A STUDY ON "CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN CIRRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE."

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**A STUDY ON "CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN CIRRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE."** is the bonafide work of **Dr.P.PRAVIN PRABHU** 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 **May 2018.**

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DECLARATION

I Dr.P.PRAVIN PRABHU declare that, I carried out this work on "**A STUDY ON "CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN CIRRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE."** at the Department of Medicine, Govt. Rajaji Hospital during the period **FEBRUARY 2017 TO JULY 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 or 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 **M.D Degree General Medicine Branch- I**; examination to be held in **May 2018.**

Place : Madurai **Dr.P.PRAVIN PRABHU**

Date :

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CONTENTS

INTRODUCTION

The main goal of this study was to evaluate the diagnostic and prognostic significance of serum prolactin concentration in cirrhosis in determining the severity of hepatic disease and its correlation with CHILD PUGH score.

Prolactin secretion follows a pulsatile pattern with characterisitic nocturnal rise. In patient with cirrhosis , associated with elevated 24 hours prolactin level and loss of circadian rhythm. Increased level of serum prolactin associated with increased risk of hepatic encephalopathy and progression of severity of hepatic disease.

Patients with end-stage liver disease have several endocrine dysfunctions, which include alterations in the functioning of the hypothalamic-pituitary-gonadal axis and the serum levels of sex hormones.

Our prospective study showed that cirrhotic men have significant alterations in the pituitary regulatory functions, and that these disorders are completely reversed after liver transplantation. In cirrhosis, excess production of SHBG in liver and increased prolactin levels were detected while exploring the cause of gynecomastia and high level of liver estrogen receptors was added to the direct suppressing effect of estrogen on Leydig cell functions [5].

Decompensated liver function leads to an alteration in the type of amino acids entering the central nervous system. Circulating concentrations of aromatic amino acids have been found to increase leading to an increase in the

synthesis of false neurotransmitters such as octopamine and phenylethanolamine.[8] These false neurotransmitters may inhibit the dopamine release contributing to hyperprolactinemia. Cases of hypogonadism have also been reported in patients with cirrhosis attributing to hyperprolactinemia.[9] A similar correlation of mortality to serum prolactin levels was observed by McClain *et al*.[10] and Sharma *et al*.[11] with a higher risk of mortality with serum prolactin values of >50 ng/ml. Mukherjee *et al*.[12] analyzed the prolactin levels in patients with hepatic cirrhosis and found a higher levels in both patients with encephalopathy and mortality.Patient with liver cirrhosis complicated by hepatic encephalopathy found to have low serum total T3, serum cortisol and high prolactin level. These are early indicators of impending hepatic encephalopathy and progression of liver disease.Serum prolactin was found to be elevated in 39 to 75 percent cirrhotic patients.

CHILD PUGH SCORING SYSTEM:

- Cirrhosis can be staged clinically. A reliable scoring system is the modified CHILD PUGH scoring system. It ranges from 5 to 15.
- Child Pugh CLASS A : Score of 5 and 6 , consistent with compensated cirrhosis.
- Child Pugh CLASS B : Score of 7 to 9 , consistent with decompensated cirrhosis.
- Child Pugh CLASS C :Score more than 10 , consistent with decompensated cirrhosis.

This scoring system includes 5 factors : serum bilirubin, serum albumin, ascites, hepatic encephalopathy and prothrombin time. It is reasonably a reliable predictor of survival and predicts the likelihood of major complications like bleeding from the varices and spontaneous bacterial peritonitis.It was also used to assess the prognosis in cirrhosis and to provide a standard criteria in listing the patient for liver transplantation.

Thus comparing the serum prolactin level with the Child pugh scoring system in assessing the severity of the liver disease and predicting the risk of complications.

AIM OF THE STUDY

PRIMARY AIM

1. To study the prevalence of hyper prolactinemia in cirrhosis.
2. To assess the relation between serum prolactin levels and disease severity, predicting complications in patients with cirrhosis.
3. To compare the efficacy of serum prolactin to that of child pugh scoring system in cirrhosis

REVIEW OF LITREATURE

CIRRHOSIS

"Cirrhosis is an irreversible liver disease with definable pathological changes are chronic damage of the hepatocytes which is not reversible, .fibrosis of the liver distorting the architecture and reactive nodular regeneration

Cirrhosis is defined "anatomically as a diffuse process with fibrosis and nodule formation". The hallmark pathological feature is extreme damage to the hepatocytes followed by replacement of liver tissue by fibrosis with nodule formation. This is mainly due to necrosis of hepatocytes, loss of reticular network &regeneration of remaining liver tissue by nodules.

Micro-nodular cirrhosis becomes macro-nodular cirrhosis with absence of hepatic inflammation and necrosis. Portal fibrosis is seen in alcoholic liver disease."

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 machrophage (kupffer cells),lymphocytes and megakaryocytes. The cascade of events following stellate cell activation mainly by selfstimulation leading to synthesis of platelet derived growth factor, transforming growth factor beta1.these stellate cells produce collagen matrix and substance that inhibit the breakdown of collagen. The substance that inhibit collagen breakdown are mettalloproteinases 2 and 9 are inturn stimulated by

TIMP 1 and 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, 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.”

ALCOHOL AND LIVER:

A strong correlation between Alcohol and cirrhosis was found out by Mathew Baillie in 1793. It is one of the rising cause of death worldwide.

Metabolism of Alcohol:

Alcohol is absorbed in the duodenum and upper part of jejunum by simple diffusion,which is delayed following a meal and increased according to the concentration of the alcohol drank. The peak level of alcohol in blood reached after 20 minutes from the time of consumption. The absorption depends on the blood flow, and it is poorly soluble in lipids ; leading to prolonged effect in females.

Alcohol cannot be stored in the body for a long time, it has to undergo oxidation to acetaldehyde by acetaldehyde dehydrogenase; the acetaldehyde forms complex with proteins to form protein adducts which is responsible for most of the symptoms related to alcohol liver injury.

Alcohol induces its own metabolism. The alternate pathway for alcohol metabolism is Microsomal ethanol oxidizing system involving cytochrome P4502E1. Alcohol induces CYP2E1 leading to hepatotoxicity of other drugs.eg Paracetamol.

"Acetaldehyde is a potent hepatotoxic which is responsible for flushing in alcoholics. It affects liver by several mechanisms.

1. Induction of steatosis more common in the zone 3, by alteration of redox potential.
2. It increases the sensitization of TNF alpha which leads to hepatic necrosis.
3. It is extremely reactive and toxic; it binds to phospholipids ,amino acid residues and reactive groups in the enzyme.

4. It helps in the emergence of new antigens to the surface.
5. It depolymerizes the protein structure and affects the normal folding of the proteins.
6. This unfolded proteins leads to “Endoplasmic reticulum stress” which leads to lipid synthesis , depletion of antioxidant and finally leading to irreversible liver damage.

PATHOGENESIS OF STEATOSIS:

In patients consuming alcohol , the early and reversible effect is accumulation of triacylglycerol in the liver, which is seen as fat droplets in the microscope has to be stained by special stains like sudan black. The accumulation of triacylglycerol is mainly due to failure of transfer of cholesterol from the liver to the periphery which is mediated by an enzyme microsomal triglyceride transfer protein , which is kept in inhibitory control by alcohol.

There will be increased damage to cell organelles particularly mitochondria leading to loss of protective effect by antioxidants leading to oxidative stress and damage to cell membranes.

Effect of cytokines:

Cytokines is responsible for most of the clinical and histological manifestations of alcohol induced liver injury.

Tumour necrosis factor alpha induces steatosis and leads to generation of reactive oxygen species and free radicals and hepatocyte apoptosis.

Interleukin 8 : responsible for activation and recruitment of neutrophils.

Clinical features related to cytokines:

- Fever
- Anorexia
- Muscle wasting
- Catabolic state
- Neutrophilia
- Decreased albumin
- Decreased bile flow
- Increased collagen
- Shock
- Mechanism of Alcohol leading to cancer:
- Lipid peroxidation
- DNA mutagenesis
- Reduced DNA methylation

Immunological liver damage

"Protein adducts formed from ethanol metabolites andhost proteins can act as neoantigens to incite humoralB - cell and cytotoxic T - cell lymphocyte responses inALD. Antibodies can be shown against acetaldehydeprotein adduct - derived epitopes andhydroxyethyl radical – CYP2E1 adducts .

Antibodies can also be seen to native CYP2E1, suggesting that autoimmune mechanisms may play a role in alcohol - related liver disease. “

“The true importance of immunological mechanisms is not clear as they may represent an epiphenomenon whereby immune responses are generatedto proteins released from hepatocytes damaged throughother mechanisms.”

Extra hepatic cancers caused by Alcohol:

- Mouth
- Pharynx and larynx
- Oesphagus
- Colon
- Breast

People prone to develop Alcohol depends on the following factors:

1. Dose of alcohol : to develop cirrhosis the dose should be 160 g /day for 8 years , the risk is more in females even at lower dose because of poor metabolism of alcohol .Liver injury is unrelated to the type of beverage used. It depends more on the pattern of drinking than the type of alcohol.
2. Daily drinking is more dangerous than intermittent drinking.
3. Diets rich in pork , unsaturated fats and poor carbohydrate diet leads to increased risk
4. Obesity

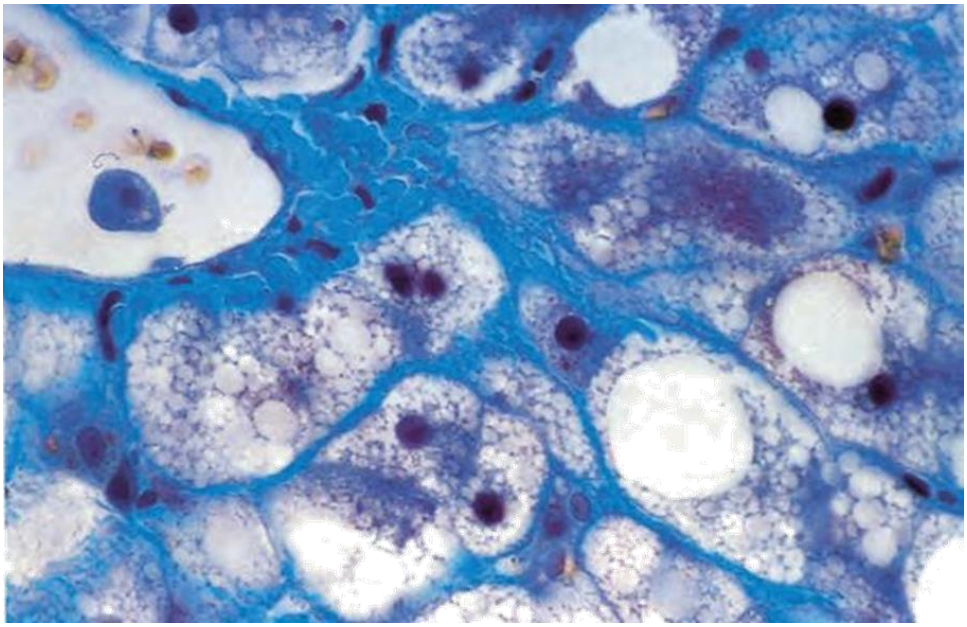
5. Hyperglycemia
6. Genetic factors

Females and Alcohol:

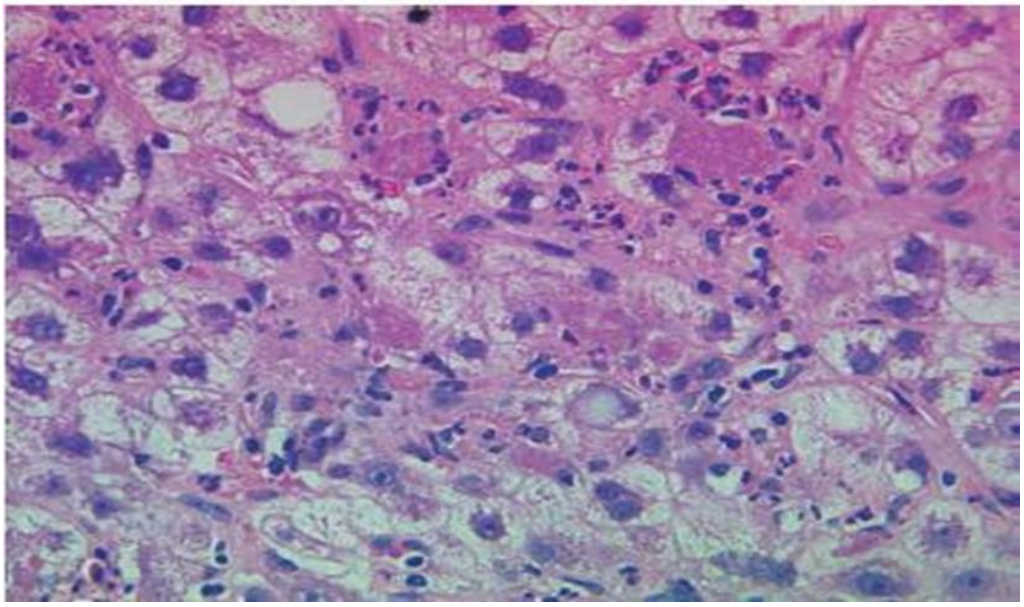
1. Alcohol is poorly soluble in lipids.
2. Prolonged action due to poor metabolism
3. Presentation will be at the final stage
4. More susceptible to liver injury
5. Relapses are more frequent
6. More rapid progression
7. Oestrogen has specific action on gut permeability leading to endotoxemia.

Non - gender - linked genetic factors

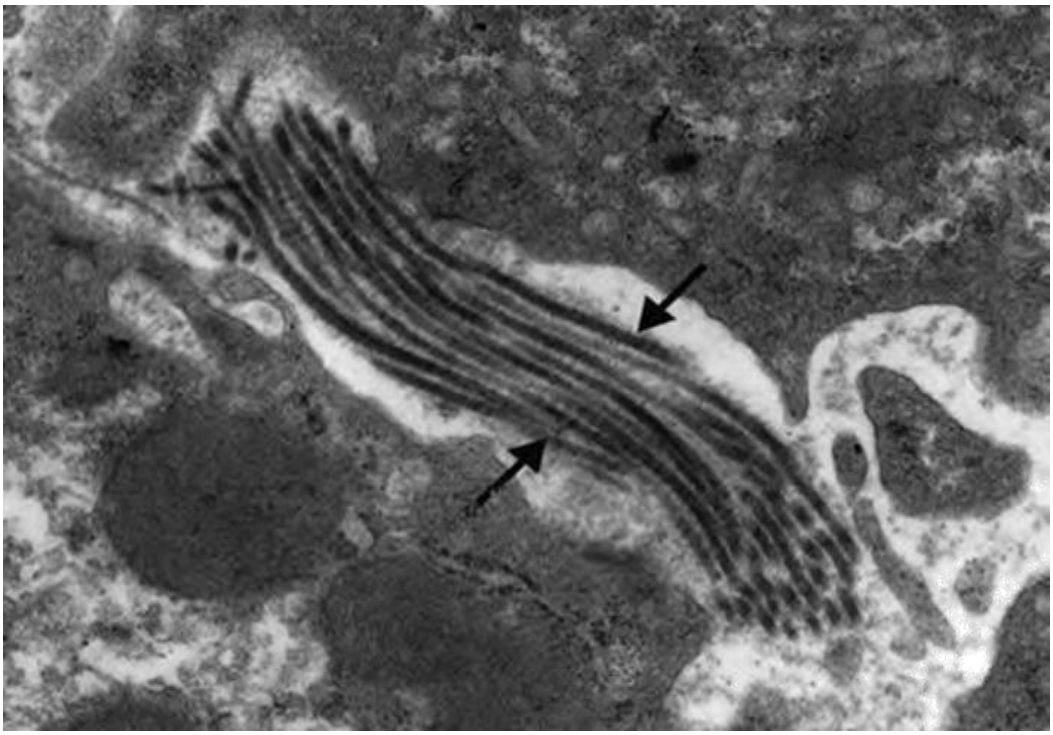
"Patterns of alcohol drinking are, at least partially, inherited; however, no specific genetic variants have been reproducibly associated with susceptibility in largestudies. Susceptibility to liver disease may also have an inherited component. Concordance rates for alcohol -related cirrhosis are three times higher in monozygotic than in dizygotic twin pairs . Alcohol – related liver damage is a polygenic disorder so multiple polymorphisms are likely to contribute. They are likelyto be in genes controlling fat accumulation ,oxidative stress. – "mediated release of proinflammatorycytokines and immunological damage . "IMAGE: Acute alcoholic hepatitis with ballooning degeneration, Mallory Denkbodies and satellitosis (neutrophil polymorph infiltrate around hepatocytes)



“IMAGE: Acute alcoholic hepatitis with ballooning degeneration, Mallory Denkbodies and satellitosis (neutrophil polymorph infiltrate around hepatocytes)



“Acute alcoholic hepatitis. Hepatocytesare ballooned and contain micro – and macrovesicular fat and clumps of purplish – redMallory ’ s alcoholic hyaline. (Chromophobeanilineblue, ×100.)”



Electron micrograph of liver in a patient with alcoholic liver disease. Note the deposition of collagen fibrils in Disse' s space (arrowed). This could interfere with oxygen and metabolite exchange between blood and hepatocytes."

HISTOLOGICAL FEATURES

- FATTY LIVER
- ALCOHOLIC HEPATITIS
- CIRRHOSIS

FATTY LIVER:

Initially microvesicular and later macroveicular fatty change occurs predominantly in zone 2 and zone3 .Mitochondrial dysfunction leads to fatty acid oxidation inhibition leads to microvesicular fat .

ALCOHOLIC HEPATITIS:

Balooning degeneration, is due to retention of water and failure of the microtubular excretion of protein from the hepatocyte cells.

Due to apoptosis , acidophilic bodies are seen.

Mallory denk bodies surrounded by a satellite of polymorphs seen as purplish red intra cytoplasmic inclusions which consists of intermediate filaments.

Giant mitochondria can be seen using Masson trichrome stain. Fibrosis is maximum around the sinusoids, this pericellular fibrosis called as “creeping collagenosis” . collagen deposition is maximal in the space of Disse leading to defect in the transport of substances .cholestasis in the bile canaliculi is associated with decreased survival.

CLINICAL FEATURES

“Patients may present for the first time with the complications of cirrhosis or may be asymptomatic and incidentally be identified during checkup for unrelated causes or because of abnormal liver tests”

In clinical terms., cirrhosis is classified in to

- Compensated form and
- Decompensated form,

“Decompensation is characterized by cirrhosis complicated by one or more following features like - jaundice, ascites, hepatic encephalopathy, bleeding varices. Ascites is usually the first sign of decompensation, whereas these features and any complication secondary to Portal hypertension is absent in compensated cirrhosis. This distinction clinically is very important because of the implication it has in the prognostication and treatment.”

“A decompensated patient may become compensated when the inciting cause or the precipitating cause is removed and thereby the prognosis may improve.

Patients who have developed complications of their liver disease and have become decompensated should be considered for liver transplantation.”

COMPENSATED CIRRHOSIS:

At this stage the cirrhotic process of the liver is not severe enough to alter the function significantly and so the patients may be asymptomatic or present with non-localizing manifestations or picked incidentally due to alteration in biochemical parameters or imaging studies Patients may have fatigue, anorexia, weight loss, flatulence, dyspepsia, abdominal pain.

On examination palmar erythema, pedal edema, spider naevi, may point towards cirrhosis.

Abdominal examination : epigastric mass which is the enlarged left lobe of the liver and splenomegaly.. The most common LFT abnormality in this group include mildly elevated transaminases, or GGT.

Confirmation is by liver imaging or liver biopsy.

Factors like bacterial infection, trauma, or medications, surgery may precipitate decompensation in a compensated cirrhosis."

DECOMPENSATED CIRRHOSIS:

These patients present with ascites, jaundice, altered sensorium,bIeeding manifestations."

LIVER PARAMETERS

"Liver function tests (LFTs) or liver biochemical tests can be used to screen for liver disease, direct diagnostic work - up, and assess severity, prognosis and response to treatment. Although the term LFT is firmly entrenched in the medical literature, this term is frankly erroneous as these

investigations provide indirect" evidence "of hepatobiliary disease. LFTs that more" accurately "reflect liver function are serum albumin, serum bilirubin and prothrombin time, which is standardizedto""the international normalized ratio (INR). As the" prevalence "of liver disease is only between 2 and 4% in the general population (higher for fatty liver disease" andviral "hepatitis), the more investigations are multiplied, the greater chance there is of a biochemical abnormality being demonstrated. A few simple tests of established value should be used and if an abnormality is found itshould be repeated to confirm it is real."

"LFT abnormalities may be classified into the" following "categories:"

"Hepatocellular (elevations predominantly in aspartate aminotransferase (AST) and alanine" aminotransferase "(ALT)); cholestatic (increases" predominantly "in alkaline phosphatase (ALP), γ – glutamyltranspeptidase(γ - GT) and bilirubin); and infiltrative(increases in ALP, γ - GT and occasionally bilirubin).The tests most useful in the diagnostic work - up of" jaundice "are the ALP, aminotransferase and bilirubin tests. An isolated rise in serum unconjugated bilirubin suggests Gilbert's syndrome, haemolysis", ineffective "erythropoiesis or use of medications such" asbunamiodyl ("cholecystographic agent) flavaspidic acid, probenicid and rifampicin."

"The severity of liver cell damage is assessed by serial measurement of total bilirubin, albumin and" prothrombin "time after vitamin K. This is reflected by theirincorporation into the Childs – Pugh (CP) score and Model for Endstage Liver Disease (MELD), which are used to estimate severity and

prognosis of liver disease and assess candidacy for liver transplantation", respectively. "Rising arterial ammonia levels also reflect severe hepatic dysfunction in" patients with acute liver failure (ALF) whereas hyperammonaemia in decompensated "cirrhosis does not always correlate with hepatic encephalopathy or progression of liver disease."

"The diagnosis of minimal hepatocellular damage may be suspected by noting minimally elevated" aminotransferases "and sometimes serum bilirubin. Patients who are heavy drinkers of alcohol with or without liver disease (ALD) may have just a raised γ - GT with or without biochemical evidence of liver damage. However, this degree of biochemical abnormality also occurs in well - compensated cirrhosis, heart failure and fever, reflecting the lack of sensitivity and specificity of these investigations for diagnosing and assessing" severity "of liver disease."

Bile pigments

"Bilirubin: "Total bilirubin is increased in cholestatic and" hepatocellular "liver disease more commonly than infiltrative disease. It is often associated with a rise in liver enzymes.Bilirubin is predominantly conjugated and water soluble. Patients with marked hyperbilirubinaemia (bilirubin > 425 μ mol/L) often have severe liver disease coexisiting with renal dysfunction or another cause of unconjugated hyperbilirubinaemia, such as haemolysis. An isolated rise in bilirubin without enzyme"elevation "should first"be fractionated to determine if the" aetiology "is familial or due to haemolysis."

"Serum bilirubin estimations are based on the van den Bergh diazo reaction, which involves the" spectrophotometric "detection of azo derivatives derived by the" reaction "of plasma with the diazonium ion of sulphanilicacid . This reaction separates bilirubin into a water - soluble direct form representing conjugated bilirubin and an indirect, lipid - soluble form representing" unconjugated "bilirubin. These diazo reactions are subject to error, particularly at low total serum bilirubin" concentrations."More accurate methods for estimation include alkaline methanolysis with chloroform extraction, high performance gas liquid chromatography (HPGLC), thin layer chromatography (TLC) and spectrophotometric determination, but are too elaborate to be clinically useful"

"Faecal inspections are an important investigation in jaundice. Clay - coloured stools indicate cholestatic" jaundice "but may also occur in hepatocellular jaundice. The colour will be normal in haemolytic jaundice. Rarely, pale stools occur in very severe bilirubin glucuronyltransferase deficiency. Bilirubin cannot be detected in the *urine* of normal subjects as bilirubin is predominantly unconjugated, insoluble in water and bound to albumin. In contrast, bilirubin glucuronides, the products of bilirubin" conjugation," are water soluble. They appear in the urine even when serum total bilirubin is normal as the renal" threshold "for glomerular filtration of conjugated bilirubin is low. Conjugated bilirubin, however, will bind covalently to albumin when jaundice is prolonged and severe, giving rise to a complex called δ bilirubin (or" bilioprotein) ".δ bilirubin has a long half - life,

cannot be renallycleared and accounts for the absence of bilirubinuria and slow resolution of jaundice in patients recovering from severe hepatobiliary disease".

"Urobilinogen

Bacterial β - glucuronidases convert bilirubin in the colon to a series of colourless tetrapyrroles collectively called urobilinogen of which 80 – 90% is normally excreted in the faeces either unchanged or as oxidized orange" derivatives "called urobilins. The remaining 10 – 20% is absorbed and undergoes an enteric circulation with re-excretion into bile by the liver while a small proportion is excreted in the urine. This complex process depends on several factors such as urine flow rate and pH.Spot urinary urobilinogen is a poor predictor of hepatic disease with a high proportion of false – negative results"

Serum enzyme tests

These tests usually indicate the type of liver injury, whether hepatocellular, cholestatic or infiltrative but cannot differentiate one form of hepatitis from another or determine whether cholestasis is intra - or extrahepatic.They are valuable in directing specific serological tests, imaging or liver biopsy to reach the diagnosis. Only a few tests are necessary and the combination of "normal ALT values should be adjusted for body mass index and sex . During pregnancy, ALT, AST and γ - GT levels, as well as bile acid and bilirubin concentrations remain within the normal range, whereas an elevated alkaline phosphatase is of placental origin during the third trimester."

“Aminotransferases

The aminotransferases (previously called aminotransaminases) catalyse transfer of amino groups from either aspartate or alanine to the keto group of α –ketoglutaricacid forming oxaloacetic acid (OAA) and pyruvic acid, respectively. These enzymes are important in gluconeogenesis as they catalyse glucose synthesis fromnon - carbohydrate sources. Enzymatic reduction of oxaloacetic acid and pyruvic acid to malate and lactate, respectively, is coupled with oxidation of the reducedform of nicotinamide dinucleotide (NADH) to nicotinamide dinucleotide (NAD). As only NADH absorbs light at 340 nm, this reaction can be followed spectrophotometrically to accurately assay these enzymes.”

“Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase or SGOT) is an isoenzyme located in the cytoplasm and mitochondria of manytissues. Although normal AST serum activity is” “cytosolic in origin, 80% of AST activity within the liver is mitochondrial and predominates in periportal hepatocytes.”

“In decreasing order of concentration AST is present in large quantities in liver, heart, skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes and erythrocytes.Macro - AST is a rare condition characterized by isolated AST elevation due to binding of AST with an immunoglobulin which is not cleared by the blood or kidneys] . It is a benign condition and is not reflective of liver disease. Markedly low AST levels have been reported in patients on chronic haemodialysis, possibly due to dialysis or pyridoxine deficiency.”

"Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase or SGPT) is a cytosolic enzyme also present in liver. Although the absolute amount is less than AST, a greater proportion is present in liver compared with kidney, heart and skeletal muscles. A serum increase is therefore more specific for liver damage than AST".

"Transferase determinations with viral serologies are useful in the early diagnosis of viral hepatitis, but there is no correlation between transferase level with eitherthe degree of hepatocyte necrosis or prognosis.Measurements should be performed promptly as these enzymes "have short half - lives (AST 12 – 22 h; ALT 37 – 47h) . Patients may develop fatal acute hepatic necrosis despite falling transaminase values".

"Routine screening may show unexpectedly raised aminotransferase levels. These are often due to non - alcoholic fatty liver disease (NAFLD), alcohol abuse, viral hepatitis and haemochromatosis. Less common causes include autoimmune hepatitis, α1-antitrypsin deficiency, Wilson's disease, drug – induced liver disease and non - hepatic disorders such as Addison ' s disease, anorexia nervosa, celiac disease and hyperthyroidism. Important causes of markedly elevated transaminases are viral hepatitis (including herpes simplex hepatitis), paracetamol(acetaminophen) or other drug - induced hepatotoxicity, ischaemic hepatitis and severe autoimmune hepatitis .Calculous biliary obstruction with cholangitis is animportant but frequently under appreciated cause of AST elevation greater than 10 times the upper limit of normal, which may improve with antibiotics over 48 –72 h despite unresolved

obstruction. Very high levels are unusual in ALD and suggest a coexisting disorder such as paracetamol toxicity or acute viral hepatitis. A ratio of AST to ALT greater than two may be useful in diagnosing ALD. This occurs because damage is primarily mitochondrial (thus more AST is released systemically) and ALT synthesis is more sensitive than AST to pyridoxal 5 - phosphate deficiency, leading to lower serum ALT levels .

“Alkaline phosphatase”

“The alkaline phosphatases (ALP) are a group of enzymes that catalyse hydrolysis of phosphate esters at neutral pH. Magnesium and zinc are important co - factors. ALP in the liver is cytosolic, associated with sinusoidal and canalicular membranes and rises in cholestasis and to a lesser extent when liver cells are damaged.”

“ALP is present, in decreasing order of quantity, in placenta, ileal mucosa, kidney, bone and liver but more than 80% of serum ALP is from the liver or bone. ALP half - life is 3 days. Bone, liver and kidney ALP are coded by the same gene and share a common protein structure but differ in their carbohydrate content. Mechanisms of the increase are believed to be related to increased hepatobiliary synthesis from enhanced translation of messenger ribonucleic acid of ALP and serum secretion through canalicular leakage into the sinusoid rather than failure to excrete ALP. Due to *de novo* ALP synthesis in acute biliary obstruction, serum levels are initially normal in contrast to marked transferase elevations. Serum hepatic ALP may be distinguished from bone ALP by isoenzyme fractionation but this is not routinely carried out as a

concomitant rise in γ - GT confirms ahepatobiliarysource.An isolated rise in ALP may also be”“of intestinal origin, as observed in patients with blood groups O and B who secrete intestinal ALP postprandially. As these enzymes may” “remain elevated for up to 12 h, levels mustbe determined under fasting conditions . Up to 52% of patients with mild isolated ALP elevations (less than two fold elevation) will have enzyme normalizationwithin 1 – 3 months although in hospitalized patients, sepsis in the absence of jaundice may account for up to 32% of cases. Raised ALP levels are sometimes observed with primary or secondary hepatic tumours, even without jaundice or involvement of bone. Increased values without jaundice are also found with other space - occupying lesions or infiltrative disease such as amyloid, abscess, lymphoma or granulomas. Non - specific mild elevations are seen in a variety of conditions including Hodgkin ’ s disease, heart failure, hyperthyroidismand up to 15% of patients with renal cell carcinoma in the absence of involvement of the hepatobiliary system or bone (Stauffer ’ s syndrome). Low ALP levelsare associated with hypothyroidism, Wilson’s disease with haemolysis, congenital hypophosphatasia, pernicious anaemia, zinc deficiency, severe hepatic insufficiency and in children recovering from severe enteritis.”

“Gamma” glutamyltranspeptidase or transferase

“Gamma glutamyltranspeptidase (γ - GT) is a membrane-bound enzyme that catalyses transfer of γ glutamyl groups of peptides such as”“glutathione to other amino acids. Levels are increased in cholestasis and hepatocellular disease and occur in the same spectrum of hepatobiliary” “diseases as elevated

ALP. γ - GT is ubiquitous but in decreasing order of abundance is present in proximal renal tubule, liver, pancreas (acinar cells and ductules) and intestine. Serum γ - GT activity arises primarily from the liver and, within the hepatobiliary system, is present in highest concentration in the epithelium lining of fine biliary ducts. The main role of this test is to confirm a raised ALP is of hepatobiliary origin".

"An isolated rise in γ - GT is seen in patients with alcohol abuse, even without liver disease, due to microsomal enzyme induction and impaired clearance (half - life of 7 – 10 days increases to 28 days). Screening for γ - GT may have led to more alcohol abusers being identified although levels do not rise in one - third of individuals. There also is no correlation between alcohol consumption and elevated serum γGT levels with hepatic γ – GT in patients with biopsy - proven alcoholic liver disease. An increased level can lead to over - investigation inan individual who has never taken alcohol or a socialdrinker who has never abused alcohol."

HEMATOGICAL MARKERS OF ALCOHOLISM

State Markers

"Chronic ingestion of large quantities of alcohol alters many physiological andbiological processes and compounds, including several blood-related (i.e., hematological) variables. Because blood samples are"relatively easy to obtain, structural and functional changes in circulating blood cells and plasma proteins potentially can form the basis of laboratory tests for screening, diagnosing, and monitoring alcoholism. Two hematological state markers

commonly used for these purposes are the presence of carbohydrate-deficient transferring (CDT) in the blood and an increase in the size of red blood cells (RBC's), as measured by the mean corpuscular volume (MCV)."

Carbohydrate-Deficient Transferrin.

"CDT is one of the newest—and perhaps the most promising—of thehematological state markers. Transferrin is an iron-containing protein in the plasma that transports iron, which is stored at various sites in the body, to the developing RBC's in the bone marrow for incorporation into hemoglobin. Transferrin molecules in the blood usually contain several carbohydrate components. In chronic heavy drinkers, however, the number of carbohydrate components in each transferring molecule is reduced, resulting in CDT. The mechanism underlying this alteration still is unclear."

"Because elevated CDT levels in the blood appear to be a specific consequence of excessive alcohol consumption, a recent study investigated the utility of repeatedly monitoring serum CDT to detect relapse among recovering alcoholics. The study found that in most of the""subjects who relapsed, the elevation of CDT levels preceded self-reported alcohol consumption by at least 28 days. These findings suggest that repeated testing of alcoholic patients for CDT permits early relapse detection and thus may lead to early intervention. Early intervention, in turn, may decrease the need to rehospitalize patients for alcohol withdrawal and prevent some of the complications associated with sustained excessive drinking. **"**

SYMPTOMS:

"Presentation in these patients may be with features of jaundice, pedal edema, abdominal distension, pruritis.

Upper GI bleed most commonly result in malena, hematemesis. Altered sensorium ranging from sleep disturbances to florid confusion and coma because of hepatic encephalopathy.

'In women, menstrual irregularities are common due to anovulation. Men, may manifest hypogonadism in the form of impotence, loss of sexual drive, testicular atrophy and infertility."

"Portal hypertension is an important complicating feature of decompensated cirrhosis and is responsible for the development of ascites and bleeding from esophagogastric varices which makes cirrhosis decompensated" .

GENERAL EXAMINATION:

Decreasing blood pressure - with progression of cirrhosis, mean arterial pressure often decreases.

- Hypertensive patients may become normotensive.
- Patients presented with mild fever (37.5 -38*C).

This is probably because of bacteremia due to gram negative organisms. Ongoing hepatocyte necrosis and development of hepatocellular carcinoma may also contribute.

Jaundice happens once the functional impairment due to hepatocyte destruction has *exceeded* the process of regeneration. The deeper the jaundice, more severe is hepatic decompensation.

"Skin findings:

Bronze pigmentation of the skin occurs in hemochromatosis. Presence of "vascular spiders" /arterial spiders/spider naevi / spider telengiectasia spider angioma. They are seen in distribution of venous drainage areas of superior vena cava. As liver function worsens, new spiders may appear. They are more frequently associated with alcoholic cirrhosis.

They occur normally in pregnancy and in some normal individuals.

Hepatopulmonary" syndrome is characterized by multiple spiders and clubbing.

"Palmar erythema": palms are warm and red in colour especially over the thenar eminence, hypothenar eminence and the pulp of the fingers. Mechanism of arterial spiders and palmar erythema may be due to estrogen excess. The estrogens are inactivated in the liver.

Serum estradiol level is normal and serum free testosterone is reduced.

High estradiol /Free testosterone ratio may he attributed to these findings.

"Leukonychia" may be related to hypoalbuminemia. "Clubbing" can occur pan digitally especially with development of hepato pulmonary syndrome or in cystic fibrosis."Hypertrophic osteoarthropathy" has also been observed.

"Dupuytrens contracture" may be present.This is characterized by thickened palmar fascia resulting from unorganized proliferation of the fibroblasts.

Head and neck findings-

Parotid enlargement, alopecia, fetor hepaticus,

KF ring in the eyes due to Wilson's disease may be present.

"Fetor hepaticus" refers to the breath of the cirrhosis patients that has a sweet pungent nature. This is because of presence of mercaptans.

***Chest findings* :**

Gynecomastia in males may be seen along with other features of feminization like change in the male pattern of pubic hair, loss of axillary hair and chest hair. Gynaecomastia is because the androstenedione that is synthesized by the adrenals gets aromatized in to estrone and finally in to estradiol in the adipose tissue.

Abdominal findings-

Abdominal examination reveal the presence of ascites, hepatomegaly, splenomegaly, and dilated abdominal wall veins.

“Ascites” — Ascites refers to excessive collection of peritoneal fluid.

Hepatomegaly” -The cirrhotic liver may be enlarged, shrunken or normal sized. On palpation, consistency is firm and nodular.

Features such as shape, consistency are to be better appreciated on palpation as the estimation of liver size correlates less accurately with imaging studies. Presence of a palpable liver in cirrhosis : alcoholic liver disease, primary biliary cirrhosis, hemochromatosis, transformation into hepatocellular carcinoma, Budd Chiari syndrome.

“Splenomegaly”- Splenomegaly in cirrhosis is due to congestion resulting from portal hypertension. correlation between splenic size and portal pressure is poor- implicating that there may be other factors contributing.

“Caput medusae” - With the development of portal hypertension,the portal venous blood gets carried through the periumbilical veins in to the umbilical vein which becomes patent in cirrhosis ,from there the blood drains in to the upper and lower abdominal veins that end up in the systemic circulation .

These veins become engorged and prominent.

Thus the portal blood gets shunted to systemic circulation. This appearance resembles the head (Caput) of the mythical Gorgon Medusa thus termed caput medusae.

Dilated abdominal veins developing in SVC obstruction and IVC obstruction should be differentiated from dilated veins due to cirrhosis.

In IVC obstruction the flow is below upwards whereas in cirrhosis the flow of the blood is away from the cause of obstruction direction or flow is to be assessed.

IVC obstruction the flow is below upwards. However since these veins in both conditions may lack valves, the flow may be bidirectional and the test may be misleading. Moreover the dilated veins due to obstruction are more commonly seen in the back and loin.

"Peptic ulcers" occur in 11% of cirrhosis patients.

Duodenal ulcers are more frequentiy encountered than *gastric* ulcers. Colonization by helicobacter pylori is higher in cirrhosis when compared to normal population. Abdominal hernias are more common in patients with ascites. They should be repaired only if severe enough to cause mortality in alcoholics.Associated chronic pancreatitis can be present which may relapse,so this should be considered a differential diagnosis in alcoholic cirrhosis patients presenting with abdominal pain.

Neurological findings - The presence of Asterixis or liver flap indicate the presence of hepatic encephalopathy.

Genitourinary findings- Testicular atrophy in males.

Endocrine changes- Hyperglycemia occurs in about 80% of cirrhotic patients in the form of glucose intolerance. Only around 10-20% are truly diabetic.

Hematologic abnormalities- Thrornbocytopenia, anemia and lencopenia can occur. The earliest abnormality to occur is thrombocytopenia and it is a marker for the development of portal hypertension.

"Pancytopenia" can even be the presenting feature in asymptomatic compensated cirrhosis. This is due to sequestration of the cells in the enlarged spleen.

Platelet count usually does not fall below .50,000.This does not per se cause bleeding but bleeding can get aggravated in the presence of coagulopathy.

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

Other abnormalities - In cirrhosis, the globulin levels are 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:

- Ultrasonography - Ultrasonography is a non-invasive routinely used investigation to diagnose cirrhosis; the size of the liver, the nodularity, the portal vein diameter, presence of 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. It may be useful when investigating liver malignancy or secondaries or pancreatic pathology.
- MRI helpfull in hermochromatosis to reveal iron overload.
- MRA can determine portal vein flow and dynamics.
- Elastography to assess the stiffness of the liver tissue is also available."

"Liver biopsy:

The gold standard investigation for diagnosing cirrhosis is liver biopsy Nowadays liver biopsy is rarely required 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."

Complication of Cirrhosis:

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Hepatorenal syndrome	Osteoporosis
Type 1	Osteomalacia
Type 2	Hematologic abnormalities
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia

"VARICES :

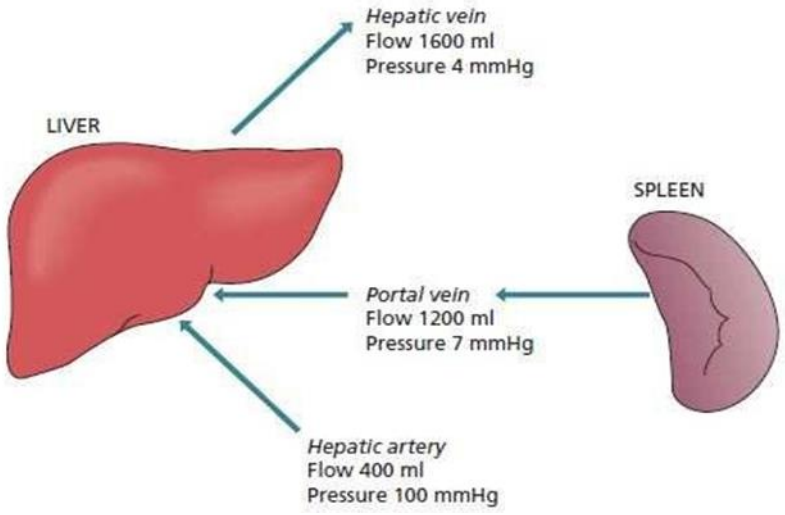
Varices are important cause for upper gastrointestinal bleeding. Varices reflects the presence of portal hypertension. Portal hypertension is defined as elevated hepatic venous portal gradient more than 5 mmHg.

Anatomy and physiology of Portal venous system :

The portal vein is formed by the confluence of the superior mesenteric and splenic veins.

Spleenic vein drains blood from the spleen, fundus of stomach and part of the pancreas. Inferior mesenteric vein drains blood from the large intestine - transverse colon,descending colon and rectum – superior two thirds usually joins the spleenic vein Superior mesenteric veins drain blood

from small intestine, large intestine, stomach , pancreas and appendix.



Portal hypertension leads to two major complications – variceal hemorrhage and ascites.

Pathophysiology of varices formation :

Anatomically collaterals usually exists between the portal venous system and the systemic venous system at certain anatomic locations. Blood flows from the systemic circulation into the portal system.

Two pathogenesis contributing to portal hypertension are

- Increased resistance to portal venous flow due to extrahepatic obstruction or intrahepatic resistance due to cirrhosis and regenerative nodules.

- Increased splanchic blood flow due to vasodilation of splanchic circulation.

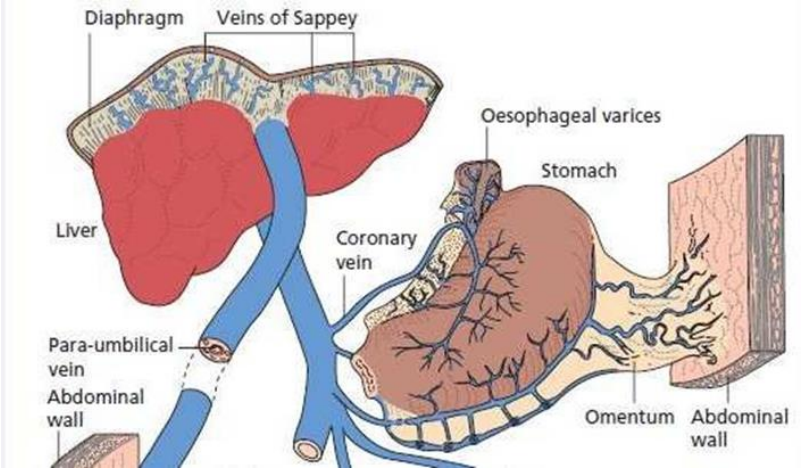
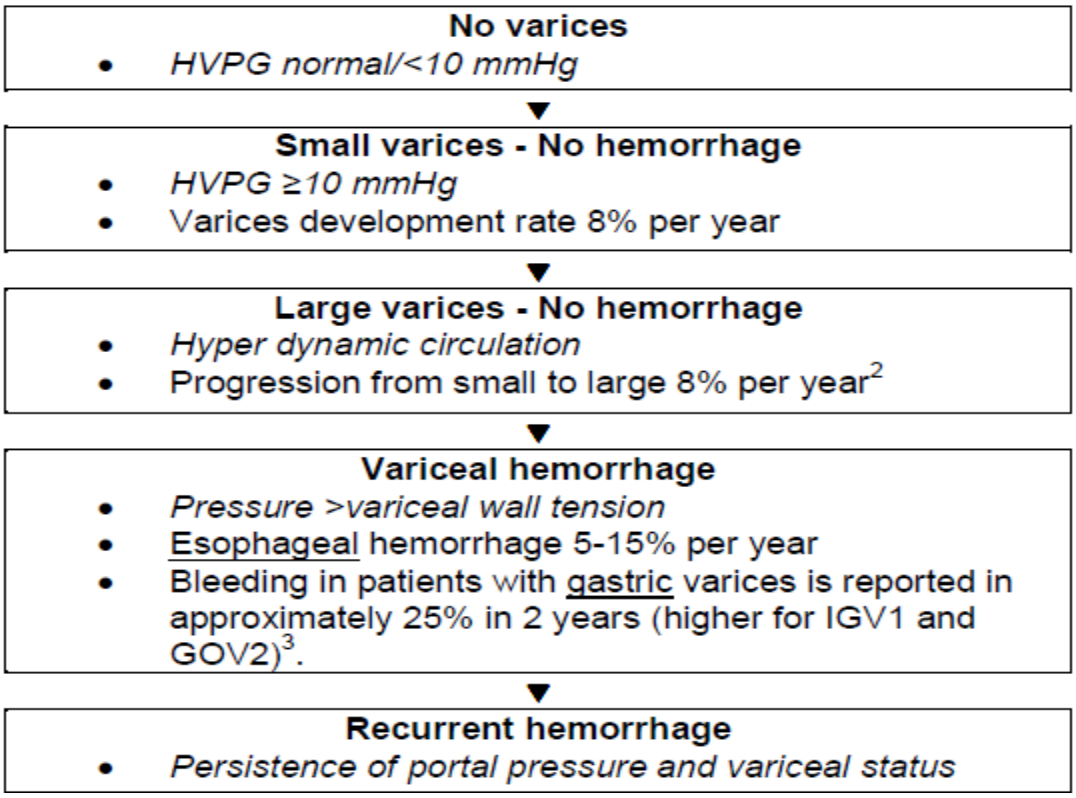


Fig. Collaterals formation at esophagus in portal hypertension

When portal hypertension develops, the resistance in the portal vessels pressure raises more than that of the systemic system, and causes reversal of flow . This is transmitted to the portosystemic junctions and the collaterals become dilated and distended

Angiogenesis and new blood vessel formation also occur with an effort to increase collataeral bed to decompress the portal hypertension but when the collateral is unable to withstand the pressure, dilation of vessels occur. further compromise leads to complication of rupture and bleeding.

Varices should be kept in mind while treating all patients with clinical picture of liver cell failure. Once diagnosis of cirrhosis is made, the patient should be subjected to endoscopy to rule out varices and appropriate management should be done. When absent, periodic review and yearly endoscopy should be done



Causes of portal hypertension

1.Prehepatic causes

Portal vein obstruction

- Idiopathic
- Cirrhosis
- Infection
- Pancreatitis
- Abdominal trauma.
- Coagulation disorders

- polycythemia vera,
- essential thrombocytosis,
- deficiencies in protein C,
- protein S deficiency,
- antithrombin 3 deficiency,
- factor V leiden
- Spleenic vein thrombosis
- Massive spleenomegaly – Banti's syndrome

2.Hepatic causes :

Presinusoidal

- Schistosomiasis
- Congenital hepatic fibrosis Sinusoidal
- Cirrhosis of any etiology
- Alcoholic hepatitis
- Postsinusoidal
- Hepatic sinusoidal obstruction

3.Post hepatic causes

- Budd-Chiari syndrome

- Inferior vena caval webs
- Cardiac causes
- Restrictive cardiomyopathy
- Constrictive pericarditis
- Severe congestive heart failure

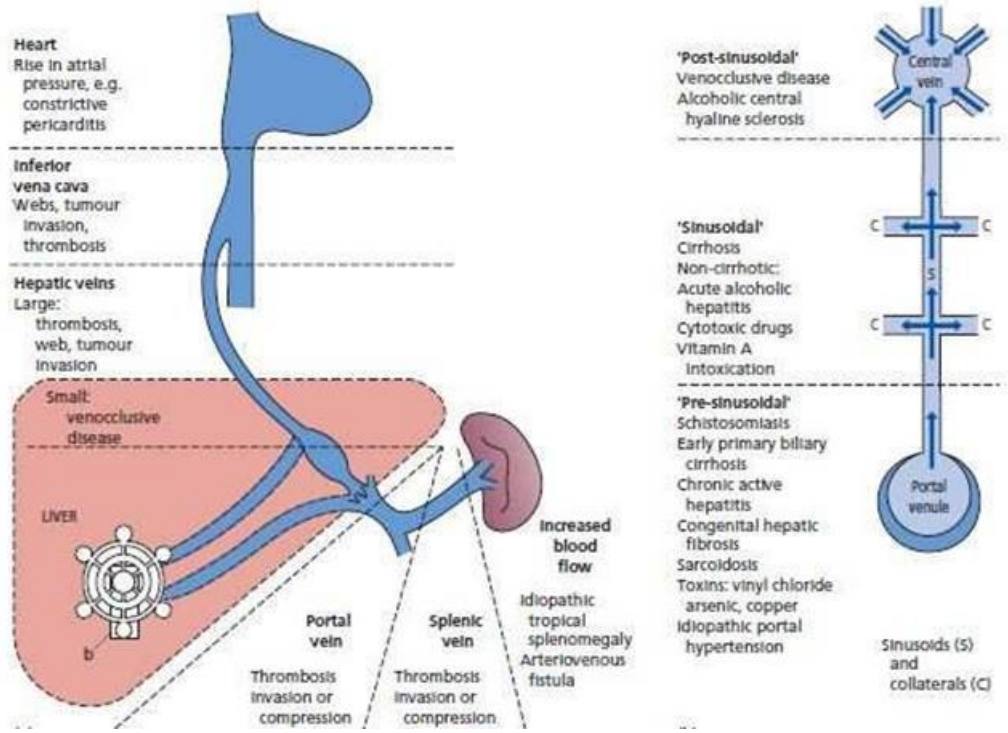


Fig.Causes of portal hypertension

Esophageal varices:

Gastroesophageal collateral bed is the common site of variceal formation and bleeding. When the HVPG exceeds 10 mm Hg, esophageal varices develops. In esophagus, the varices along the lower 2 to 3 cm submucosa lies very superficial, have fragile thin wall and so why bleeding usually occurs at this site. These vessels do not communicate with the

periesophageal veins and therefore cannot easily be decompressed(8)*.

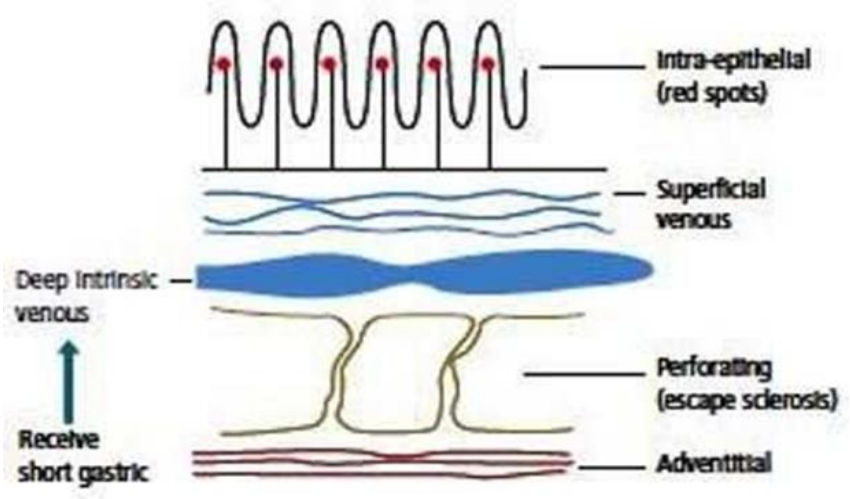


Fig: Esophagus - subcutaneous venous plexus

Esophageal varices may be small – less than 5mm or large –greater than 5 mm.Small varices progress with time into large varices. The predictors of first bleeding include the size of varices, severity of cirrhosis (Child B or C), variceal pressure (>12 mm Hg), and the endoscopic presence of red wale marks (5).

“Gastric varices :

Gastric varices occur less common than esophageal varices around 5 – 30% (5) of portal hypertension. Bleeding occurs in about one-fourth of them. Gastric varices can occur in isolation or as extension of esophageal varices.

Gastic varices are classified according to the site and association with esophageal varices. (*Sarrin et al*.)

Gastroesophageal varices [2]

- Type 1 varices - extend along the lesser curvature.
- Type 2 varices - extend along the fundus. They are longer and more tortuous than GOV1

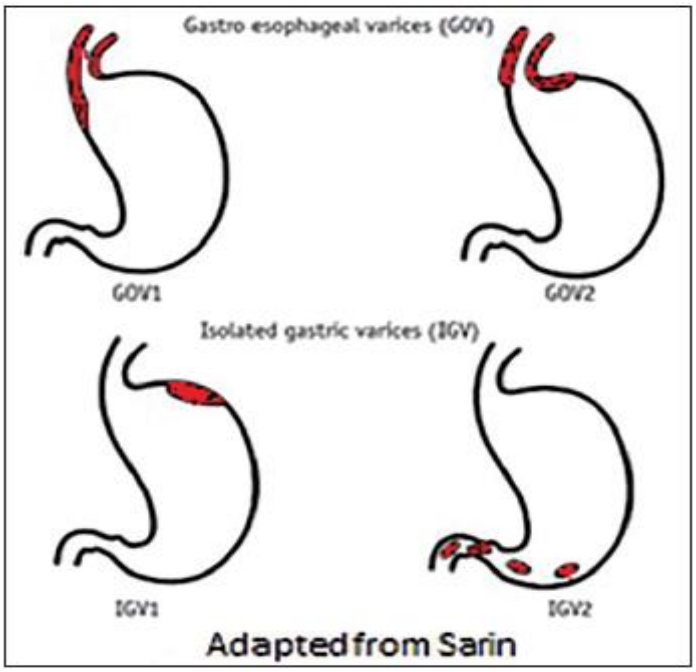
Isolated Gastric varices [2] :

- Type 1 - fundus and tend to be tortuous and complex
- Type 2 - body, antrum, or around the pylorus.

Isolated gastric varices at fundus may occur due to spleenic vein thrombosis and should be ruled out.

Ectopic varices:

Varices may occur anywhere in the gastrointestinal tract.when present in GI tract other than esophagus and stomach, they are termed as ectopic varices. They are difficult to identify and continue be a concealed source of bleeding.once identified the appropriate treatment modalities are not well established. Management Endoscopy has evolved as the principal diagnostic as well as therapeutic tool in management of upper gastrointestinal bleed. Endoscopy era has made to review the etiology of upper GI bleed as the most common cause varies with region. It helps in identifying individuals and categorising them accordingly to be managed by primary prophylaxis in newly diagnosed cirrhotic or need for endoscopic intervention or surgery.



HEPATO PULMONARY SYNDROME:

Diagnostic criteria for Hepato Pulmonary Syndrome consist of the following:

1. The presence of liver disease and / or portal hypertension
2. An elevated room air alveolar-arterial oxygen gradient [P(A-a) O_2 gradient] > 15mmHg or > 20mmHg when age > 65years.
3. Evidence of intrapulmonary vascular dilatations in the basal parts of the lungs
4. Absence of other significant cardio pulmonary disease

A relationship between the liver and the lung was first noted by Fluckiger based on his observation of a women with cirrhosis , cyanosis and clubbed digits.Kennedy and Knudson(1997) described the word “hepatopulmonary syndrome” which is characterized by hypoxemia and intrapulmonary vascular dilatations(ref 6).Hepatopulmonary syndrome is a

complication of liver disease,especially portal hypertension.It is most commonly associated with chronic liver disease, although it has also been described in the context of acute liver disease. The clinical features of Hepato Pulmonary Syndrome are due to both hepatic and pulmonary dysfunction.More than 80% of patients present with symptoms of liver disease, the remainder experience dyspnea as their initial symptom. Hypoxemia,platypnea and orthodeoxia are characteristic findings.Impaired oxygenation is confirmed when Arterial blood gas analysis demonstrates an elevated room air alveolar-arterial oxygen gradient [P(A-a) O_2 gradient] > 15mmHg or an arterial oxygen gradient (pao_2) of < 80mmHg while breathing room air(ref 7).Intrapulmonary vascular dilatations may be identified by contrast enhanced echocardiography, macroaggregated albumin scanning, and pulmonary arteriography. contrast enhanced echocardiography is generally preferred because it is more sensitive than macroaggregated albumin and less invasive than pulmonary arteriography(ref 8). contrast echocardiography is performed by injecting a contrast material usually agitated saline and then performing echocardiography. under normal circumstances, the contrast opacifies only the right heart chambers because it is filtered by the pulmonary capillary bed. However contrast may opacify the left heart chambers if a right to left intracardiac or intrapulmonary shunting is present. With an intracardiac shunt, contrast appears in the left heart within three heart beats after injection. In contrast, with an intrapulmonary shunt, contrast generally appears in the left heart three to six heart beats after its appearance in the right heart. In patients with liver disease,

detection of an intrapulmonary right to left shunting is considered indicative of Intra Pulmonary Vascular Dialatations. pulmonary arteriography is generally reserved for excluding alternative causes of hypoxemia, pulmonary hypertension and large direct arteriovenous communications. Three angiographic patterns were described.Type 1 minimal pattern was characterised by normal to finely diffuse,spidery abnormalities.It was associated with severe hypoxemia,orthodeoxia and a good response to 100% inspired oxygen. The type 1 minimal pattern may evolve into a type 1 advanced pattern, which was characterized by a diffuse spongy or blotchy angiographic appearance. It is less responsive to 100% inspired oxygen. Type 2 discrete pattern was characterized by localized arteriovenous communications and is associated with poor response to supplemental oxygen.(ref 8). At present, the most effective and only radical treatment is liver transplantation. Cirrhotic patients who are on the waiting list for an liver transplantation have a shorter survival period if they develop Hepato Pulmonary Syndrome. Therefore, it is suggested that all cirrhotic cases should be followed closely for Hepato Pulmonary Syndrome and should have priority in the waiting list."

"Hepato Pulmonary Syndrome is an important complication of cirrhosis,causing dyspnea and cyanosis in cirrhotic cases. There is no relation between the development of Hepato Pulmonary Syndrome and the severity of cirrhosis."

LIVER AND GLUCOSE

“ROLE OF LIVER IN GLUCOSE METABOLISM

1. Liver is the organ of glucose production and glucose consumption
2. It is exposed to insulin concentration in the portal circulation which is 3 – 10 times more the systemic circulation.
3. Sole site of glycol regulatory action of glucose
4. Absorbed hexose’s reach liver before reaching muscle and adipose tissues.

Liver has storage of glucose and glycogen about 70gm aat a time. 75% of hepatic glucose output comes from gluconeogenesis.

Contribution of liver in glucose homeostasis depends on the following factors:

1. Sensitivity of hepatocytes to small increments in insulin levels
2. Ratio of insulin to glucagon
3. Responsiveness of glycogenolysis and gluconeogenesis to hormonal modulation.

HEPATOGENOUS DIABETES

INTRODUCTION

Hepatogenous diabetes is a common complication of diabetes. The liver plays a very important role in glucose metabolism. Thus, in the presence of chronic liver disease, the homeostasis of glucose metabolism is impaired and results in glucose intolerance and diabetes mellitus (DM) type 2.About 50% -

80% of cirrhotic patients have IGT and 30% - 40% develop DM. Sometimes, DM in cirrhosis may be subclinical, since fasting serum glucose may be normal. In these cases, it is necessary to perform an oral glucose tolerance test (OGTT) to detect an impairment of glucose metabolism . Also DM increases the risk of complications of cirrhosis and reduces survival rate. Moreover these patients having increased peripheral resistance and altered adipocyte sensitivity. To compensate for insulin resistance (IR) pancreatic insulin secretion increased.

MECHANISM:

DM can increase fibrosis, incidence of hepatocellular carcinoma, and resistance to antiviral therapy in patients with cirrohosis. DM may be involved in the progression of liver fibrosis and inflammation through diverse mechanisms: it is likely that adipokine production (such as leptin and Tumor necrosis factor-alpha, which activate inflammatory pathways exacerbating liver injury) is increased by insulin resistance. Leptin and oxidative stress associated with liver inflammation may activate transforming growth factor beta 1(TGF-β1), which is one of the most potent profibrogenic cytokines produced in the liver. TGF-β1 activates hepatic stellate cells which are the major source of collagen and extracellular matrix proteins.

CLINICAL IMPLICATIONS:

DM increases the incidence of severe infections by inducing immunosuppression. Cirrhotic patients with DM have a higher prevalence of infections compared to non-diabetic ones.Spontaneous bacterial peritonitis was

more frequent in patients with cryptogenic cirrhosis(which is associated with DM) compared to those with cirrhosis of other causes. These infected patients had higher mortality due to sepsis, liver failure, and hepatorenal syndrome. In addition, DM may increase the risk of variceal bleeding, as postprandial hyperglycemia that occurs in diabetic patients produces splanchnic vasodilatation and increases the flow and pressure of the porto systemic venous system. Also, esophageal variceal bleeding increases the risk of infection and death by inducing bacterial intestinal translocation. DM has been also associated with increased risk of hepatic encephalopathy.

Hepatogenous diabetes is less associated with retinopathy, cardiovascular and renal complications and more frequently associated with hypoglycemic episodes as a result of impaired liver function. Liver disease abnormalities (low intravascular coagulability, low cholesterol, lower prevalence of hypertension) as well as shorter duration of DM may explain relatively lower rate of diabetic complication in chronic liver disease".

Hepatitis B:

Around 2 billion people in the world are infected with Hepatits B virus.out of them 400 million are chronically infected. Most of them are asymptomatic carriers and most of them will progress to chronic hepatitis, decompensated liver disease and hepatocellular carcinoma. HBV may be attributed to one of the main cause for hepatocellular carcinoma and it is the second leading carcinogen while tobacco remains the first worldwide.

According to the prevalence of chronic Hepatitis B ,it can be classified as :

- Highly prevalent : more than 8 percent
- Intermediate prevalent : 2 to 5 percent
- Low prevalent : less than 2 percent

Countries with high prevalence are : south East Asian countries and China Intermediate prevalance : central Asia and Mediterranean countries

Low prevalance : USA ,Australia and New Zealand

Overall the prevalance of the disease is reduced due to increased awareness and hepatitis B Vaccination and also due to health education and better sanitation.

“CHRONIC HEPATITIS B :

Chronic hepatitis B represents a series of liver diseases due to etiology and severity in which hepatic necrosis and inflammation persists for more than 6 months .

Post viral chronic Hepatitis and Alcoholic liver disease are the major causes of decompensated Chronic Liver Disease.

Other causes for Chronic Liver Disease:

- Auto immune hepatitis
- Wilson disease
- Non alcoholic fatty liver disease
- Hemochromatosis
- Cryptogenic cirrhosis
- Drug induced and Metabolic disorders.

According to the immune reaction , it is classified into,

- Immune tolerant stage
- Immune clearance stage
- Quiescent stage

Immune tolerant stage:

Neonatal period is considered as immune tolerant phase where in there is very little immune reaction and less damage to the liver and mild elevation in the transaminase level but there is very high viral load and HBeAg positivity.

Immune clearance phase :

Age 10 to 20 is considered as highly reactive immune phase that produces high clearance of viruses and extensive liver damage. Enzyme elevation in this phase is very high and HBV load is very low.

Quiescent stage :

In older age immune response is very low and it is called quiescent stage wherein both HBV DNA and enzyme elevation is very low.

They rarely progress to chronic hepatitis. Presence of HbsAg greater than 6 months is considered as chronic hepatitis B.

Estimated 5 year survival rate of progression to Chronic Hepatitis B:

Chronic hepatitis leading onto cirrhosis : 10 to 20 percent

Compensated cirrhosis to Decompensated Cirrhosis : 20 to 30 percent

Compensated cirrhosis turning into hepatocellular carcinoma : 5 to 15 percent

Survival rate :

- For compensated cirrhosis – 85 percent at 5 years
- Decompensated cirrhosis – 55 to 70 percent at first year and 15 to 35 percent at 5 years.

Factors modifying the course of Hepatitis B Infection:

Duration and amount of viral replication :

Presence of viral replication can be assessed with markers like HBeAg positivity and HBV DNA levels. The more the duration and extent of viral replication decides the progression of patient to cirrhosis and hepatocellular carcinoma. HBV DNA levels are used as a primary marker now and it has been

incorporated into the guidelines for treatment of CHB patients. Chronic Hepatitis B should be treated to avoid the progression of liver disease.

2.Alcohol use :

Heavy alcohol consumption along with HBV leads to faster progression of liver disease as does the risk of HCC and development of cirrhosis.

3.Hepatitis C :

When co-infection of HCV and HBV occurs , manifestations of HCV predominates, with very low level of replication but the rate of progression to cirrhosis and carcinoma much faster. The rate of fulminant failure is increased in both HBV and HCV infection on CHB patients.

Indication of Anti viral therapy in CHB patients:

There are many guidelines for treatment of which the newly published one is German Guidelines:

1. 1.HBV DNA level > 2000 IU/ml or >10,000 copies/ml
2. Any elevation of ALT and histological grading and staging.
3. Patient with cirrhosis or advanced cirrhosis and detectable viremia
4. Reactivation of HBV replication due to immunosuppression, should be avoided by preventive therapy.
5. alcohol and drug consumption are not a contra indication for treatment
6. Antiviral in pregnancy: Lamivudine and tenofovir continued during pregnancy.

Goals of therapy for HBV:

Aim of treatment is to prevent the progression of liver disease to cirrhosis or hepatocellular carcinoma

Clinical parameters used in assessment are :

1. Loss of HBeAg in a HBeAg positive patient with the development of anti HBE . This is called e antigen seroconversion..
2. Loss of HBsAg and development of anti HBs
3. Normalisation of serum transaminases
4. Very low or undetectable viral DNA level
5. Histological improvement in liver biopsy

Drugs used for chronic hepatitis B :

1. 1.Lamivudine
2. 2.Adefovir
3. 3.telbivudine
4. 4.tenofovir
5. Pegylated interferon 2 alpha”

Prolactin

Causes of hyperprolactinemia:

1.physiological hypersecretion:

- Pregnancy

- Lactation
- Chest wall stimulation
- Sleep and stress

2.hypothalamic pituitary stalk damage:

- Tumours
- Craniopharyngioma
- Suprasellar pituitary mass
- Meningioma
- Dysgerminoma
- Metastases
- Empty sella
- Lymphocytic hypophysitis
- Adenoma with stalk
- Compression
- Granuloma
- Rakhthes cyst
- Irradiation and trauma
- 3.pituitary hypersecretion:
- Prolactinoma and acromegaly

4. Systemic disorders:

- Chronic renal failure’
- Hypothyroidism
- Cirrhosis
- Epileptic seizures
- Pseudocyesis

Drug induced hyper secretion:

Dopamine receptor blockers:

- Atypical antipsycotics
- Phenothiazenes
- Haloperidol
- Thioxanthine
- Metoclopramide
- Dopamine synthesis inhibitors: alpha methyldopa
- Catecholamine depletors :reserpine
- Opiates
- H2 antagonists
- Calcium channel blockers
- Fluoxetine

- Estrogens
- Thyrotropin releasing hormone

“Hyper prolactinemia is defined as prolactin level more than 200 ug /L Most common cause : PRL secreting pituitary adenoma Chronic renal failure elevates prolactin level by decreasing the peripheral clearance Primary hypothyroidism is associated with mild hyperprolactinemia due to compensatory increase in thyrotropin releasing hormone

- Lesion of the hypothalamic pituitary region:

  Disrupts the dopamine synthesis
- Portal vessel delivery
- Lactotrope response

Prolactin level in the range of 100 to 300 ug/L

- Hypothalamic disorders
- Infiltrative disorders
- Radiation induced damage
- Presenting features:

Amenorrhea ;galactorrhea and infertility are the hallmark of hyperprolactinemia. Vertebral bone mineral density can be reduced.

- Decreased libido
- Weight gain

- Mild hirsuitsm

In men : loss of libido and infertility and visual loss are the presenting complaints. Osteopenia ,decreased beard growth and reduced muscle mass secondary to decreased testosterone.

Galactorrhea is sometimes associated with acromegaly.

Lab investigations:

- Basal fasting morning PRL level < 20 ug/L
- Hypothyroidism will be excluded by measuring TSH and T4 level.
- Prolactinoma : Tumors arise from the lactrotrophe cells, accounts for 50 percent of the cases
- Male to female ratio= 20 :1
- Tumour size correlates with the PRL level
- Micoadenomas < 1cm in diameter
- Macro adenomas more than 1cm invade the parasellar regions and impinge on the nearby structures.
- Value more than 250 ug/L correlates with macroadenoma.
- MRI should be performed in all patients with hyperprolactinemia.it is important to remember that hyperprolactinemia caused by non lactotrope cells is also corrected by treatment with dopamine agonists.despite failure to shrink the underlying mass.

- Prolactin suppression by dopamine agonists does not necessarily indicate that the underlying mass is a prolactinoma.
- Treatment goal for prolactinoma:
- Control of hyperprolactinemia
- Reduction of tumour size
- Restoration of menses and fertility
- Resolution of galactorrhea
- MRI and visual field check up shoukd be done 6 monthly to reduce the tumour size.

Drugs used : bromocriptine and cabergoline”

Pregnancy and prolactin :

The size of pituitary increases with pregnancy due to stimulatory effects of oestrogen. bromocriptine is used safely in pregnancy without any tetratogenic side effects.

For women taking bromocripitine desire pregnancy, mechanical contraception should be used for three regular menstrual cycles to allow for conception timing.

Cabergoline is a long acting with high D2 receptor affinity .it is not recommended for use in women whose fertility is desired.

“CHILD PUGH SCORE:

It is a reasonably reliable predictor of survival in many liver diseases. It helps in predicting the complications of liver diseases like cirrhosis, oesophageal varices and spontaneous bacterial peritonitis.

Cirrhosis can be staged according to the scoring system.

Cirrhosis can be staged clinically. A reliable scoring system is the modified CHILD PUGH scoring system. It ranges from 5 to 15.

Child Pugh CLASS A : Score of 5 and 6 , consistent with compensated cirrhosis.

Child Pugh CLASS B : Score of 7 to 9 , consistent with decompensated cirrhosis.

Child Pugh CLASS C :Score more than 10 , consistent with decompensated cirrhosis.

This scoring system includes 5 factors : serum bilirubin, serum albumin, ascites, hepatic encephalopathy and prothrombin time. It is reasonably a reliable predictor of survival and predicts the likelihood of major complications like bleeding from the varices and spontaneous bacterial peritonitis.It was also used to assess the prognosis in cirrhosis and to provide a standard criteria in listing the patient for liver transplantation.

Thus comparing the serum prolactin level with the Child pugh scoring system in assessing the severity of the liver disease and predicting the risk of complications.

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)			

Model for End Stage Liver Disease (MELD) Score

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

NOTES:

- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

“Hepatic encephalopathy:

In patients with cirrhosis, there is a wide range of neuropsychiatric abnormalities ranging from clinically indescrinible changes in cognition to obvious changes in the intellect,behaviour ,motor function and consciousness. It has a detrimental effect on the survival of the patient.

Both hepatocellular failure and portosystemic shunt plays a vital role in the development of hepatic encephalopathy. Cirrhosis is the most common cause of hepatic encephalopathy. Gut derived neurotoxins predominantly ammonia, escape hepatic detoxification and impinge in the brain, there ammonia is detoxified by astrocytes ; leading to low grade cerebral edema and impairs the neuronal function.

Classification of hepatic encephalopathy:

- Overt hepatic encephalopathy
- Episodic hepatic encephalopathy
- Persistent hepatic encephalopathy
- Minimal hepatic encephalopathy

Overt Hepatic Encephalopathy:

It may arise over a period of hours or days in patient who has been previously stable, occurs intermittently and more frequently. There is a normalcy period between the episodes. Personality changes include childishness, irritability and loss of concern for family members. Intellectual

deterioration varies from mid confusion to gross disorientation ; visual spatial agnosia ;constructional apraxia and writing becomes indistinct.

Reduction of spontaneous movement ; fixed stare ,apathy and slowness and brevity of responses . Day time sleepiness is the earliest feature to detect hepatic encephalopathy, sometime it progress to delirium

Changes in motor function : rigidity and disorders of speech production, tremors ,astrexis, hyper or hyporeflexia , choreo athetoid movements, Babinsky sign and transient focal symptoms. Astrexis is caused by impaired inflow of joint and other afferent information to the brainstem reticular formation .the tremors are absent at rest , less marked on movement and maximum on sustained posture. These movements also see in arms, jaw, neck , protruded tongue and tightly closed eyelids and ataxic gait. A flapping tremor also called Liver palms seen in heart failure , renal failure ,severe heart failure ,hypomagnesemia and phenytoin intoxication

Speech become monotonus and slurred. Deep tendon reflexes are exaggerated .Increased muscle tone leading to exaggeration of reflexes and plantar become flexor and extensor in deep stages of coma.

Excessive appetite, muscle twitching, grasping and sucking reflex present Visual disturbance like reversible cortical blindness and alternating gaze deviation present.

EPISODIC HEPATIC ENCEPHALOPATHY:

It present in patients who are clinically stable.

PERSISTENT HEPATIC ENCEPHALOPATHY:

It presents as worsening of predominant clinical features rather than change in conscious level.

There will be predominance of Parkinson features ;cerebellar signs and choreoathetoid movements

MINIMAL HEPATIC ENCEPHALOPATHY:

Patients presents with abnormalities in cognition and neurophysiological variables but patient is clinically stable.

Hepatic myelopathy:

Patient presents with progressive spastic paraparesis without sensory impairement or spintcher dysfunction. It is due to degeneration of spinal cord.

Neurological Examination:

1. Higher mental status should be examined.
2. Grading system is used to assess the mental status West Haven criteria and Glasgow Coma scale is used for assessing the mental status.
3. Psychometric analysis has to be done
    - Number Connection tests A AND B
    - Line tracing
    - Serial dotting
    - Digital symbol tests

4. Psychometric hepatic encephalopathy score has given to predict the clinical state of the patient.

- EEG: shows progressive slowing of the alpha waves; and slowing of delta waves.
- Triphasic waves present in severe encephalopathy.
- Evoked potentials; smooth pursuit eye movements are used as neurophysiological tests.
- Functional and cerebral imaging :
- Cerebral and cerebellar atrophy
- Hyperintensity in MRI : due to deposition of manganese reflects pallidal deposition.
- Total body manganese is increased : impaired biliary excretion; hepatic failure and the presence of portosystemic shunting of blood.
- CEREBRAL MR Spectroscopy: reflects the cerebral metabolic process ; it is due to reduction in the myoinositol and choline resonance and increase in excitatory neurotransmitters.
- Radiotracer imaging like SPECT AND PET are used
- Blood ammonia increased and serum zinc level decreaed in patients with hepatic encephalopathy.
- CSF glutamine concentration is useful in assessing the severity of hepatic encephalopathy.
- Hepatic encephalopathy:pathogenesis

Two key factors in the development of encephalopathy are hepatocellular failure and porto systemic shunting.

1. Gut derived neurotoxins
2. Brain water homeostasis
3. Oxidative /nitrosative stress
4. Astrocyte dysfunction
5. Alterations in cerebral neurotransmission.

Consequences of Astrocyte swelling:

1. Activation of extracellular regulated protein kinases
2. Activation of NMDA receptors
3. Upregulation of peripheral Benzodiazepene receptors
4. Modulation of amino acid transport
5. Modulation of multiple ion channels
6. Induction of oxidative and nitrosative stress
7. Increased ph in the endocytotic vesicles
8. Alteration in cerebral neurotransmission
9. Finally leading to neuronal dysfunction

Alteration in cerebral neurotransmission:

- Increase in GABAergic transmission
- Decrease in glutaminergic pathway
- Increased synthesis of neurosteroids

- Serotonin and Dopamine level is decreased due to increased metabolism of monoamine oxidase A and increase in number of receptors
- Dopamine level is decreased due to increased metabolism and increased concentration of Homovanillic acid in the urine
- Extra pyramidal features are present in encephalopathy
- Acetylcholine levels are reduced and rivastigmine gives a cognitive betterment.
- Adenosine further aggravates the excitatory and inhibitory neurotransmitter imbalance

Factors precipitating hepatic encephalopathy:

- Gastrointestinal bleeding
- Sepsis
- Electrolyte imbalance : hyponatremia; hypokalemia
- Starvation
- Dehydration
- Constipation
- Excess protein load
- Alcohol misuse
- TIPS INSERTION, surgery"

"HORMONAL CHANGES IN CIRRHOSIS:

In cirrhosis, adrenal insufficiency occurs by number of mechanisms,

1. Low level of HDL Cholesterol
2. Negative effect of cytokines on hypothalamus
3. Increased conversion of cortisol to inactive cortisone

Thyroid function in Cirrhosis of Liver:

1. Thyroid dysfunction leading to decreased peripheral conversion of T4 to T3. Describing as " low T3 Syndrome".
2. It is completely reversible with liver transplantation

Prolactin and Cirrhosis:

- Normally prolactin is associated with characteristic nocturnal rise, and a characterisitic circadian rhythm.
- Loss of circadian rhythm is characteristic of cirrhotic patients.
- Suppression of hypothalamic pituitary axis.
- Increased sex hormone binding globulin.

.MATERIALS AND METHODS

STUDY POPULATION:

SOURCE OF DATA:

The study will be conducted on 100 patients admitted to Government Rajaji Hospital & Madurai Medical College during the study period from February 2017 to July 2017.

Inclusion criteria:

All patients with cirrhosis of liver.

EXCLUSION CRITERIA:

1. History of chest wall trauma
2. Cranial surgery/ irradiation
3. Pituitary or hypothalamic disease
4. Chronic renal failure
5. Herpes zoster
6. Seizure disorder
7. Patient on medications known to elevate prolactin level.

ANTICIPATED OUTCOME:

Serum prolactin levels were elevated in cirrhosis patients with higher child pugh class, as well as in the complications thus making it a useful biomarker for severity of the disease and predicting the risk of complications.

DATA COLLECTION

Informed consent will be obtained from all patients to be enrolled for the study. In all the patients relevant information will be collected in a predesigned proforma..The patients are selected based on clinical examinations, biochemical tests and ultrasound abdomen. Patients were subjected to routine cirrhosis work up. In all cirrhotic patients serum prolactin level is measured and it is correlated with Child Pugh score in assessing the disease severity and the risk of compilcations.

LABORATORY INVESTIGATIONS

a) Complete blood count,

b) Liver function test,

c) Renal function test,

d) Urine routine,

e) Serum electrolytes and serum prolactin level

f) HBsAg,

g) HCV,

h) Prothrombin time, aPTT and INR

i) Electrocardiogram,

j) Echo

k) Chest X ray,

l) USG abdomen

DESIGN OF STUDY: Prospective study.

PERIOD OF STUDY:6 MONTHS (February 2017 to July 2017)

COLLABORATING DEPARTMENTS:

- DEPARTMENT OF MEDICAL GASTROENTEROLOGY
- DEPARTMENT OF ENDOCRINOLOGY
- DEPARTMENT OF BIOCHEMISTRY
- DEPARTMENT OF RADIOLOGY

ETHICAL CLEARANCE: Clearance obtained

CONSENT: Individual written and informed consent obtained.

- CONFLICT OF INTEREST : NIL
- FINANCIAL SUPPORT : SELF

STATISTICAL ANALYSIS:

All data were entered in Excel 2007 and statistical analysis was performed using the statistical software SPSS 16.0.Data were expressed as frequency (with percentages), median values (with range (min, max)). For continuous variables, Mann Whitney U-test was performed to find the differences between two groups and for categorical variables Pearson's chi-square test was performed.Results were defined as statistically significant when the *P* value (2-sided) was less than 0.05

OBSERVATION AND RESULTS

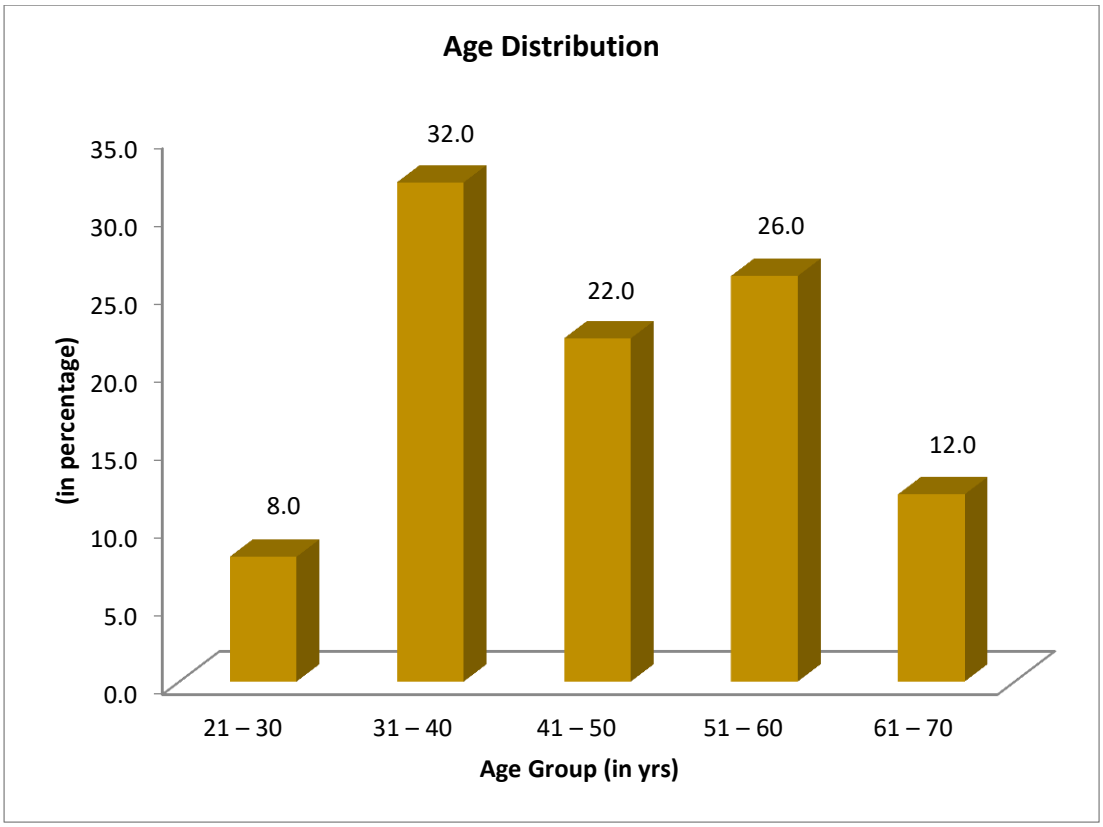
1.AGE DISTRIBUTION:

TABLE 1 AND 2: AGE DISTRIBUTION AMONG PATIENTS PRESENTING WITH CIRRHOSIS OF LIVER

Age (in yrs)	
N	50
Mean	45.8
SD	11.7
Minimum	26
Maximum	70

Age group (in yrs)	**n (%)**
21 – 30	4 (8.0)
31 – 40	16 (32.0)
41 – 50	11 (22.0)
51 – 60	13 (26.0)
61 – 70	6 (12.0)
Total	50 (100.0)

FIG 1: BAR DIAGRAM SHOWING THE AGE DISTRIBUTION OF LIVER FAILURE PATIENTS



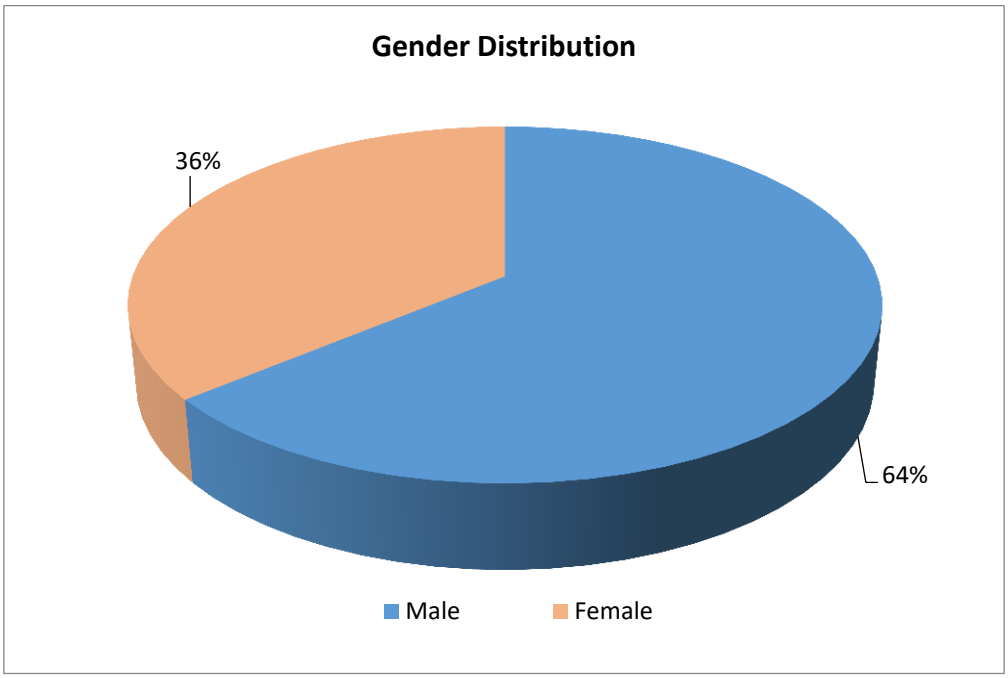
Comment : More people are in the age group of 31 to 40 yrs.

1.Gender distribution:

Table 2 : Gender distribution in patients presenting with cirrhosis of liver

Gender	n (%)
Male	32 (64.0)
Female	18 (36.0)
Total	50 (100.0)

FIG 2: PIE CHART SHOWING THE GENDER DISTRIBUTION OF CIRRHOTIC PATIENTS

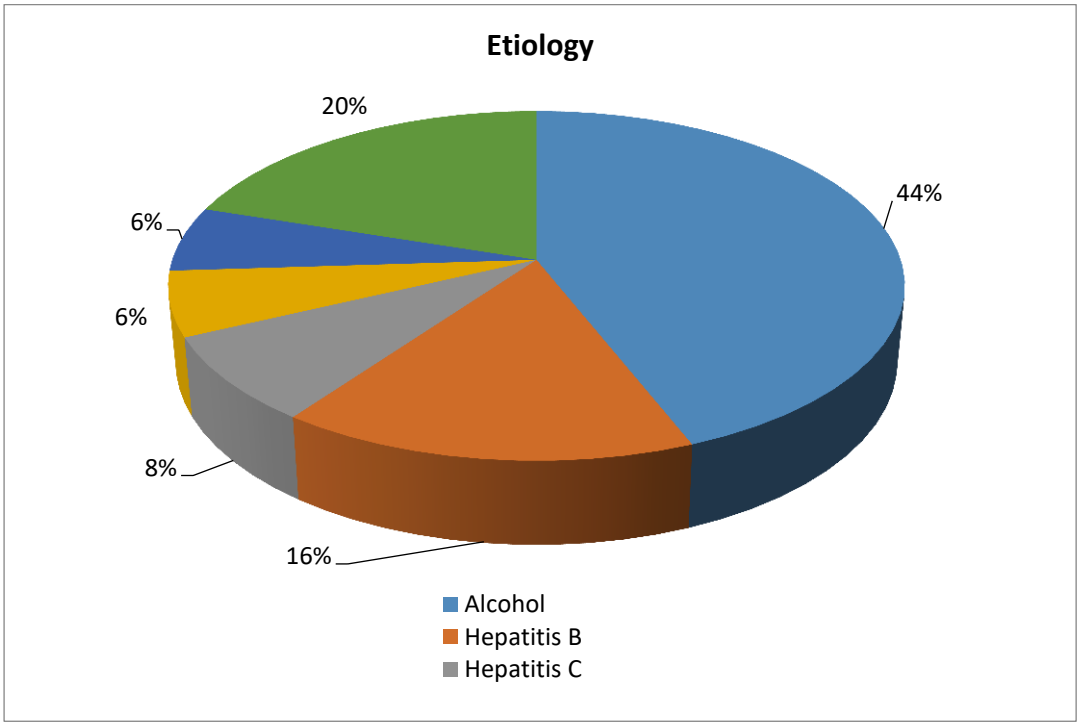


3. ETIOLOGICAL CLASSIFICATION:

TABLE 3: ETIOLOGICAL CLASSIFICATION OF CIRRHOSIS OF LIVER

Etiology	n (%)
Alcohol	22 (44.0)
Hepatitis B	8 (16.0)
Hepatitis C	4 (8.0)
Alcohol + Hepatitis B	3 (6.0)
Alcohol + Hepatitis C	3 (6.0)
Others	10 (20.0)
Total	50 (100.0)

FIG 3: ETIOLOGICAL CLASSIFICATION OF CIRRHOSIS



4. SEVERITY OF ASCITES IN STUDY POPULATION:

FIG 4 : SEVERITY OF ASCITES IN STUDY POPULATION

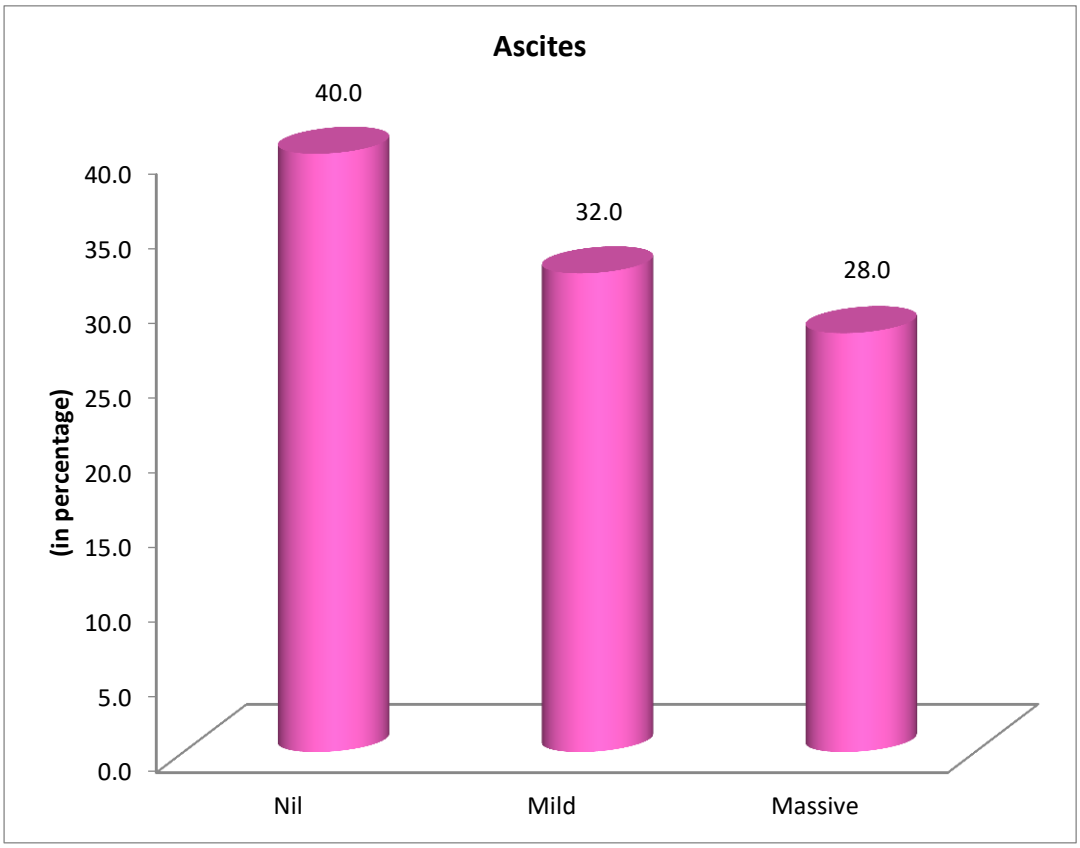


TABLE 4 : SEVERITY OF ASCITES IN STUDY POPULATION:

Ascites	n (%)
Nil	20 (40.0)
Mild	16 (32.0)
Massive	14 (28.0)
Total	50 (100.0)

5. GRADING OF ENCEPHALOPATHY:

FIG 5: GRADING OF ENCEPHALOPATHY IN CIRRHOTIC PATIENTS

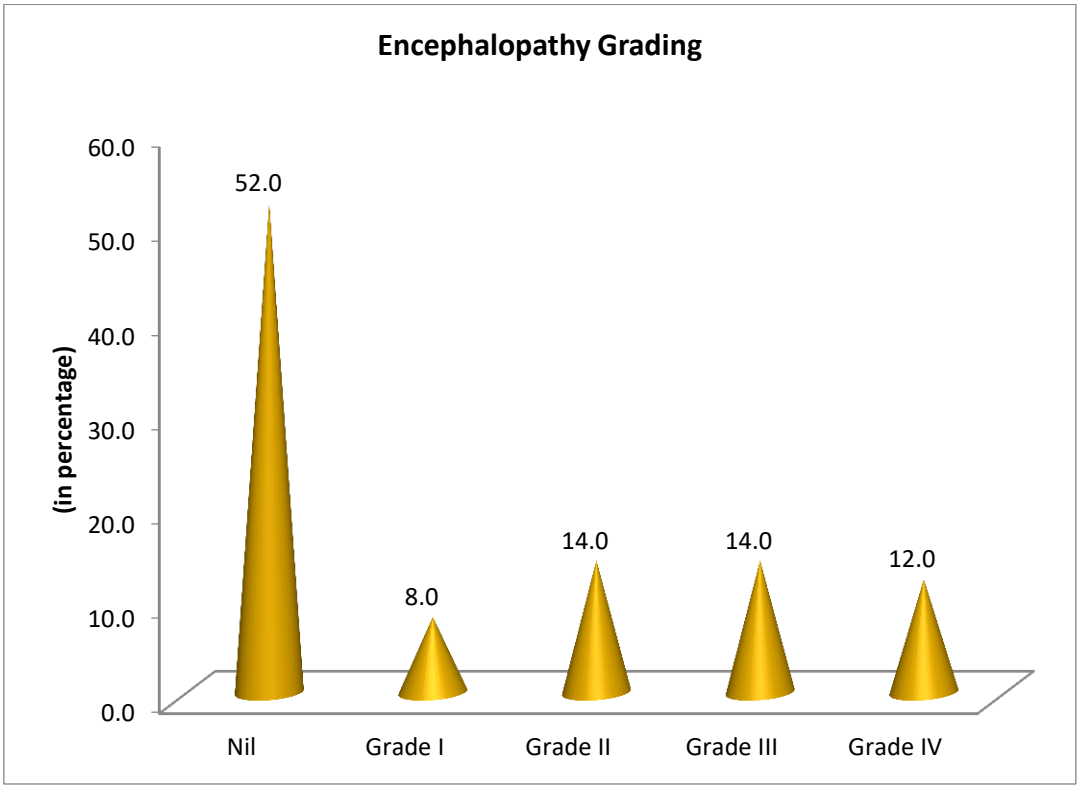
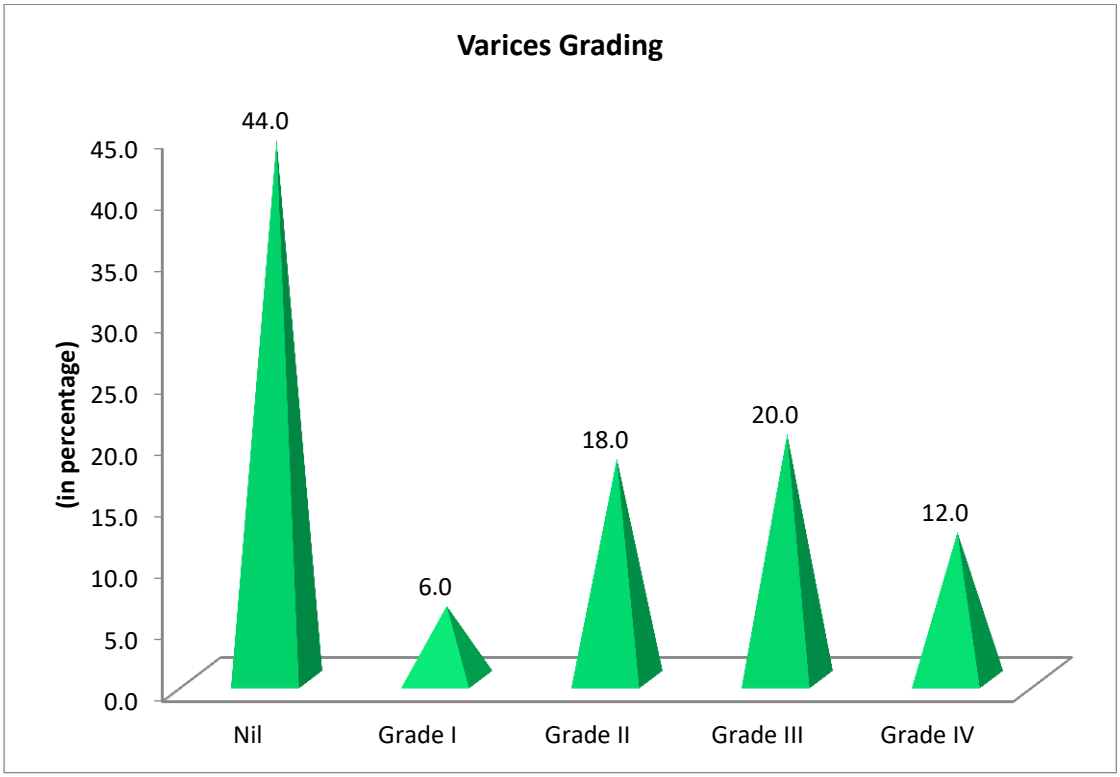


TABLE 5 : GRADING OF ENCEPHALOPATHY IN STUDY POPULATION

Encephalopathy Grading	n (%)
Nil	26 (52.0)
Grade I	4 (8.0)
Grade II	7 (14.0)
Grade III	7 (14.0)
Grade IV	6 (12.0)
Total	50 (100.0)

6. GRADING OF VARICES IN STUDY POPULATION

FIG 6: DIAGRAM PREDICTING THE VARICEAL GRADING IN ENCEPHALOPATHY



Varices Grading	n (%)
Nil	22 (44.0)
Grade I	3 (6.0)
Grade II	9 (18.0)
Grade III	10 (20.0)
Grade IV	6 (12.0)
Total	50 (100.0)

TABLE 6 : VARICEAL GRADING IN STUDY POPULATION

7.CORRELATION OF PROLACTIN VALUE WITH VARICEAL GRADING

TABLE 7 : CORRELATION OF SERUM PROLACTIN LEVEL WITH SEVERITY OF VARICES

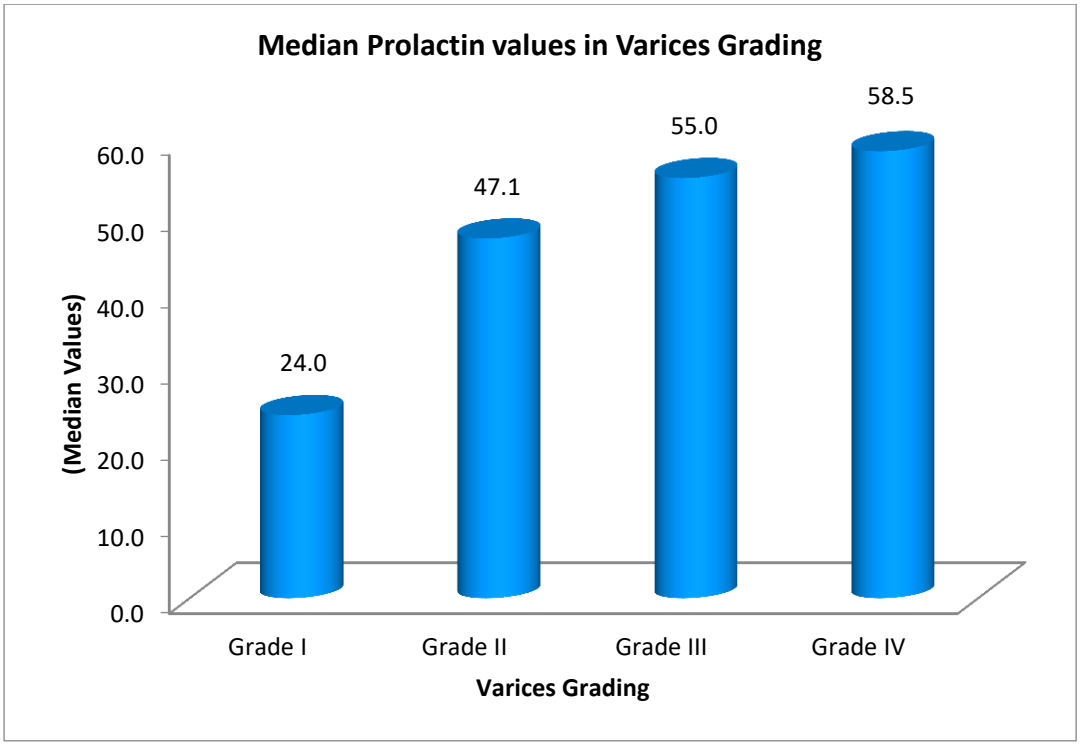


TABLE 7: CORRELATION OF SERUM PROLACTIN LEVEL WITH SEVERITY OF VARICES

	Varices Grading			
	Grade I (n=3)	Grade II (n=9)	Grade III (n=10)	Grade IV (n=6)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Prolactin	24.0 (8.0, 40.0)	47.1 (31.1, 60.3)	55.0 (47.7, 59.2)	58.5 (54.5, 61.7)
p-value	0.043 (Significant)			

8.HEPATIC ENCEPHALOPATHY

TABLE 8: PATIENTS PRESENTING WITH AND WITHOUT HEPATIC ENCEPHALOPATHY

	Encephalopathy	
	Without Encephalopathy (n=26)	With Encephalopathy (n=24)
	Median (IQR)	Median (IQR)
Prolactin	8.6 (7.9, 14.0)	56.5 (47.3, 59.9)
p-value	<0.001 (Significant)	

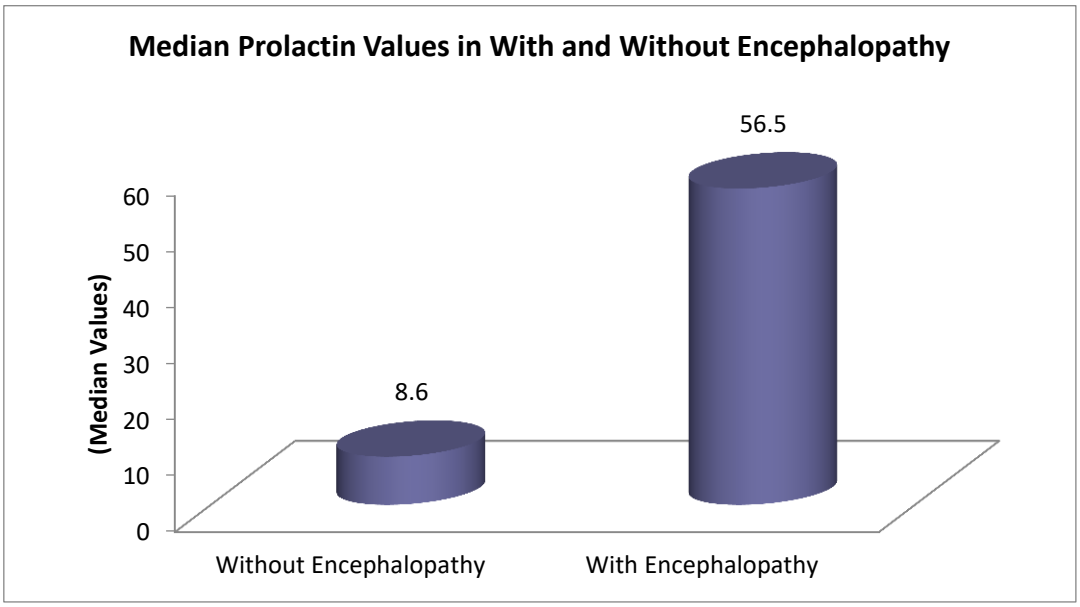


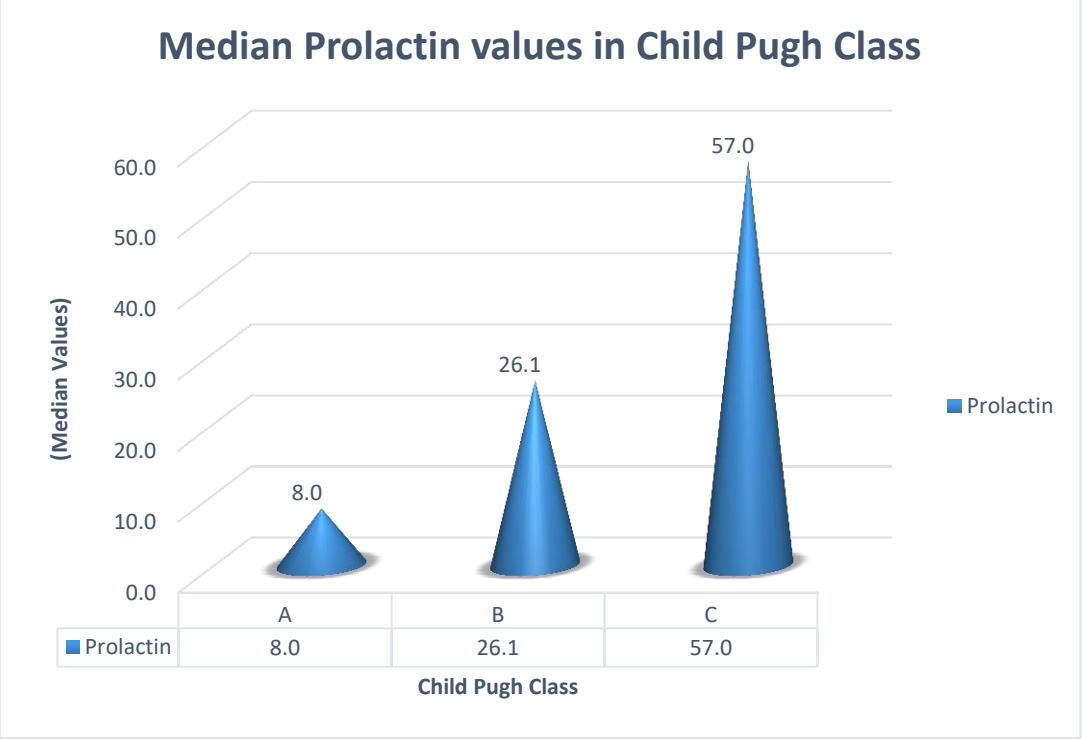
FIG 8: SHOWING THE CORRELATION OF SERUM PROLACTIN VALUE WITH HEPATIC ENCEPHALOPATHY

9.CHILD PUGH SCORE TO PROLACTIN

TAB 9 : CORRELATION OF SERUM PROLACTIN TO CHILD PUGH SCORE

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Child Pugh-Score	9.32	3.5	0.930	<0.001 (Significant)
Prolactin	33.3	22.7		

FIG 9 : DIAGRAM SHOWING CORRELATION OF PROLACITN WITH CHILD PUGH SCORE



	Child Pugh/Class		
	A (n=19)	B (n=7)	C (n=24)
	Median (IQR)	IQR)	Median (IQR)
Prolactin	8.0 (7.0, 9.7)	26.1 (20.2, 33.0)	57.0 (48.5, 60.0)
p-value	<0.001 (Significant)		

DISCUSSION

Prolactin level in hepatic dysfunction is always controversial.

Among the neurotransmitter alteration, the principal one to be documented was dopamine. Dopamine is limited by the fact that it cannot be measured in any of the body fluids or brain. Since dopamine exerts negative control over prolactin, few studies from the west have shown prolactin to be a prognostic marker.[1,2]

Elevation of prolactin is attributed mainly to the fall in dopamine levels in the

tuberoinfundibular tract. Hormonal disturbance in cirrhosis has been evaluated by few researchers, and the studies have established lower T3 and cortisol levels with raised prolactin in the serum.[3] Decompensated liver function leads to an alteration in the type of amino acids entering the central nervous system. Circulating concentrations of aromatic amino acids have been found to increase leading to an increase in the synthesis of false neurotransmitters such as octopamine and phenylethanolamine.[8]

In our study population of 50 cirrhotic patients of various etiologies, Alcohol tops the list in males with most of them are in the age group of 31 to 40 years. , while in females viral etiologies play an important role.

On comparing the Prolactin level, with the various complications of chronic liver disease like Ascites , oesophageal varices and hepatic

encephalopathy we are able to find a significant correlation with the severity of the disease.

The mean prolactin value found to be 56ng/ml in patients with massive ascites ; and in patients with grade 3 or 4 varices it is found to be around 55 ng/ml and 58 ng/ml respectively. Thus it has better correlation with severity of disease in our study population. A similar correlation of mortality to serum prolactin levels was observed by McClain *et al*.[10] and Sharma *et al*.[11] with a higher risk of mortality with serum prolactin values of >50 ng/ml.

Prolactin release in human beings is normally associated with a pulsatile pattern, but a constant 24 h elevation has been found in patients with cirrhosis liver.[3] Cases of hypogonadism have also been reported in patients with cirrhosis attributing to hyperprolactinemia.[4]

Although few researchers have associated the levels of prolactin with Child–Pugh's category of cirrhosis patients,the present study had few patient numbers in each of the categories ,the prolactin value found to be significantly correlate with the CHILD PUGH CLASS in assessing the severity of the disease.

Mean prolactin value was found to be , 8.0, 26 and 56 ng/ml in Child Pugh Class A ,B and C found to be increasing correlating with the severity of the disease.

Mukherjee *et al*.[12] analyzed the prolactin levels in patients with hepatic cirrhosis and found a higher levels in patients with encephalopathy and mortality.

In patients with and without encephalopathy, mean prolactin value found to be 56ng/ml and 8ng/ml .Thus prolactin level founds to be significantly correlated with the patients having encephalopathy. Also, the authors found out a direct correlation between the clinico-biochemical severities of the condition and mortality. They also found out a cut-off level of 50 ng/ml of prolactin to predict the mortality, Koller *et al*.[4].

Thus prolactin level not only help in assessing the severity of the disease , it also helps in predicting the complications at an earlier stage of the disease process.

CONCLUSION

Prolactin level rises in hepatic cirrhosis ,with the loss of normal circadian rhythm. Since the dopamine level cannot be directly measured in the body fluids , we used prolactin to measure the severity of the liver disease, as it is normally kept under the check of dopamine .Prolactin level significantly correlates with severity of the liver disease and predicting the risk of complications and helpful in preventing them. The rise in prolactin level also had a synonymous relationship with the Child Pugh Scoring system thus validating the use of Prolactin as a prognostic marker in hepatic cirrhosis.

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.

PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints:

Past History:

H/o DM, HT, CKD, CVD, DRUG INTAKE, CAD, Thyroid disorders,

Alcohol intake

Clinical Examination:

General Examination:

Consciousness,

Pallor,

Jaundice,

Clubbing,

Lymphadenopathy,

Hydration status

Vitals:

PR

BP

RR

SpO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

a) Complete blood count

b) Renal function test

c) Liver function test

d) Urine routine

e) Serum electrolyte

f) HBsAg

g) HCV

h) Prothrombin time ,aPTT and INR

i) Serum prolactin

j) Electrocardiogram

k) Echo

l) Chest X ray

m) USG abdomen

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Pravin prabhu
Course	:	PG in MD., General Medicine
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Correlating of serum prolactin level to child pugh scoring system in cirrhosis of liver in assessing the severity of the disease
Ethical Committee as on	:	02.06.2017

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

DEAN
Madurai Medical College
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Gmail pravin prabhu <drpravin1706@gmail.com>

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