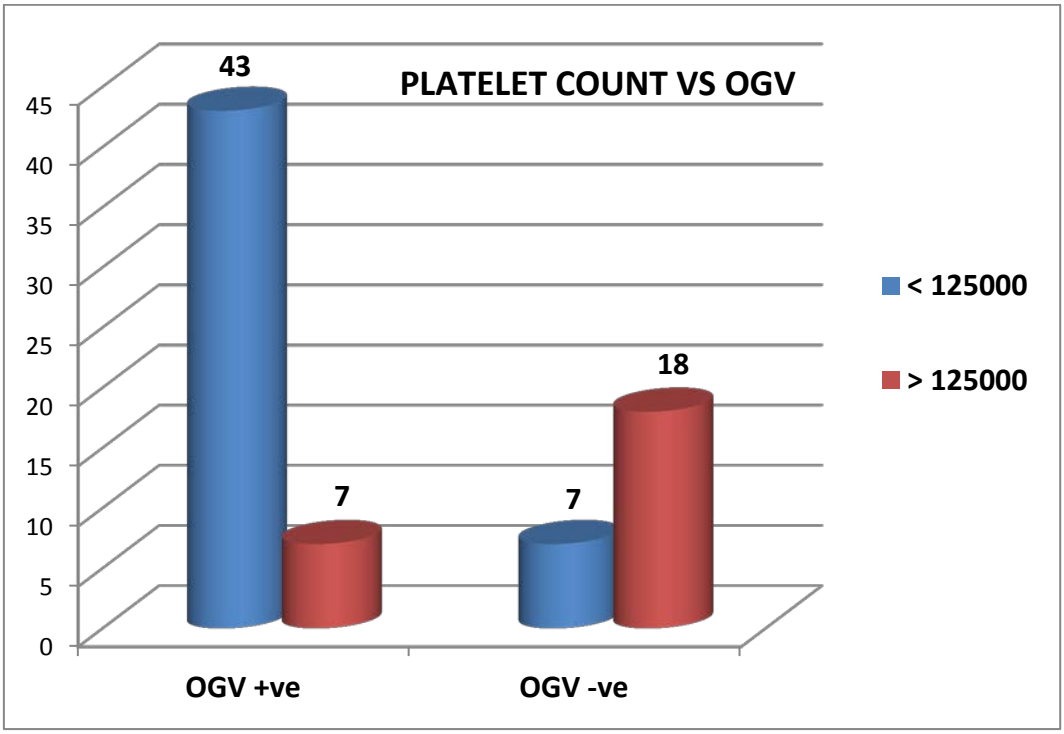
In our study 44 patients with spleen diameter > 150 mm developed oesophageal varices constituting 88% of the study with a P value of< 0.012 ,which is significant but it is less significant than the association of platelet spleen diameter ratio with presence of OGV.

Correlation of Platelet count with oesophageal varices.

PLATLET COUNT	OGV +ve	OGV –ve
< 125000	43	7
> 125000	7	18
Total	50	25

Chi square test was applied. Degree of freedom is 1.

P Value < 0.027.This is statistically significant.



Comment :

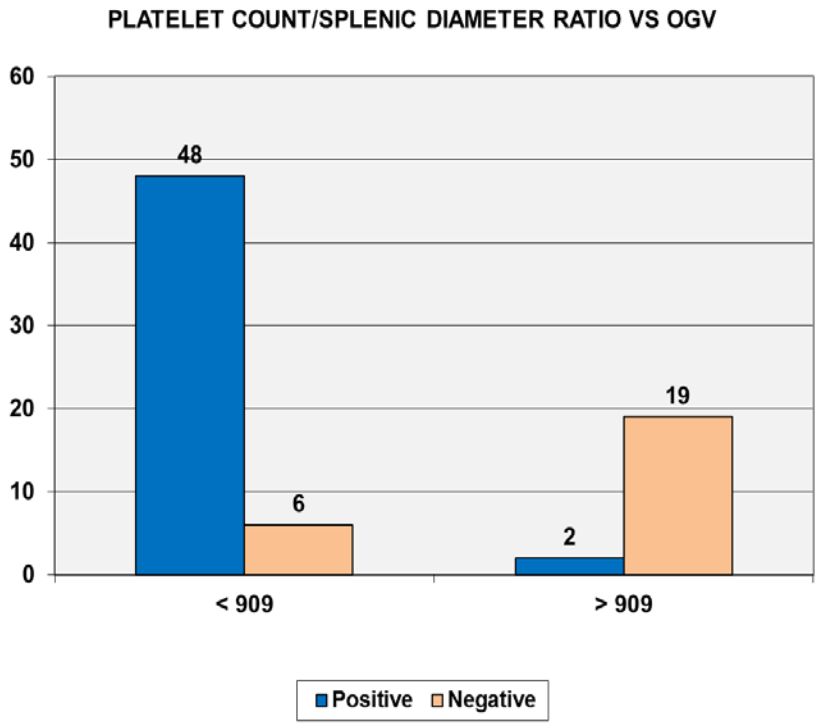
In our study out of 75 patients 43 patients with platelet count > 125000 developed oesophageal varices constituting 86%.The P value is < 0.027 which is significant but this is less than that of the PC/SD ratio association with oesophageal varices.

Correlation of Platelet count Spleen diameter ratio with oesophageal varices.

RATIO	Positive	Negative
< 909	48	6
> 909	2	19
TOTAL	50	25

Chi square test was applied. Degree of freedom is 1.

The p value was found to be <0.007.This is statistically significant.



Comments.

In our study out of 75 patients, 50 patients developed oesophageal varices. Out of 50 patients, 48 had PC/SC ratio of < 909 which has a signicant P value < 0.007 with sensitivity of 96% and specificity of 90.48%.

The positive predictive value of the study is 88.8% and the negative predictive value is 90.4%.

DISCUSSION

About 1/3rd of patients with chronic decompensated liver disease, face the life threatening complication of UGI bleed. The risk of bleeding from varices increases in the subsequent years after diagnosis and is an important cause of mortality . This complication can be effectively managed prophylactically by nonselective beta blockers. Hence it emphasises the need for a good screening procedure to prevent the complications.

Many studies were conducted based on platelet count- spleen diameter ratio as a non invasive predictor of oesophageal varices in patients with cirrhosis. This study reduces the social and financial burden to the patient and this also improves the compliance of patients.

In this study 75 patients of chronic liver disease were chosen based on clinical, biochemical and ultrasonographic features, irrespective of etiology of the disease. Then the patients were subjected to biochemical investigations like Hb%, serum bilirubin, serum proteins, serum albumin, SGOT, SGPT, prothrombin time, ultrasonogram for diagnosis of cirrhosis.

In the first part of the study , platelet count and measurement of spleen by measuring the long axis of the spleen sonographically was done

in all the patients. In the second part of the study, patients were subjected to upper GI endoscopy to look for the presence of varices.

Patients with a prior history of variceal bleeding or prior documented varices were excluded from the study. Patients on beta blocker prophylaxis were also excluded from the study.

The use of this combined parameter is of interest and this hypothesis is evidenced by clinical and other biochemical parameters. Thrombocytopenia in cirrhosis is multifactorial it may be due to decreased platelet survival, impaired production of thrombopoietin or destruction, increased splenic sequestration due to hypersplenism. This led to the concept of taking spleen diameter hence thrombocytopenia can be attributed to hypersplenism.

The use of this ratio normalises the platelet count to splenic sequestration since platelet count alone can be misleading and cannot be solely attributed to portal hypertension.

AGE OF STUDY POPULATION

Incidence of cirrhosis was maximum in the age group > 50 years. Mean age was 45.94 with a standard deviation of 8.4.The youngest patient in our study was 31 years and oldest was 58 year.

GENDER DISTRIBUTION

Out of the 75 patients of whom 68 were males and 8 were females. Males constituted 89% of the study population. Males predominated our study.

In our study the majority of the patients presented with complaints of jaundice, abdominal distension. Other symptoms were swelling of legs, easy fatiguiability.

ALCOHOLISM

Among 75 patients studied 88% of the patients were found to be alcoholics. History of blood transfusion was seen in 12% of patients.

PLATELET COUNT

Majority of the patients had a platelet count between 85,000 to 1,25,000/cubic mm .The mean platelet count in our study was 121360+_17315. The P value is of <0.027 though it is significant as

single value, the significance is less when compared to combined parameter.

SPLENIC DIAMETER

Spleen diameter in our patients ranged from 140 – 180 mm. The mean spleen diameter is 157+_12.89. The P value is < 0.012 it is less significant than PC/SD ratio.

PC/SD Ratio and oesophageal varices.

Among the 75 patients, a total of 50 patients had esophageal varices on upper gastrointestinal endoscopy. Out of these, 48 patients had a platelet count/splenic diameter <909. The remaining 2 patients had a ratio of >909.

A total of 54 patients in the study had a ratio of <909 in the study. Varices were absent in 4 of them. The mean platelet count spleen diameter ratio of patients with out varices was 961.98 and the mean platelet count spleen diameter ratio of patients with varices was 689.62. Hence, using a ratio of 909 as cutoff, 96% of patients with varices were detected (sensitivity-96% and specificity-90.48%). The P value <o.oo7 which is more significant than using a single parameter. The positive predictive value is 88.% and the negative predictive value is 90.4%.

This is in accordance with the study conducted by Gianni, Botta, Borro in which they evaluated prognostic and diagnostic accuracy of the platelet/spleen diameter ratio for the presence of varices. They included 106 cirrhotic patients with out varices at initial screening endoscopy and endoscopy was carried in these patients. These patients were followed by excluding who lost their follow up or died before undergoing control endoscopy. During follow up 27 patients(40%) developed varices. Patients with higher PC/SD RATIO ($p<0.0001$) as well as ratio > 909 were less likely to develop varices ($p< 0.0005$). At follow up, PC/SD ratio < or = 909 had 100% negative predictive value and 84% efficiency in identifying the presence of varices.

Another study by Ying L1 et al was done to assess the performance of PC/SD ratio for diagnosis oesophageal varices.This was a meta analyais. The Fagan plot was used for calculating PC/SD for oesophageal varices. If PC/SD ratio was below 909 for varices, post test probability was 87%, while if PC/SD RATIO was at or over 909, the post test probability was only 9%. This study decreases the need for invasive procedure in chronic liver disease patients.

This is in accordance with the study done in DHQ Hospital by Khalld amln et al 95 patients are included secondary to Hepatitis C virus. 47 patients (49.5%) were male and 48 (50.5%) were females. The mean

age of the patients was 57 years. The maximum patients were 38% and were in the range of 51-60 years. The mean platelet count to spleen diameter ratio of all the patients was 834.48. The mean platelet count to spleen diameter ratio of patients without varices was 1162.41and those with varices was 704.28. Considering > 909 as normal as a predictor of oesophageal varices the specificity(true negative case) is 81.48%. Positive predictive value is 92.42% and negative predictive value was found to be 75.86%.

Limitations of the study

- Sample size is small.
- The study would be more precise if the etiological work up is done for all patients.
- Grading of varices cannot be done with the cut off value 909 for all patients.

SUMMARY

In our study, fifty patients with newly diagnosed cirrhosis without prior history of gastrointestinal bleeding were subjected to clinical evaluation. All patients underwent biochemical tests, like liver function tests, complete blood counts, renal function tests, prothrombin time, ultrasonography of the abdomen to confirm the presence of cirrhosis and to record the spleen bipolar diameter and ascites.

Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them. We tried to identify non-invasive parameters for predicting esophageal varices in Cirrhotic patients. We assessed the role of Platelet count/Splenic diameter ratio for predicting esophageal varices in cirrhotic patients. Presence of varices increases as patients progress to decompensated liver disease. (Child Pugh grade B & C). Decrease in the platelet count **is** associated with higher grades of esophageal varices in patients with cirrhosis of liver. Ultrasound measurement of Spleen bipolar diameter also predict the presence of higher gradesof esophageal varices . When a cut off value of Platelet count/ splenic diameter ratio of $\leq 909$was applied in order to take in to consideration the decrease in platelet

count due to hypersplenism; it was found to be a good predictor of presence and grade of esophageal varices . The sensitivity of PC/SD Ratio of ≤909 in predicting presence of esophageal varices was 96% with its positive predictive value was . The study found that there is significant sensitivity and positive predictive value enough to show the presence of varices in the study group. The use of Platelet count and Platelet count/ Splenic diameter ratio in appropriate subgroups of cirrhotic patients for screening and follow up of esophageal varices can substantially reduce the cost of healthcare and discomfort for patients as well as reduce burden on Endoscopy units.

CONCLUSION

Higher grades of esophageal varices exists with lower platelet and larger spleen size. Lower the platelet count spleen size ratio, higher the incidence of varices and higher the grades.

- Inverse correlation exists with platelet count and ratio of platelet count with spleen diameter in relation to presence and grading of esophageal varices
- Platelet count and platelet count with spleen size ratio can be used as non invasive markers of presence of esophageal varices
- From our study we conclude that presence of a lower PC/SD ratio determine the presence of varices and can hence identify the subset of patients who require endoscopy for the prophylactic management of esophageal varices.
- This can help in decreasing the burden on the endoscopy units and can help avoid unnecessary screening endoscopies
- Apart from being noninvasive, platelet count, spleen bipolar diameter and the PC/SD ratio is a relatively inexpensive test. as platelet counts and abdominal ultrasounds would be obtained on all cirrhotic patients routinely as part of their clinical workup.

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PROFORMA

Case no :

Name: Age and Sex : IP no. :

Occupation : Address :

Date of Admission : Date of Discharge :

Chief Complaints :

Yellowish discoloration of urine and eyes

Abdominal Distension

Swelling of legs/scrotum/labium

Decreased urine output

Hemetemesis

Malena

Breathlessness

Loss of appetite / Vomiting

Altered behaviour/involuntary movements

Rashes/ other skin lesions

Constipation

Past History :

History of Diabetes / Hypertension / CAD / Thyroid disorder /

CAD / Chronic lung disease

History of Drug intake / Blood transfusion

Personal History : Smoker / Alcoholic – Amount per day & how long

Clinical Examination

General examination:

Vitals : PR- BP- RR- Urine Output:

Consciousness / Oreintation / Pallor / Icterus / Cyanosis / Clubbing / Pedal edema / Axillary & pubic hair / Parotid enlargement / Testicular atrophy / Flapping Tremor / KF Ring / Constructional Apraxia

Abdomen :

Other systems :

CVS- RS- CNS-

CLINICAL DIAGNOSIS :

Investigations:

Hb TC DC Urine : Albumin Sugar Deposits

Blood Sugar: Fasting Postprandial

Blood Urea : Serum Creatinine:

Total Bilirubin: Direct Indirect

Total Protein Albumin Globulin

SGOT(AST) SGPT(ALT)

Prothromin time Platelet count

Peripheral blood smear.

Ultrasonagram abdomen for splenic diameter:

Course of patient in hospital :

Treatment given :

Outcome :

S.NO	AGE	SEX	SIGN OF LIVER CELL FAILURE	ALCOHOLIC	BLOOD TRANSFUSION	HB	SR.BILLRUBIN	SR.PROTEIN	ALBUMIN	PT	PLATLET COUNT	SPLEE DIAMTRE(mm)	RATIO	O G V
1	45	M	+	+	-	10	1.7	6.5	2.5	19	110000	140	785.71	+
2	39	M	+	+	-	12	2.1	7	2.1	23	105000	156	673.07	+
3	38	M	+	+	-	13.1	1.4	6.2	2.3	19	93000	153	607.84	+
4	40	M	+	-	+	12.3	2.5	6.1	2.5	23	114000	167	682.63	+
5	49	M	+	+	-	11.5	1.8	6.7	2.8	19	126000	158	797.46	-
6	38	M	+	+	-	9.2	3.2	6.5	2.1	21	110000	165	666.66	+
7	45	M	+	+	-	10.1	1.8	6.1	2.8	21	140000	141	992.9	+
8	29	M	+	-	+	13.1	2.5	6.4	2.9	19	104000	155	670.96	+
9	52	M	+	+	-	11.5	1.8	6.1	2.5	21	98000	160	612.5	+
10	32	M	+	+	-	12	2.3	6.4	3.1	17	151000	136	1118.85	-
11	38	M	+	+	-	12.1	2.5	7	3.5	19	107000	170	629.41	+
12	38	M	+	+	-	12.5	2.1	6.1	2.8	16	122000	164	743.9	+
13	52	M	+	+	-	11.5	2.8	6.2	2.4	23	133000	145	917.24	+
14	51	M	+	+	-	13.1	3.5	7	2.5	19	99000	145	682.75	+
15	44	M	+	+	-	12	3.6	6.5	1.8	19	116000	165	703.03	+
16	46	M	+	+	-	12.5	2.5	6.1	2.5	18	104000	172	604.65	+
17	53	M	+	+	-	12.1	2.5	6.1	2.4	19	137000	136	1007.32	-
18	49	M	+	+	-	11.5	2.1	5.8	2.9	25	145000	138	1050.72	-
19	38	M	+	+	-	11.5	2.3	5.9	3.1	19	114000	162	712.5	+
20	33	M	+	+	-	12	1.3	5.5	2.5	23	122000	171	713.45	+
21	39	M	+	+	-	13	2.2	6.5	2.2	19	101000	154	655.84	+
22	31	M	+	+	-	11.5	2.2	6.5	2.2	19	101000	154	655.84	+
23	37	M	+	+	-	12.5	2.5	5.8	3.5	24	94000	181	519.33	+
24	42	M	+	+	-	11.5	1.6	5.5	3.1	27	92000	173	531.79	+
25	51	M	+	+	-	10.5	2.6	6.3	2.1	21	153000	145	1055.17	-
26	53	M	+	+	-	10	2.1	6.1	2.8	18	113000	161	701.86	+
27	56	F	+	-	+	10.6	1.9	6.1	3.1	17	142000	137	1036.44	-
28	36	M	+	+	-	10.5	1.83	6.8	3.3	21	107000	155	648.48	+
29	33	M	+	+	-	11.5	2.6	5.8	2.5	19	121000	165	780.64	+
30	57	F	+	+	-	9.8	2.3	6.3	2.1	16	137000	128	1070.38	-

31	56	F	+	+	-	10.5	1.9	6.4	2.1	19	131000	134	977.61	-
32	37	M	+	+	-	11	1.8	6.5	2.1	27	113000	152	734.4	+
33	57	M	+	-	+	10.5	2.1	6.1	2.5	21	104000	173	601.15	+
34	43	M	+	-	+	11	2.8	5.8	2.3	23	93000	164	567.07	+
35	45	M	+	+	-	10.3	3.1	5.9	3.1	25	128000	143	895.1	-
36	51	M	+	+	-	11.2	2.1	6.6	2.7	23	167000	153	1024.53	-
37	49	F	+	-	-	10.5	1.9	6.3	2.1	21	147000	138	1065.21	-
38	45	M	+	+	-	10.3	3.1	5.9	3.1	25	121000	165	612.12	+
39	31	M	+	+	-	11	1.8	6.1	2.5	26	118000	173	641.61	+
40	57	M	+	+	-	10.5	2.4	6.1	2.5	24	121000	172	703.48	+
41	38	M	+	+	-	10.1	1.6	6.3	3.1	21	118000	165	715.15	+
42	56	F	+	+	-	9.8	1.7	6.4	2.6	19	137000	155	1014.81	-
43	59	F	+	-	-	10.1	2.9	6.5	2.5	23	129000	135	955.55	-
44	36	M	+	+	+	11.1	1.3	6.1	2.5	19	125000	171	730.99	+
45	42	M	+	+	-	12.3	1.5	5.9	2.4	17	111000	165	672.72	+
46	57	M	+	+	-	11.4	2.1	7	2.3	21	103000	161	639.75	+
47	39	M	+	+	-	10.5	2.9	6.5	2.1	23	110000	173	635.83	+
48	42	M	+	+	-	12.1	2.5	6.6	2.1	26	122000	173	705.2	+
49	59	M	+	+	-	9.5	2.6	6.3	2.7	20	131000	125	1048	-
50	56	M	+	+	-	10.6	2.8	5.9	3.1	19	121000	155	780.64	-
51	47	F	+	+	+	12.2	2.1	6.4	2.7	22	123000	163	754	+
52	57	M	+	+	-	11.5	1.9	6.6	2.5	25	108000	155	696.77	+
53	43	M	+	+	-	11.1	1.8	6.5	2.1	24	125000	173	722.54	+
54	38	M	+	+	-	11.5	2.6	6.6	2.6	19	157000	147	1027.21	-
55	39	M	+	+	-	11.5	2.9	6.3	2.3	21	160000	172	930.23	-
56	52	M	+	+	-	9.2	2.5	6.2	2.5	21	110000	163	674.84	+
57	53	M	+	+	-	10.1	1.8	6.1	2.1	23	127000	151	841.05	-
58	51	M	+	+	-	10.5	1.7	6.5	3.9	19	99000	162	611.11	+
59	39	M	+	+	-	11.5	2.9	6.4	2.3	21	155000	165	939.39	-
60	52	M	+	+	-	10.5	2.1	6.8	2.1	19	124000	152	815.78	-
61	41	M	+	+	-	12	3.1	6.7	2.4	15	108000	177	610.16	+
62	57	F	+	-	-	10.5	2.8	6.6	2.2	23	110000	163	674.84	+
63	39	M	+	+	-	10.9	2.4	5.9	2.6	21	118000	179	659.21	+
64	41	M	+	+	-	10.7	2.7	6.1	2.5	19	149000	153	973.85	-
65	46	M	+	+	-	11.3	1.7	6.3	2.3	19	137000	149	919.68	-

66	41	M	+	+	-	9.5	1.9	6.3	2.1	27	121000	149	812.08	-
67	57	M	+	+	-	10.1	2.1	6.1	3.1	29	112000	173	647.39	+
68	42	M	+	+	-	11.1	1.6	6.5	3.1	20	120000	165	727.27	+
69	55	M	+	+	-	9.1	2.1	6.2	3.1	25	124000	152	815.78	+
70	57	M	+	+	-	10.5	1.9	6.5	3.5	19	143000	151	947.01	-
71	57	M	+	+	-	11.1	2.1	6.4	3.1	19	139000	147	945.57	-
72	55	M	+	+	-	9.1	2.1	6.2	3.1	25	126000	152	828.94	+
73	52	M	+	+	-	10.5	1.6	6.1	2.8	25	111000	151	735.09	+
74	57	M	+	+	-	10.1	2.1	6.7	2.4	29	125000	151	827.81	+
75	39	M	+	+	-	11.1	1.9	6.9	2.6	21	110000	171	643.27	+

Ref.No.6506/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 11.09.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . **Convenor**

Sub: Establishment – Madurai Medical College, Madurai-20 – Ethics Committee Meeting – Meeting Minutes - for August 2014 – Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 05th August 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the Ethical Committee

Name of P.G.	Course	Name of the Project	Remarks
Dr.R.Vishnupriya drvaprabhu1997@gmail.com	**PG in MD (General Medicine), Govt. Rajaji Hospital and Madurai Medical College, Madurai**	**"Platelet count-splentic diameter ration as a non-invasive predictor of esophageal varices in patients with cirrhosis"**	**Approved**

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical Committee

11.9.14

DEAN/Convenor
Madurai Medical College &
Govt.Rajaji Hospital, Madurai- 20.

11/9/14

To
The above Applicant
-thro. Head of the Department concerned

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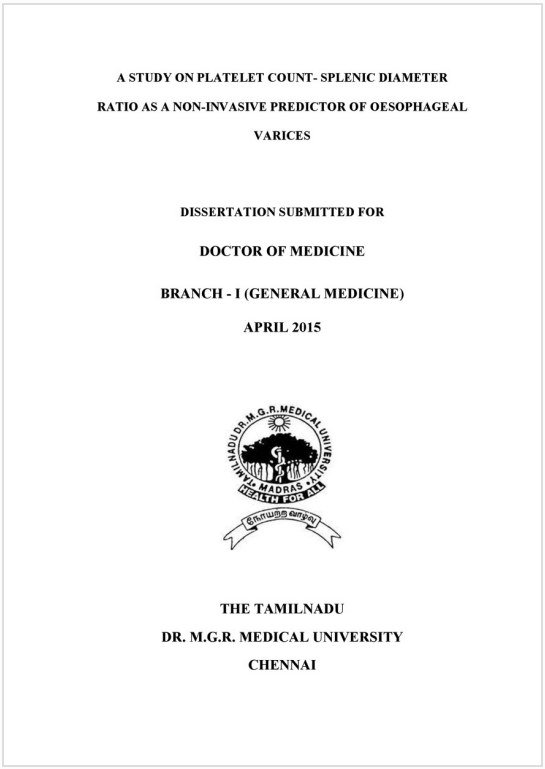

A STUDY ON PLATELET COUNT- SPLENIC DIAMETER RATIO AS A NON-INVASIVE PREDICTOR OF OESOPHAGEAL VARICES

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

APRIL 2015

THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

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