A Dissertation on

A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD-PUGH SCORING IN CIRRHOSIS CHENNAI – 600 001.

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

APRIL 2017

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. RAJASEKARA PANDIAN .T.K,** Post - Graduate Student (JUNE 2014 TO MAY 2017) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**A STUDY TO CORRELATE SERUM PROLACTN AND CHILD-PUGH SCORING IN CIRRHOSIS, CHENNAI – 600001"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2017.

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DECLARATION

I, **Dr. RAJASEKARA PANDIAN .T.K ,** declare that I carried out this work on "**A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD-PUGH SCORING IN CIRRHOSIS, CHENNAI - 600001**" at the Medical wards of Government Stanley Hospital during the period March 2016 to July 2016. I also declare that this bonafide work or a part of this work was not submitted by me or any other 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 fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

DR. RAJASEKARA PANDIAN .T.K

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A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD PUGH SCORING IN CIRRHOSIS

INTRODUCTION

Cirrhosis is derived from greek word kirrhos meaning tawny or orange and osis meaning condition[1]. It is an end stage complication of continuous inflammation of liver parenchyma secondary to multiple etiologies. The leading causes of cirrhosis is viral hepatitis and alcohol[1] .Chronic liver disease progresses to cirrhosis may occur in weeks as in complete biliary obstruction or years in chronic hepatitis.

EPIDEMIOLOGY

The prevalence of cirrhosis is not known exactly, in USA the prevalence is about 0.15% ,there are many undiagnosed cirrhosis secondary to NASH and Hepatitis C. Similar level of prevalence is noted in Europe and Asia. Another factor which underestimates cirrhosis prevalence is compensated cirrhosis.

Around 80% of persons on infection with hepatitis C will develop chronic infection. Around 20% of those with chronic infection will go on to develop cirrhosis. Mostly these persons will be alcoholic and true incidence of hepatitis C related cirrhosis cannot be estimated.[2]

Around 5% will develop chronic infection after encounter with hepatitis B virus. Cirrhosis will occur in around 20% of the patients with chronic infection.[2]

Hemochromatosis leads to cirrhosis in 2% of affected women and 10% of affected men. There are no specific data regarding percentage of patients with other parenchymal liver disease developing cirrhosis.

REVERSAL OF FIBROSIS

Observations from clinical and experimental studies has given hopeful results that when the inciting agent is removed ,there is improvement in hepatic histology as shown after relieving of obstruction in cholestatic jaundice. The pathways targeted for reversing the fibrosis are angiotensin, tyrosine kinase receptor , matrix degrading proteases and integrins. These pathways aim at reversing the activated hepatic stellate cell by apoptosis, senescence, deactivation. Only early stages of fibrosis is reversible, not late stages.[3]

PROGNOSIS

On comparing with normal population, patient with decompensated cirrhosis will have 10 fold increased risk of death. Patients with compensated cirrhosis will have 5 fold increased risk of death . Median survival of patients with compensated cirrhosis is 9 to 12 years while patients with decompensated cirrhosis is 2 years.[4]

In Danish population study, survival probability of cirrhosis patients was estimated to be 66% at 1 year , 38% at 5 years ,22% at 10 years. In Danish study median survival of cirrhotic patients without complications was 4 years, 1 year survival of 83% for compensated cirrhosis ,80% with variceal bleeding,71% with ascites , 51% with ascites and variceal bleeding and 36% with hepatic encephalopathy.[4]

Prognosis depends not only on the cirrhosis severity but also on the comorbid illness present. Scores available to determine the severity of cirrhosis are child-pugh-turcott scoring and meld score and Von willebrand factor levels. Apart from the complications arising from cirrhosis infections and renal failure are also important cause of mortality in cirrhosis.[4]

REVIEW OF LITERATURE

Cirrhosis is a complication occurring in the liver following continuous exposure to agents causing hepatic inflammation and damage. The hepatocytes are replaced by fibrotic tissue and normal liver architecture replaced by nodular hepatocyte regeneration. Due to loss of functioning hepatocytes, various derangements occur in the body manifesting as jaundice, ascites, pedal edema, portal hypertension, hypoalbuminemia and leading to complications such as spontaneous bacterial peritonitis, hematemesis, hepatorenal syndrome, hepatopulmonary syndrome, hepatic encephalopathy, hepatocellular carcinoma, cirrhotic cardiomyopathy. Not all cirrhosis will have both fibrosis and nodularity like nodular regenerative hyperplasia characterized by only

nodularity and no fibrosis , schistosomiasis characterized by symmer pipestem fibrosis and no nodules.[5]

CLASSIFICATION

Cirrhosis classification is based on morphological and etiological types

Morphological classification

Macronodular : nodular size more than 3mm

Micronodular : nodular size less than 3mm

Mixed pattern : both macronodules and micronodules are seen.

Etiological classification

It is based on biochemical, histological ,genetic and epidemiological data by which the likely agent determined.

Cryptogenic cirrhosis etiology is most to be non alcoholic steatohepatitis.[5]

ETIOLOGY OF CIRRHOSIS

Infections(hepatitis B,C,D)

Alcohol

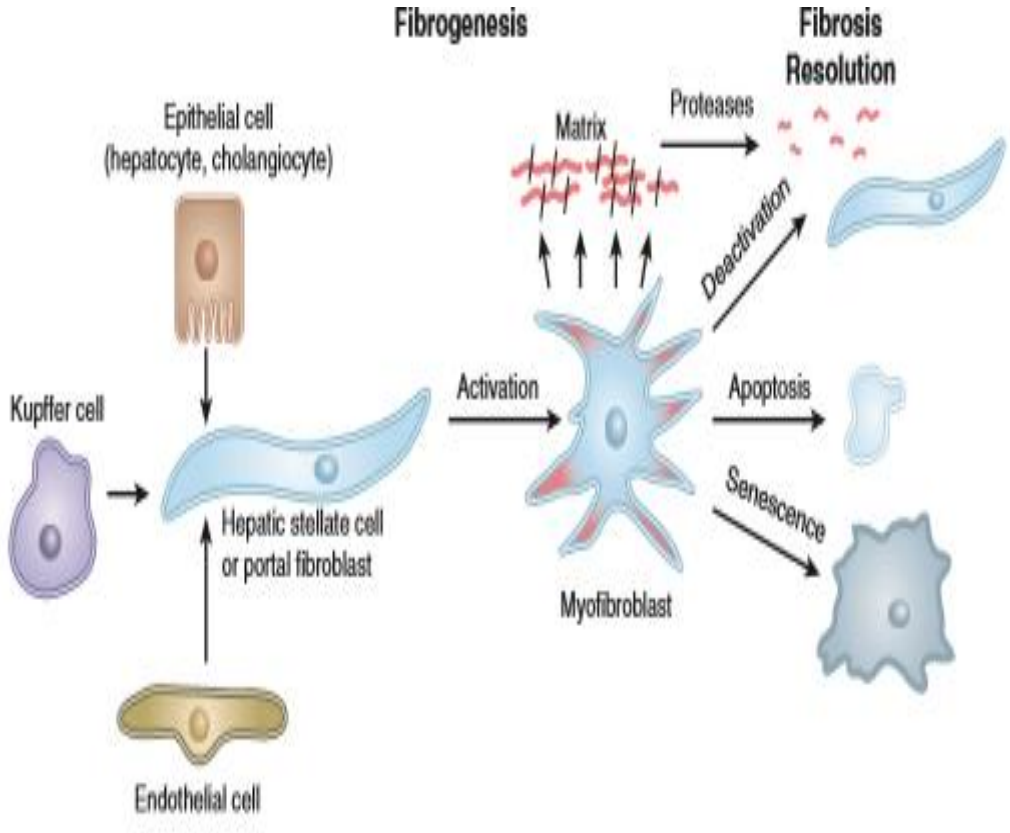
Autoimmune hepatitis

Cholestasis (primary biliary cirrhosis, secondary biliary cirrhosis, primary sclerosing cholangitis)

Metabolic (Wilson, hemochromatosis, alpha1 antitrypsin deficiency)

Vascular(budd-chiari syndrome, cardiac cirrhosis, sinusoidal obstruction syndrome).[5]

PATHOGENESIS OF CIRRHOSIS OF LIVER



Hepatic stellate cells are the principal cells which on activation leads to fibrotic changes in the liver architecture. These cells are located in the space of disse ,lying albuminal to the sinusoidal endothelial cells. On activation stellate cells transform to myofibroblast , characterized by contractility , motility and actin expression.The matrix produced by stellate cells ,fibronectin is the earliest

matrix, which leads to production of other matrix which leads to deposition of collagen and fibrosis occurs.

Among the various pathways of stellate cell activation, most implicated are the kinase activation pathways mediated through platelet derived growth factor and integrin signalling pathways. Other cells apart from hepatic stellate cells having a role in cirrhosis are hepatic epithelial cell and portal fibroblast. Hepatic fibroblast when injured as in case of cholestatic injury in primary biliary cirrhosis and primary sclerosing cholangitis leads to cirrhosis .Epithelial cell injury following apoptosis ,cell necrosis will attract stellate cells . Recently sinusoidal epithelial cells are also implicated in development of fibrosis. Angiogenesis also implicated as it leads to activation of stellate cells by paracrine pathways .[6]

AST/PLATELET RATIO INDEX:

BONACINI CIRHOSIS DETERMINANT SCORE:

LOK INDEX:

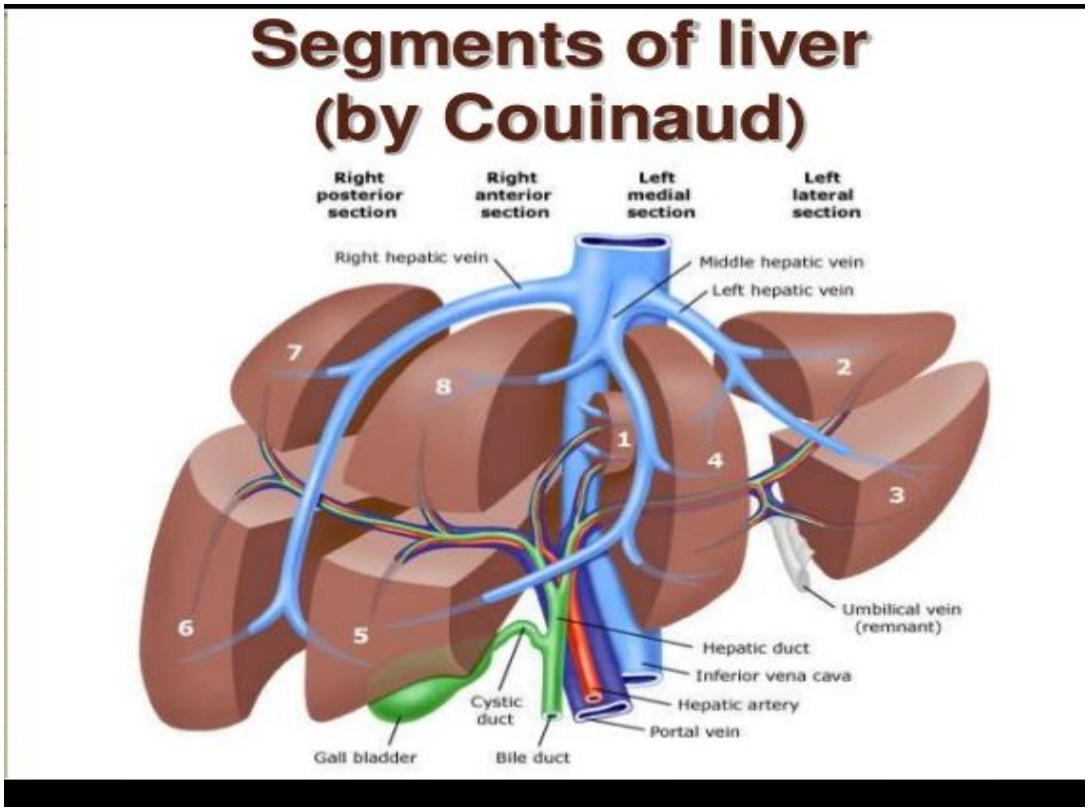
AST/platelet ratio index (APRI)[*]
(AST/upper limit of normal AST) × (100/platelet count [$\times 10^3$/mm^3])

Bonacini cirrhosis discriminant score (CDS)[†]
Platelet score + ALT/AST ratio score + INR score

Score	Platelets ($\times 10^3$/mm^3)	ALT/AST ratio	INR
0	>340	>1.7	<1.1
1	280-340	1.2-1.7	1.1-1.4
2	220-279	0.6-1.19	>1.4
3	160-219	<0.6	-
4	100-159	-	-
5	40-99	-	-
6	<40	-	-

Lok index[‡]
exp (log odds) / [1 + exp(log odds)]
log odds = − 5.56 − (0.0089 × platelet count [$\times 10^3$/mm^3]) + (1.26 × AST/ALT ratio) + (5.27 × INR)

ANATOMY OF THE LIVER



Liver is surrounded by parietal peritoneum except in the bare area of liver , which is in direct contact with diaphragm. The peritoneal reflections around the bare area of liver are superior coronary ligament , inferior coronary ligament ,right triangular ligament and left triangular ligaments. Liver as traditionally taught has four lobes named as right lobe ,left lobe, caudate and quadrate lobe of liver. The falciform ligament divides liver into right and left lobe , the quadrate lobe is defined by gallbladder fossa ,porta hepatis and ligamentum teres ,caudate lobe is delineated by inferior venacava groove, porta hepatis and ligamentum venousum fissure. These division is anatomical and not functional division. The true right and left lobe of liver is separated by cantlie's line, an imaginary line drawn from bed of gall bladder fossa and notch of inferior vena cava. Functional division of liver is determined by the arterial blood supply, portal venous blood supply, biliary drainage and hepatic venous drainage, as two segments and these segments are further divided into subsegments . Many functional systems are defined but mostly used system is Couinaud (based on portal and hepatic veins) and other system is Healey and Scroy(based on bile duct distribution). The subsegments are assigned from one to eight with the caudate lobe assigned number 1 and other subsegments in clockwise rotation. [8]

VASCULAR SUPPLY

The liver approximately receives blood supply from both hepatic artery and portal vein. Hepatic artery supplies around 60% of oxygen and 30% of blood supply. Portal vein supplies 70% of blood and 40% of oxygen. Hepatic artery arises from celiac trunk, sometimes it may arise from superior mesenteric artery. Common variations are left hepatic artery arising from left gastric artery and right hepatic arising from superior mesenteric artery. Portal vein is formed by the confluence of superior mesenteric vein and splenic vein. Venous drainage is by three hepatic veins draining into inferior vena cava . [9]

GLISSON'S CAPSULE

It is an intra parenchymal fibrous sheath covering the arteries, portal veins and bile ducts except hepatic veins.

NERVE SUPPLY

Hepatic nerve plexus which runs along portal vein and hepatic artery. Sympathetic fibres arise from the celiac plexus , whereas parasympathetic arises from the anterior and posterior vagal trunks. Although the function of nerve supply is still not clear ,activation results in vasoconstriction of blood vessels.

Referred pain is perceived in the T9 – L2 segment, around hypochondrium and umbilicus.

LIVER CELL TYPES

HEPATOCYTES

These cells are polyhedral approximately 20-30micrometre in size. Around 30% of cells are binucleate and polarized cells. The plasma membrane has three surfaces sinusoidal surface, canalicular surface, contiguous surface. The sinusoidal and canalicular surface has microvilli. Space of disse is the space between sinusoidal villi and endothelial villi.

BILE DUCT EPITHELIAL CELLS

It comprises of large and small subpopulations of cells, whose size correlates roughly to the diameter of intra hepatic bile ducts. Endoplasmic reticulum is well developed in large cholangiocytes than small cholangiocytes. These cells are highly polarized.

HEPATIC SINUSOIDAL ENDOTHELIAL CELLS

These cells contribute around 20 % of liver cells. These cells have fenestrations and extensions that form sieve like plates. These cells do not form intracellular junctions and simply overlap each other. There is no basement membrane and fenestra are present through which the plasma communicates with sinusoidal cells.[10]

KUPFFER CELLS

These are specialized tissue macrophages which constitute around 80% - 90% of tissue macrophages overall in the body. Remove toxic pathogenic material

from blood reaching liver through portal vein. The cells are located in sinusoidal lumen and are in direct contact with endothelial surface. Numbers increase following injury by infectious , inflammatory and chemical agents.[11]

STELLATE CELLS

Otherwise known as Ito cells or perisinusoidal cells, located in the peri sinusoidal space of disse. Special stain used is gold chloride, routine histological appearance is cell with multiple fat lobules. Stellate cells constitute around 5%-8% of total liver cells. It is quiescent normally. Stellate cells store vitamin –A as retinol esters.

PITCELLS

These cells are the natural killer cells of the liver. Located in sinusoidal lumen along with kupffer cells, adhered to the wall of sinusoids. Cytoplasm contains dense granules which appear as pits , hence the name. The pit cells are short lived and are replenished from extrahepatic sources. Similar to systemic natural killer cells, pit cells represent OX-18 antigen . They donot represent pan-T cell marker and OX-19. The source of pit cells is still not clear. They might have a role to play in graft rejection.

LIVER FUNCTIONS

The liver has many functional capabilities in the form of synthetic , catabolic, metabolic and detoxification . Synthetic functions include synthesis of plasma proteins, clotting factors, glycogen synthesis , bile acid synthesis, carbohydrate

,protein, lipid metabolism. These functions will be altered in cirrhosis and these changes result in complications occurring in cirrhosis.

Around 100 grams of glycogen is synthesised and stored in hepatocytes via glycogenesis. When needed by body these glycogen is broken down into glucose and supplemented to the body.

Liver also has main function in the protein metabolism both synthesis and catabolism. Aminoacids are also synthesised by the liver . Clotting factors are also synthesised by the liver like fibrinogen, prothrombin, labile factor, antihemophillic factor A , christmas factor ,stuart prower factor , Hageman factor, fibrin stabilizing factor also with protein c, protein s, antithrombin. The first factor to decrease is antihemophilic factor because of its short half life followed by Christmas factor and stuart prower factor . Labile factor is not vitamin k dependent factor ,so prolonged prothrombin time secondary to vitamin k deficiency can be ruled out from liver dysfunction. Labile factor can also be used as a prognostic marker in patients with acute liver cell failure. Values below 20% of normal is a poor prognostic sign.[11]

In lipid metabolism cholesterol synthesis occurs along with triglycerides. Liver secretes bile which is needs for the emulsification of fat and absorption of vitamin K from diet. Part of bile is stored in gall bladder and secreted into duodenum. It also produces insulin like growth factor-1, that has an important role in childhood growth and has anabolic action in adults.

Albumin accounts for around 65% of total plasma proteins. Each day around 12-14 grams of albumin is synthesised by liver. Half-life of albumin is 21 days. Hypoalbuminemia occurs secondary to decreased production or expanded plasma volume. It is commonly seen in chronic liver disease and less commonly in acute liver cell failure. Hypoalbuminemia is not specific for paerenchymal liver disease also occurs in glomerular and gastrointestinal losses. Globulins are elevated nonspecifically in chronic liver disease. The pattern of elevation may provide clue to the primary liver disease[12].

Elevated IgG – Autoimmune hepatitis

Elevated IgM – Primary biliary cirrhosis

Elevated IgA- Alcoholic liver disease.

ASSESSMEMT OF LIVER FUNCTION

Liver function test includes test for hepatic synthetic, excretory , necroinflammatory activity or cholestasis. Abnormal liver biochemistry tests may be the first clue to liver disease. Normal or minimally abnormal liver biochemical tests doesnot preclude significant liver disease .

SERUM BILIRUBIN

Serum bilirubin is mostly the first evidence of underlying liver disease. Clinically detectable when serum bilirubin level more than 3mg/dl. Associated passage of dark urine or pale stool before eye manifestation occurs. Bilirubin is a metabolised product of heme rich proteins or enzymes . Following its

release into blood it is bound with albumin , taken up by hepatocytes and metabolically converted from water insoluble form to water soluble form by glucuronide conjugation. The conjugated bilirubin is secreted via canalicular membrane into bile. When serum levels of conjugated bilirubin rises, it binds with albumin to form delta bilirubin ,so it is not excreted so bilirubin level decreases after few days of recovery until these delta bilirubin are metabolized by liver. Few amount of excreted conjugated bilirubin is reabsorbed after deconjugation and intestinal bacterial action reduced to urobilinogens and reabsorbed by the enterohepatic circulation Hyperbilirubinemia is classified into unconjugated , conjugated and very high bilirubin levels.

Unconjugated bilirubinemia (less than 7 mg/dl) occurs secondary to hemolysis, ineffective erythropoiesis, gilberts syndrome.

Conjugated bilirubinemia occurs in dubin jhonson syndrome, rotor syndrome, bile transport protein defects, intrahepatic or extrahepatic cholestasis.

Very high bilirubin levels more than 30mg/dl signifies hemolysis alomg with parenchymal liver pathology or biliary obstruction . More than 60mg/dl occurs in hemoglobinopathies and along with acute hepatitis and obstructive jaundice.

Urine bilirubin positivity indicates increased conjugated hyperbilirubinemia. Urinary urobilinogen is found in patients with hemolysis, gastrointestinal hemorrhage or hepatocellular disease. Absence of urobilinogen in urine is suggestive of obstructive pathology of bile ducts.

Serum bilirubin is measured by van den bergh reaction, indirect bilirubin is estimated from subtracting direct bilirubin from total bilirubin.

SERUM AMINOTRANSFERASES

These are intracellular enzymes released from damaged hepatocytes .

Aspartate aminotransferase found in both cytosol and mitochondria .Other tissues from which it will be released following injury is heart ,kidney ,brain , pancreas, skeletal muscle. Also called as serum glutamic oxaloacetic transaminase. Normal AST levels 10 to 40 units/l.

Alanine aminotransferase is found only in cytosol ,highest concentration in liver, more specific for liver injury than aspartate amino transferase. In men level upto 30u/l is normal , in females level upto 19u/l is normal. Also called as serum glutamic pyruvic transaminase.

In alcoholic hepatitis aspartate amino transferase levels are less than 10 times the normal and a ratio of 2:1 is maintained between aspartate aminotransferase and alanine aminotransferase. The lower elevation of alanine aminotransferase is secondary to decreased pyridoxal phosphate in alcoholics[13].

In viral ,toxic and ischemic hepatitis enzyme levels will be in a ratio of 1:1 and will be more than 1000u/l. Mild to moderate elevations are seen in chronic viral hepatitis , autoimmune hepatitis ,hemochromatosis ,Wilson disease, alpha1 antitrysin deficiency.[13]

SERUM ALKALINE PHOSPHATASE

This enzyme not in hepatocyte , present in biliary canalicular membrane . Alkaline phosphatase has multiple isoenzyme forms. This test is sensitive for detection of biliary tract obstruction. Half life of alkaline phosphatase is 17 days. Levels remain elevated upto 1 week release of obstruction. The elevation is secondary to increased synthesis from liver apart from leakage from bile duct cells and removal from circulation by hepatocytes. Isolated elevation of alkaline phosphatase occurs in infiltrative liver diseases such as tumour, abscess , granulomas,and amyloidosis. High levels are seen in sclerosing cholangitis, primary biliary cirrhosis, sepsis, acquired immunodeficiency diseases and drug related cholestatic liver injury. Other than liver other causes of elevated alkaline phosphatase are bone , intestine ,kidney , placenta. Other causes are pagets disease of bone , intestinal obstruction, osteoblastic bone secondaries. The hepatic and non hepatic cause of elevated alkaline phosphatase can be differentiated by estimating either serum gamma glutamyl transpeptidase or 5 nucleotidase. Low levels of alkaline phosphatase is seen in hypothyroidism, pernicious anemia , fulminant Wilsons disease, zinc deficiency, congenital hypophosphatasia[14].

GAMMA GLUTAMYL TRANSPEPTIDASE

It is found in many different organs , high concentrations are seen in cells lining biliary canaliculi. It is a sensitive indicator but not specific for hepatobiliary disease. Elevations are seen in diabetes mellitus, myocardial

disease, pancreatic disease, renal failure. It is an inducible enzyme elevated following intake of phenytoin or alcohol. Half life is around 26 days. Its role as marker of alcohol abuse detection is limited. Major use to rule out bony causes of elevation of elevated alkaline phosphatase[15].

5’ NUCLEOTIDASE

It is found in liver canaliculi and sinusoidal plasma membrane. Elevated 5 nucleotidase along with alkaline phosphatase is specific for hepatobiliary dysfunction[16].

LACTATE DEHYDROGENASE

Lactate dehydrogenase has 5 isoenzymes of which liver specific is LDH5 isoenzyme. Elevated in conditions like shock, hepatocellular necrosis, cancer and hemolysis.

TEST FOR HEPATIC METABOLIC FUNCTIONS

ANTIPYRINE CLEARANCE

Metabolism done by cytochrome P-450 enzyme system . In chronic liver disease the metabolism time prolonged ,so halflife is increased. Good relation exists between antipyrine half life and disease severity. Disadvantage is multiple blood sampling is required[17].

AMINOPYRINE TEST

It is based on detecting 14 carbon labelled carbon dioxide in breath after administration of dimethyl amino antipyrine. Impairment occurs in both acute and chronic liver disease. In patients diagnosed to have chronic liver pathology and alcoholic hepatitis, prognosis can be assessed by doing this test[18].

CAFFEINE CLEARANCE TEST

Estimated in saliva or serum after oral intake. The accuracy is similar to the aminopyrine breath test . Not useful in estimating minor liver dysfunctions. Abnormal results possible in persons with smoking and proton pump inhibitors like cimetidine[18].

GALACTOSE ELIMINATION CAPACITY

It is cleared from blood by phosporylation of galactose in liver 30- 40 minutes after oral or intravenous administration. Hepatic functional mass is indicated when serum has more than 50mg/dl. When blood level is less than 50mg/dl it denotes about the blood flow to liver. Clearance is impaired in acute and chronic liver disease . Also in patients with metastatic hepatic neoplasms . In obstructive jaundice clearance is not impaired[18].

LIDOCAINE METABOLITE

Monoethlyglcinexylidide is a product of hepatic metabolism of lidocaine . Assessed by fluorescence polarization immune assay . It provides prognostic information about chance of life threatening effects . Assessment of the viability of donor liver allografts is done by this test[18].

OTHER LIVER FUNCTION TESTS

SERUM BILE ACIDS

Bile acids are products of cholesterol metabolism in liver along with conjugation either with taurine or glycine and excreted from liver as bile . Bile acids are helpful in fat micelles emulsification and absorption through lymphatics in the small intestine. Enterohepatic circulation is a mechanism by which part of bile acids secreted is reabsorbed. Secondary bile acids form by the action of intestinal bacteria by deconjugation. Serum bile acids raise is a marker of hepatobiliary pathology . No advantage over measuring a single bile acid or total bile acids . Normal serum bile acids with elevated unconjugated hyperbilirubinemia likely indicate hemolysis and or gilbert syndrome.

SYNTHESIS OF UREA

Urea is obtained from metabolism of proteins . The excretion from body occur from urine and intestine where urea is lysed to ammonia and carbon dioxide. Urea production can be assessed from estimation of urine urea excretion and blood urea nitrogen .It is not useful for assessment of liver dysfunction in compensated cirrhosis[18].

BROMOSULPHALEIN

Bromosulphalein clearance after intravenous dosing was used to assess liver synthetic function . But this test fell out of favour because of reports of severe

allergic reactions, lack of accuracy in distinguishing hepatocellular from obstructive jaundice[18].

INDOCYANINE GREEN

It is metabolized by the liver after intravenous administration. Bloodlevel estimated after 20 minutes of administration. The hepatic clearance of indocyanine green is through liver and it is minimally toxic. Its reliability in assessment of liver dysfunction not better than child pugh turcotte scoring[18].

PATHOLOGY OF CIRRHOSIS[19]

Liver biopsy is performed in selected patients in whom clinical, biochemical , radiological data are not suggestive of cirrhosis.

GROSS EXAMINATION

Liver surface is irregular, with multiple yellowish nodules , depending on the stage of cirrhosis ,liver may be enlarged secondary to regenerating nodules or shrunken as in end stages of cirrhosis.

PATHOLOGIC CRITERIA FOR CIRRHOSIS

Regenerating nodules

Fibrosis

Regenerative hyperplasia

Abnormal hepatic architexture

Hepatocellular abnormalities

Fragmentation of the samples

Dysplasia

Hepatocellular abnormalities

pleomorhism

INFORMATION FROM MICROSCOPY

Presence of fibrosis

Cause of cirrhosis

Grade of cell activity

SPECIAL METHODS AND STAININGS

Iron content estimation for hemochromatosis

Per iodic acid Schiff and diastase for alpha-1 antitrysin

Copper content for wilson

Immunohistochemistry for hepatitis B virus

Polymerase chain reaction for hepatitis C virus.

CLINICAL FEATURES

Cirrhosis has protean manifestations. A patient with cirrhosis may present with few or all or none of the following findings

General features

Fatigue , fever, weightloss, wasting, malaise.

Gastrointestinal

Parotid salivary gland enlargement , loose stools, gall stones, bleeding from the bowel(esophageal, rectal and stomal varices, portal hypertensive gastropathy)

Changes in hematology

Anemia (folic acid deficiency, zieve syndrome, hyperspleenism induced pancytopenia), decreased platelet and white blood cell count, impaired clotting, consumption coagulopathy, iron overload toxicity.

Respiratory features

Decreased blood oxygen levels, portopulmonary hypertension, altered ventilation perfusion, hyperventilation, reduced pulmonary diffusion , hepatic hydrothorax(usually right sided, in patients with cirrhosis without primary pulmonary and cardiac disease)

Hepatopulmonary syndrome(triad of an increased alveolar arterial gradient while breathing room air , intravascular dilatations and liver disease) characterized by orthodeoxia, clubbing and hypoxemia. Intrapulmonary shunting evidenced with constrast enhanced bubble echocardiography. In absence of liver transplantation mortality is high. Condition reverses after liver transplant.

Cardiac complication is secondary to hyperdynamic circulation because of vasodilatation.

Renal complications is due to aldosterone release in view of decreased intravascular volume , hepatorenal syndrome.

Endocrine changes

Hypogonadism (loss of libido, testicular atrophy, decreased amounts of

testosterone for male patients)

Infertility , loss of secondary sexual characteristics, dysmenorrhoea for female patients.

Feminization (palmar erythema, breast enlargement, hair loss, loss of axillary and trunk hair, spider naevus) and diabetes mellitus.

Nervous system complications

Hepatic encephalopathy and its types such as spastic paraplegia and acquired hepato -cerebral degeneration. Peripheral nerve involvement , non dominant parietal lobe involvement in the form of asterixis.

Skeletal and Muscular system

Muscle mass loss secondary to protein catabolism, clubbing ,periosteal pain, synovial reaction, osteodystrophy secondary to liver diseases, muscle spasms, paraumbilical hernia due to muscle weakness.

Skin related changes

Spider naevus, nail changes(azure lunules, terry nails, muerckes nails),scratch marks secondary to itching in cholestatic disease , palmar erythema, dupytrens contracture, clubbing, jaundice, caput medusa, easy bruising.

DIAGNOSIS OF CIRRHOSIS

Physical examination

Characteristic features of chronic parenchymal liver disease like palmar erythema, spider naevus, dupyterns contracture , breast enlargement, testicular atrophy.

Portal hypertension features like spleenomegaly, fluid collection in peritoneum, dilated veins around umbilicus, hyperdynamic circulation indicated by tachycardia, cruveilhier baumgarten syndrome(collateral through patent umbilical vein)

Hepatic encephalopathy features like , flapping tremors, altered sleep pattern , fetor hepaticus. And other features like jaundice, parotid enlargement, scanty trunk and axillary hair.

CHILD PUGH SCORING[19].

CLINICAL AND LAB CRITERIA	POINTS		
	1	2	3
ENCEPHALOPATHY	NONE	GRADE I or II	GRADE III or IV
ASCITES	NONE	MILD TO MODERATE (DIURETIC RESPONSIVE)	SEVERE (DIURETIC RESISTANT)
BILIRUBIN	<2	2-3	>3
ALBUMIN (g/dl)	>3.5	2.5-3.5	<2.5
PROTHROMBIN TIME (SECONDS OVER CONTROL)	<4	4-6	>6
INR	<1.7	1.7	1.7-2.3
CLASS A	5-6		
CLASS B	7-9		
CLASS C	10-15		

LABORATORY EVALUATION

Hepatocellular injury pattern causes elevations of aspartate aminotransferase and alanine aminotransferase. 2:1 ratio of AST/ ALT in alcoholic patients. In chronic hepatitis of most etiology except alcohol will have AST/ALT ratio equl to 1 . As the chronic hepatitis progresses ,the ratio becomes same or reversed AST/ALT.

Tests for cholestasis

Alkaline phosphatase, conjugated and unconjugated bilirubin , gamma glutamyl transpeptidase and 5 nucleotidase.

Tests for synthetic function

Assessed by prolongation of prothrombin time [20]and serum albumin level.

TEST TO DETERMINE THE ETIOLOGY

Viral markers for both hepatitis B and C virus, polymerase chain reaction to determine RNA or DNA , serum iron, total iron binding capacity , ferritin, genetic mutation for HFE gene mutation, urine copper levels and serum ceruloplasmin levels , alpha -1 antitrypsin level and protease inhibitor, for diagnosing autoimmune hepatitis serum immunoglobulins level are estimated , autoantibodies : antinuclear antibody, antimitochondrial antibody, anti liver

kidney microsomal antibody,anti smooth muscle antibody for primary biliary cirrhosis amd autoimmune hepatitis respectively. Alpha feto protein level to screen for hepatocellular carcinoma.

IMAGING STUDIES

Abdominal ultrasonography which is non invasive ,relatively inexpensive ,can easily detects ascites , biliary dilatation, screening for hepatocellular carcinoma, duplex doppler ultrasonography for hepatic and portal vein patency[21].

Computed tomography, expensive than ultrasonography, findings in cirrhosis are non –specific, may be helpful in the diagnosis of hemochromatosis, increased density of liver is suggestive[21].

Magnetic resonance imaging

Non invasive, expensive than computed tomography, better mode to differentiate suspicious liver lesions, can assess the hepatic vasculature status without constrast and Doppler ultrasound, may detect iron overload (black hypointense liver), magnetic resonance cholangiography for biliary tree imaging[21].

Radionuclide studies

Technetium-99 sulfur colloid may help in detecting cirrhosis(increased uptake in bone marrow and spleen and not by liver)[22].

Esophago gastroduodenoscopy to determine esophageal varices

LIVER BIOPSY

Gold standard for diagnosis of cirrhosis, done by either percutaneous or transjugular or laparotomy or laparascopy. Complication possible are bleeding , infection, pneumothorax, pain ,hypotension[23].

TREATMENT

Treatment options present for a few causes of cirrhosis like phlebotomy for hemochromatosis, d-peniciilamine for Wilsons disease ,avoidance of alcohol for alcohol induced cirrhosis, peg interferon alpha for chronic hepatitis C, for hepatitis B lamivudine , adefovir, entecavir, telbivudine, tenofovir , steroids for autoimmune hepatitis, ursodeoxycholic acid for primary biliary cirrhosis.

Treatment also aims towards preventing of complications and for occurred complications

Every 6 month screening with ultrasound and serum alpha fetoprotein levels for hepatocellular carcinoma.

Vaccination is advised for patients with cirrhosis for hepatitis A and hepatitis B.

Cirrhotic patients should avoid alcohol and hepatotoxins.

In end stage cirrhosis , liver transplantation is treatment of choice if the patient is appropriate candidate.

COMPLICATIONS OF CIRRHOSIS

Portal hypertension ,ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma, hepatorenal syndrome.

Portal hypertension

It is defined as increase in portal venous pressure gradient leading to opening up of collaterals which form communication between portal and systemic veins which help the portal blood to bypass the liver. The ultimate change occurring is the increased intrahepatic endothelin and decreased intrahepatic nitric oxide . The normal portal pressure is 5 to 10mmhg. Portal hypertension is said to present when portal pressure is more than 12mmhg. The normal portal blood flow is 1 to 1.5 ltr/minute. Portal hypertension is caused by multiple etiologies among which cirrhosis of liver is also one among the important cause[24]. Portal hypertension is classified as prehepatic, intrahepatic and posthepatic.

Intrahepatic causes is further classified into presinusoidal , sinusoidal ,post sinusoidal.there is overlap present in this classification system.

CAUSES OF PORTAL HYPERTENSION

Clinical effects of portal hypertension

Varices :gastroesophageal, anorectal, retroperitoneal and stomal.

Portal hypertensive gastropathy, enteropathy and colopathy.

Caput medusa

Ascites and hepatic hydrothorax

Spontaneous bacterial peritonitis.

Spleenomegaly and hyperspleenism

Hepatic encephalopathy.

Portal pressure measurement

In majority of cases the diagnosis of portal hypertension is based on clinical findings, however in some cases portal pressure measurement is done. Patency of the portal vein is assessed first before measuring the pressure. Two types of measurement are available direct and indirect. Direct measurement is accurate ,invasive , and expensive. Indirect measurement is less invasive ,safer and preferred method over direct measurement.

Treatment of portal hypertension

Pharmacotherapy

Two classes of drugs are used for the trearment of portal hypertension vasoconstrictors and vasodilators.

Vasoconstrictors used are vasopressin, somastostatin, nonselective beta blockers. These drugs reduce splanchnic blood flow that leads to a reduction in portal blood flow and pressure.

Vasodilators used are nitroglycerin, long acting nitrates , prazosin, angoitensin inhibitors. These drugs act by altering resistance by inducing changes in the intrahepatic perivenular and perisinusoidal myofibroblats and smooth muscles, there by reducing the pressure[25].

Non selective beta blocker therapy is indicated for patients in child –a and b classes, good compliance to medications and no contraindications for beta blockers.

Endoscopy

Variceal ligation of the varices has comparable success rate those achieved with propanalol.

Surgical

Eventhough portosystemic shunt surgery markedly decrease the development of variceal hemorrhage there have been reports of increased incidence of hepatic encephalopathy and decreased survival . Shunt procedures is not indicated for the prevention of initial variceal hemorrhage.

Treatment options for failed medical therapy

Transjugular intrahepatic portosystemic shunt

For low risk individuals portosystemic shunt surgery is an option.

Liver transplantation should always be considered in patients with end stage liver disease.

Management of non esophageal varices related to portal hypertension

Gastric varices that extend 5cm below the gastroesophageal junction has high risk of bleeding , application of cyanoacrylate glue has been more effective than variceal banding. Complications include bacteremia and glue embolization.

Portal hypertensive gastropathy is a common complication of portal hypertension but significant bleeding is uncommon. Only pharmacologic therapy has a role, no role for endoscopic ligation. Severity varies from diffuse mosaic mucosal pattern to diffuse mucosal haemorrhages.

Management of acute variceal bleeding

Endoscopic variceal ligation is the treatment of choice in acute variceal haemorrhages. Success rate is around 80% to 90% in initial control of variceal bleeding [26]. Pharmacologic drugs used in acute variceal bleeding is vasopressin , nitroglycerin ,somatostatin, octreotide analogues .treatment should be continued for 5 days. Rarely ballon tamponade is used nowadays but still useful in cases with endoscopic and pharmacological treatment failure.

Ascites

It is the pathologic accumulation of fluid in peritoneal cavity. Around 85% of cause is secondary to cirrhosis. The theory explaining the accumulation of fluid are underfill theory, overfill theory and peripheral arterial vasodilatation. The ascites in cirrhosis is usually insidious onset , acute onset ascites is seen in

buddchiari syndrome ,pancreatic ascites following acute pancreatitis.it can be detected clinically by shifting dullness when peritoneal fluid is more than 1500ml. Ultrasound can detect as minimal as 100ml of ascitic fluid[27] .

Grading of ascites

Grade-1 detectable after careful clinical examination

Grade-2 easily detected but small amount

Grade -3 obvious but not tense

Grade-4- tense

Refractory ascites is the one which cannot be removed or prevented by medical therapy. The two types of refractory ascites are diuretic resistant and diuretic intractable ascites. Diuretic resistant ascites is lack of response to salt restriction and maximum diuretic use. Diuretic intractable ascites is complications that preclude the use of diuretics.

Analysis of ascitic fluid

New onset ascites , routine admission or readmission of patients with ascites,clinical features suggestive of ascitic fluid infection such as fever, abdominal pain ,elevated total count, encephalopathy and renal impairment. Ascitic fluid is tapped by Z tract technique so prevent continuous oozing of ascitic fluid from tapping site .There is no contraindication for ascitic fluid tapping ,even in coagulopathy tapping is done. It gives clue regarding the cause of ascites. The various parameters estimated in ascitic fluid is cell count

,protein , sugar, culture, albumin, total protein,amylase, lactate dehydrogenase , gram stain, triglyceride, bilirubin, cholesterol, alpha fetoprotein, fibronectin. The single most important investigation is cell count to rule out ascitic fluid infection.

Serum ascites albumin gradient

A saag of 1.1g/dl or more is suggestive of portal hypertension induced ascites , a low saag indicates non portal hypertension induced ascites.

High SAAG ascites: cirrhosis, alcoholic hepatitis, cardiac ascites, massive liver metastases, fulminant hepatic failure, budd chiari syndrome, portal vein thrombosis,sinusoidal obstruction syndrome,acute fatty liver of pregnancy, myxedema, mixed ascites.

Low SAAG ascites: peritoneal carcinomatosis, pancreatic ascites , tuberculous peritonitis, biliary ascites, nephritic syndrome,connective tissue disordes, post operative lymphatic leak, intestinal obstruction or infarction.

Treatment of ascites

Establishing the cause of ascites is the important aspect of diagnosis. The possible reasons for the ascites in case of cirrhosis of liver are variceal bleed, hepatocellular carcinoma with or without portal vein thrombosis, non compliance with diuretics , use of non steroidal anti inflammatory drugs ,iatrogenic.

Sodium restriction is the main stay of treatment of ascites. Sodium intake less than 2grms/day is a realistic goal. Salt restricted diet alone will eliminate ascites in around 10% of cases.

Diuretic therapy

Required in 90% of individuals with ascites, especially those with moderate and tense ascites. Complications limiting the use of diuretics are azotemia, electrolyte abnormalities, intravascular hypovolemia, hepatic encephalopathy.

Diuretic approach

Spiranolactone is the diuretic of choice for single agent therapy of ascites. It is less potent natriuretic,hypokalemia uncommon, long half life of spiranalactone so once daily dosing is enough. Maximum dosing is 400mg.

Combination of spiranalactone and furosemide is the most effective treatment for ascites with sodium restriction. The initial dosing of spiranalactone is 100mg and that of furosemide is 40mg. Maximum dosage reached with spiranalactone is 400mg/day and that of furosemide is 160mg/day.

Management of diuretic refractory ascites

Large volume paracentesis- draining around 5ltrs of ascitic fluid by therapeutic paracentesis. Transjugular intra hepatic portosystemic shunt should be considered in patients frequently requiring large volume paracentesis. Liver transplantation to be considered for suitable candidates.

ASCITIC FLUID INFECTIONS

Ascitic fluid infections can classified as the following categories

Spontaneous bacterial peritonitis, culture negative neutrocytic ascites, monomicrobial non neutrocytic bacterascites , polymicrobial bacterascites, secondary bacterial peritonitis.

SPONTANEOUS BACTERIAL PERITONITIS has a positive ascitic fluid culture and polymorphonuclear cell count more than 250cells/cumm. There should be no intraabdominal surgical source of infection. The most common organism are Escherichia coli, streptococcus pneumonia , klebsiella pneumonia. Fungi doesnot usually cause spontaneous peritonitis but can occur in immunocompromised individuals. Treatment is with third generation cephalosporins particularly cefotaxim 2grms intravenous 8^{th} hrly for 5 days. Alternate regimens include fluoroquinolones and amoxicillin clavulanic acid[28].

CULTURE NEGATIVE NEUTROCYTIC ASCITES has a negative ascitic fluid culture but polymorhonuclear cell count more than 250cells/cumm. There should be no intra abdominal source of infection. It represents resolution of bacterial infection from translocation of gut bacteria secondary to antibacterial properties of ascitic fluid[29].

Both spontaneous bacterial peritonitis and culture negative neutrocytic ascites have similar mortality rates , both entities has to be treated.

Other causes of neutrocytic ascites should be considered such as peritoneal carcinomatosis, pancreatitis , tuberculuos peritonitis, peritonitis related to connective tissue diseases, hemorrhage into ascitic fluid.

MONOBACTERIAL NON NEUTROCYTIC ASCITES is a variant of spontaneous bacterial peritonitis in which culture yields a single organism but neutrophil count less than 250cells/cumm. In this situation patient should be monitored carefully for development of symptoms of fever , abdominal pain. Repeat ascitic fluid cell count should be done and should be treated if patient becomes symptomatic or cell count levels more than 250cells/cumm[30].

POLYMICROBIAL ASCITES indicates polymicrobial growth on culture with cell count less than 250cells/cumm. The reason is inadvertent bowel perforation during paracentesis . Decision regarding treatment is based on cell count ,treatment is with broad spectrum antibiotics covering both gram positive, gram negative organisms and anaerobic organisms[31].

SECONDARY BACTERIAL PERITONITIS is intrabdominal infection occurring in the presence of surgical source of infection like ulcer perforation, gall bladder perforation, hepatic abscess rupture. The cell count is more than 250cells/cumm and culture grows multiple organisms. Other findings indicate secondary bacterial infection are glucose less than 50mg/dl, elevated lactate dehydrogenase, total protein greater than 1grms/dl. Secondary peritonitis should be suspected if repeat paracentesis shows increased cell count even after treatment with appropriate antibiotics.

HEPATIC ENCEPHALOPATHY

It is a complication arising secondary to liver failure in which the sensorium is affected [32].The important aspect of diagnosis is significant liver disease should be present. Hepatic encephalopathy is of three types

TYPE-A – Related with acute liver failure

TYPE- B-Opening up of collateral circulation in the absence of liver disease.

TYPE-C – Related to chronic and end stage liver disease and portal hypertension.

Type C related hepatic encephalopathy has been graded as 4 stages in west haven grading of hepatic encephalopathy.

SONIC(SPECTRUM OF NEUROCOGNITIVE IMPAIRMENT IN CIRRHOSIS) newer classification has been introduced since 2011. According to which hepatic encephalopathy is divided into three class unimpaired , covert and overt hepatic encephalopathy[33].

Overt hepatic encephalopathy : varied spectrum of neurologic and neuropsychiatric manifestations present.

Covert or minimal hepatic encephalopathy : cirrhosis patient with normal mental and neurologic status on clinical examination but exhibit reversible and quantifiable neurophysiologic and neuropsyciatric abnormalities.

Clinical scales for assessment of OVERT hepatic encephalopathy

West haven criteria.

Hepatic encephalopathy scoring algorithm[33].

Clinical hepatic encephalopathy staging scale[34].

PATHOLOGY OF HEPATIC ENCEPHALOPATHY

There is no single theory which adequately explains the mechanism of hepatic encephalopathy. The various theory are increased ammonia secondary to failure in conversion to urea by liver and bypass of portal circulation through opened collaterals of portosystemic circulation. The ammonia crosses the blood brain barrier and causes changes in astrocytes that cause swelling of brain cells.

Inflammatory mediators and cytokines play a role along with hyperammonemia by altering the permeability of blood brain barrier, microglial activation and subsequent production of neurosteroids.

Increased benzodiazepine like compounds in the brain, manganese accumulation in basalganglia and alteration in tryptophan metabolism.

Recurrent hepatic encephalopathy : two hepatic encephalopathy episodes in one year.

Covert hepatic encephalopathy : normal neurological examination with neuropsychiatric test abnormality.

Persistent hepatic encephalopathy : low grade hepatic encephalopathy(covert encephalopathy and grade 1 encephalopathy) mental status changes with no disorientation. High grade hepatic encephalopathy (stage 2 to stage 4) mental status changes with disorientation. Spastic paraparesis is a rare variant of hepatic encephalopathy.

WEST HAVEN CRITERIA

STAGE	FEATURES
STAGE 0	NO ENCEPHALOPATHY
STAGE 1	SHORT ATTENTION SPAN, EUPHORIA OR DEPRESSION, ASTERIXIS MAY BE PRESENT
STAGE 2	LETHARGY OR APATHY, DISORIENTATION, ASTERIXIS USUALLY PRESENT
STAGE 3	SOMNOLENT, BUT RESPONSIVE TO VERBAL COMMENT SEVERE DISORIENTATION, ASTERIXIS ABSENT
STAGE 4	COMA

Laboratory tests in hepatic encephalopathy

Blood ammonia levels are not frequently measured as it doesnot change the treatment . There is not much difference in the value of venous ammonia and arterial ammonia levels. Laboratory errors occur while collection of sample and the most common errors are improper collection technique and incorrect transportation, hemolysis or use of heparin lock during venous puncture , smoking, pollution of laboratory atmosphere.

ELECTROENCEPHALOGRAM

The main eeg criterion is slowing of the mean frequency. Sensitivity varies from 43% to 100%.

CRITICAL FLICKER FREQUENCY TEST.

Based on the relation that reinal gliopathy reflects the cerebral gliopathy in hepatic encephalopathy. Correlates well with traditional pencil and paper psychometric test used to dignose hepatic encephalopathy. It helps in discriminating stage 0 hepatic encephalopathy from covert and overt encephalopathy[35].

MAGNETIC RESONANCE IMAGING

The features observed in magnetic resonance imaging are cortical atrophy, hyperintensity in t1 weighted images of basal ganglia. Proton MR spectroscopy detects a consistent increase in glutamine to glutamate signal .

TREATMENT OF HEPATIC ENCEPHALOPATHY

Generalised care for the unconscious patient . identification of the precipitating factors like sepsis,gastrointestinal hemorrhage, constipation,dietery protein overload,dehydration,hypokalemia ,alkalosis, poor compliance with lactulose therapy. Empiric therapy involves gut cleaning by enemas and administration of lactulose syrup 15 ml initially and increased to 30ml till two to three bowel movements are achieved.

Second line management involves administering gut sterilising agent like rifaximine 550mg twice daily, metronidazole 250mg four times daily, neomycin 500 mg four times daily.

Response to treatment

Patients with overt encephalopathy ,recovery is possible within 72hrs after commencing treatment. Failure to reverse following treatment ,other secondary causes should be considered like wernicke encephalopathy ,subdural hemorrhage , dehydration secondary to lactulose administration.

Type A hepatic encephalopathy

These account for small number of cases of hepatic encephalopathy, the precipitating factor is unclear, poor response to adequate treatment,cerebral edema and intracranial hyprtension are common in these group of patients and often lethal.

Management of intractable or recurrent hepatic encephalopathy

Liver transplantation and Modification of existing portosystemic shunt are the options available for intractable or recurrent hepatic encephalopathy.

Hepatorenal syndrome

It is elevation of serum creatinine more than 1.5 mg/dl ,occurring in a patient with advanced liver disease and portal hypertension. It occurs due to decreased glomerular filtrarion rate and renal plasma flow, secondary to changes occurring in systemic hemodynamics and activation of endogeneous vasoactive system[36].

Pathogenesis

There is a arterial vasodilatation that occurs by mechanisms not known secondary to portal hypertension. Vasodilatation occurs mainly in splanchnic circulation ,there by vasoconstrictor systems are activated which causes compensation for systemic vasodilatation.

Diagnostic criteria for hepatorenal syndrome

Cirrhosis with ascites

Serum creatinine level greater than 1.5mg/dl.

Lack of improvement in serum creatinine level after 2 days following diuretic withdrawal and volume expansion with albumin.

Lack of underlying kidney disease as shown by proteinuria less than 500 mg/day or recent use of nephrotoxic agents.

Absence of shock

Hepatorenal syndrome is classified into two types type-1 hrs seen in patients with cirrhosis going for sudden decompensation and type -2 hrs seen in patients with long standing refractory ascites.

Type-1 hepatorenal syndrome

Rapidly rising serum creatinine with level reaching more than 2.5mg/dl within 2 weeks. Occurs following bacterial infection ,gastrointestinal hemorrhage or therapeutic paracentesis without plasma expansion. Median survival time is 2 weeks.

Type-2 hepatorenal syndrome

Moderate and stable renal failure occurs . It occurs with relatively preserved liver , median survival is approximately six weeks.

It is important to rule out other causes of acute kidney injury in cirrhosis like acute tubular nescrosis, glomerular disease, druginduced kidney injury , prerenal azotemia.

Treatment of hepatorenal syndrome

Liver transplantation is the treatment of choice in patients with hepatorenal syndrome.

Medical management is by administration of a vasoconstrictor and a volume expander

Terlipressin 2mg every 4-6hrly along with albumin administration has reversed the renal injury in 60% of patients[37]. Recurrence of hepatorenal syndrome is around 50% and retreatment is effective.

Cirrhosis patients are assessed in severity by application of child pugh scoring which consists of the following variables albumin, ascites, bilirubin, prothrombin time, international standardized ratio, encephalopathy and each variable is assigned a score based on its severity of derangement. There was no serum biomarker which reflects on the severity of cirrhosis. Recently serum prolactin has been studied as a possible biomarker for the estimation of cirrhosis severity. The possible explanations given for the elevation are ,deranged aminoacid metabolism which leads to decreased dopaminergic levels in central nervous system which also has a role as prolactin inhibiting factor. There by as the severity of cirrhosis increases and the aminoacid metabolism also deranged causing secondary elevation of serum prolactin. In few studies serum prolactin levels has been demonsrared as a individual mortality indicator irrespective of cirrhosis severity by child pugh scoring[38,39,40].

PROLACTIN

It is also called as lactogenic or mammotrophic or galactopoetic hormone. Prolactin is synthesized in the acidophil cells . physiologically the cell increase in number and constitute over 50% of pituitary acidophils. It contains 198 aminoacids, molecular weight 25000 , halflife of 20minutes. It receptors has

similarity to growth hormone receptors . Normal serum prolctin levels in males -2 to 18ng/ml, female – 2 to 29ng/ml.

CONTROL OF SECRETION

Stimulus for prolactin secretion act via stimulating prolactin releasing factor , prolactin secretion increases 2-3hrs after sleeponset, various stress leads to increase in prolactin secretion, pregnancy , breast stimulation , primary hypothyroidism , dopamine antagonist, adrenergic blockers and section of pituitary stalk.

STIMULI THAT INHIBIT PROLACTIN SECRETION

Primarily the control of prolactin secretion is mediated through prolactin inhibiting factor, secreted tonically by hypothalamus into the pituitary by hypothalamo-pituitary portal vessels. Dopamine is the main prolactin inhibiting factor. Drugs like serotonin antagonists and dopamine agonists will inhibit prolactin secretion.

ACTIONS OF PROLACTIN

Plays an important role in the development of the mammary gland and in milk synthesis. Leads to differentiation of lobules into alveoli . Immediately after delivery prolactin stimulates galactosyltransferase activity leading to synthesis of lactose. High prolactin levels inhibit lutenising hormone and leads to anovulation.

HYPERPROLACTINEMIA

Since prolactin levels varies with various stimulus appropriate estimation is done by measuring early morning fasting levels, normally it should be less than 20ng/ml.

Whenever hyperprolactinemia is present it is important to rule out secondary causes such as drug induced, hypothyroidism , chronic kidney disease. After exclusion of secondary causes primary pituitary mass lesion should be ruled out by imaging, around 10% of cases of hyperprolactinemia will have micropituitary adenoma which is not pickedup by brain imaging.

RELATION BETWEEN PROLACTIN AND CIRRHOSIS

Cirrhosis is a end stage pathology of liver following chronic inflammation , which is diagnosed based on clinical , biochemical , imaging features . Its severity is being assessed by child pugh scoring which has variables indicating the liver function status. There is no serological biochemical marker till now which has been predicting the severity of liver damage and comparable to child pugh scoring.

Recent studies has found that serum prolactin levels has been increased in patients with cirrhosis ,without any other cause for elevation present in these patients. The rise is also comparable to the severity as assessed by child pugh scoring. In few studies very high serum prolactin has been determined to be as a mortality indicator when levels cross 50ng/ml. Few studies has not shown

consistent result and elevated prolactin in cirrhosis should evaluated separately.

CONCEPT PAPER FOR- A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD PUGH SCORING IN CIRRHOSIS

BACKGROUND INFORMATION :

Cirrhosis is a chronic condition affecting the liver characterized by replacement of hepatocytes by fibrous tissue , due to loss of hepatocytes , various derangements occur in the body manifesting as ascites ,esophageal and gastric varices, portal hypertension , hyperspleenism, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome.

The various causes of cirrhosis are alcoholconsumption, viral infections , metabolic causes(Wilsons disease, alpha 1 antitrysin deficiency, hemochromatosis), primary biliary cirrhosis, primary sclerosing cholangitis.

The severity of cirrhosis is usually assessed by child pugh scoring which consists of the following variables albumin , ascites, bilirubin, prothrombin time , international standardized ratio and hepatic encephalopathy.

Recently studies has been conducted to determine a appropriate serum marker for assessing the severity of cirrhosis . prolactin has been determined to increase in cirrhosis and its level has been found to correlate to severity assessed by child pugh scoring .

Normal serum prolactin levels

Males : 2 to 18ng/ml

Females : 2 to 29ng/ml.

OBJECTIVE:

To determine the correlation between serum prolactin levels and child pugh scoring in cirrhosis patients

PLACE OF STUDY:

Department of medicine ,Stanley medical college and hospital.

STUDY POPULATION:

100 patients of cirrhosis of varied etiology.

Age more than 18 years.

STUDY DESIGN

Longitudinal study

OPERATIONAL DEFINTION

Diagnosis of cirrhosis is based on clinical , biochemical evidence and the presence of esophageal varices , ascites with albumin gradient more than 1.1grms/l.

INCLUSION CRITERIA:

All cirrhosis patients of varied etiology.

Age more than 18 years.

EXCLUSION CRITERIA:

Acute liver cell failure

Headinjury

Hypothyroidism

Drugs increasing serum prolactin levels

Chronic kidney disease

Cranial surgery.

METHODOLOGY:

A total of 100 cirrhosis patients admitted in medical wards in Stanley hospital Chennai are included in the present study. Informed consent will be obtained from each patients. Patients are subjected for clinical examination and followed by relevant investigation. Patients improvements will be observed once in 3 days till discharge.

Patients will undergo the following investigations

Complete blood count

Random blood sugar

Renal function test

Liver function test

Serum ascitic fluid analysis

Prothrombin time and INR

Viral markers

Ultrasound abdomen

Oesophagogastroduodenoscopy

Serum prolactin

Child pugh scoring and West haven criteria are applied to the subjects to determine severity of cirrhosis and grading of hepatic encephalopathy.

WEST HAVEN CRITERIA

STAGE	FEATURES
STAGE 0	NO ENCEPHALOPATHY
STAGE 1	SHORT ATTENTION SPAN, EUPHORIA OR DEPRESSION, ASTERIXIS MAY BE PRESENT
STAGE 2	LETHARGY OR APATHY, DISORIENTATION, ASTERIXIS USUALLY PRESENT
STAGE 3	SOMNOLENT, BUT RESPONSIVE TO VERBAL COMMENT SEVERE DISORIENTATION, ASTERIXIS ABSENT
STAGE 4	COMA

CHILD PUGH SCORING

ENCEPHALOPATHY	NONE	GRADE I or II	GRADE III or IV
ASCITES	NONE	MILD TO MODERATE (DIURETIC RESPONSIVE)	SEVERE (DIURETIC RESISTANT)
BILIRUBIN	<2	2-3	>3
ALBUMIN (g/dl)	>3.5	2.5-3.5	<2.5
PROTHROMBIN TIME (SECONDS OVER CONTROL)	<4	4-6	>6
INR	<1.7	1.7	1.7-2.3
CLASS A	5-6		
CLASS B	7-9		
CLASS C	10-15		

BENEFITS OF STUDY

If association determined, serum prolactin can be used as a marker for determining severity of cirrhosis.

Groups

Groups	Definition	Number
Elevated Prolactin Group	• **Male - > 18ng/ml** • **Female- > 29ng/ml**	91
Normal Prolactin Group	• **Male -2 to 18ng/ml** • **Female-2 to 29ng/ml**	9

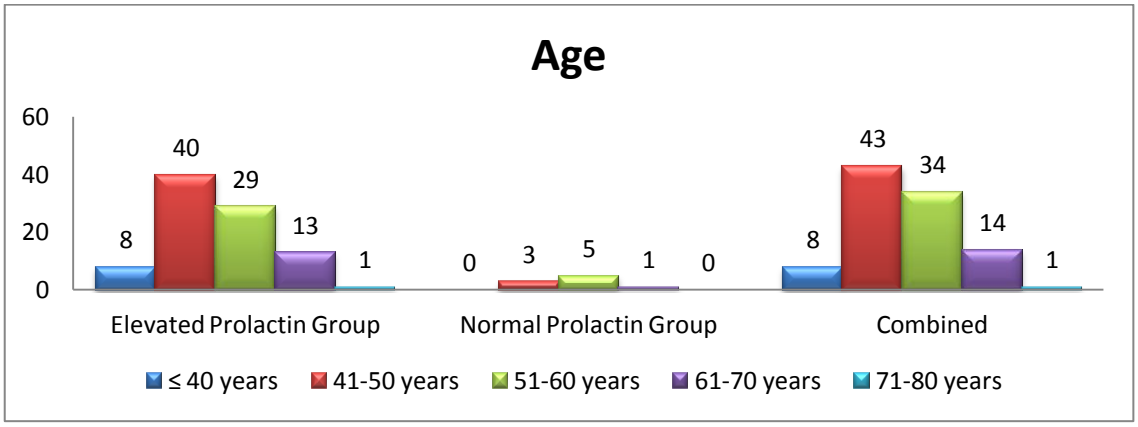
Null Hypothesis

Null Hypothesis : H0	Elevated prolactin group equal in effect compared to normal prolactin group
Alternate Hypothesis : H1	Elevated prolactin group hazardous in effect compared to normal prolactin group

Data Analysis

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

Age



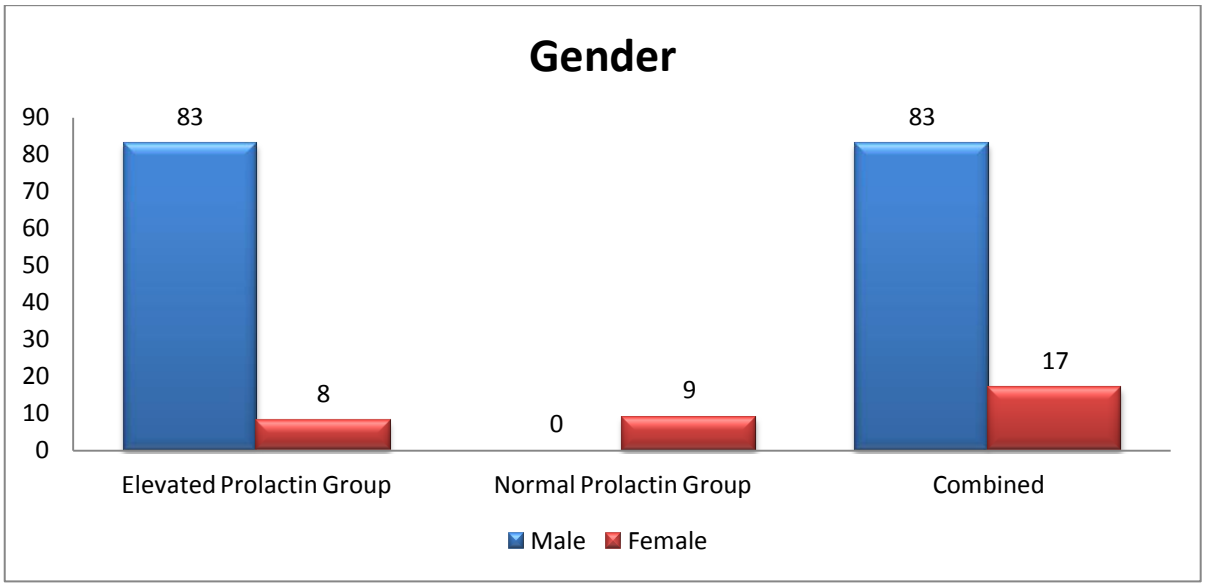
Age	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
≤ 40 years	8	0	8	8.79	0.00	8.00
41-50 years	40	3	43	43.96	33.33	43.00
51-60 years	29	5	34	31.87	55.56	34.00
61-70 years	13	1	14	14.29	11.11	14.00
71-80 years	1	0	1	1.10	0.00	1.00
Total	91	9	100	100	100	100

Age Distribution	Elevated Prolactin Group	Normal Prolactin Group	Combined
Mean	50.74	53.11	50.95
SD	8.94	6.72	8.76
P value			0.4407

Unpaired t Test

Among the study patients, there was no statistically significant difference in relation to age distribution between elevated prolactin group (mean=50.74, SD=8.94) and normal prolactin group (mean=53.11, SD=6.72) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in age distribution between the study groups.

Gender



Gender	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Male	83	0	83	91.21	0.00	83.00
Female	8	9	17	8.79	100.00	17.00
Total	91	9	100	100	100	100
P value				<0.0001		

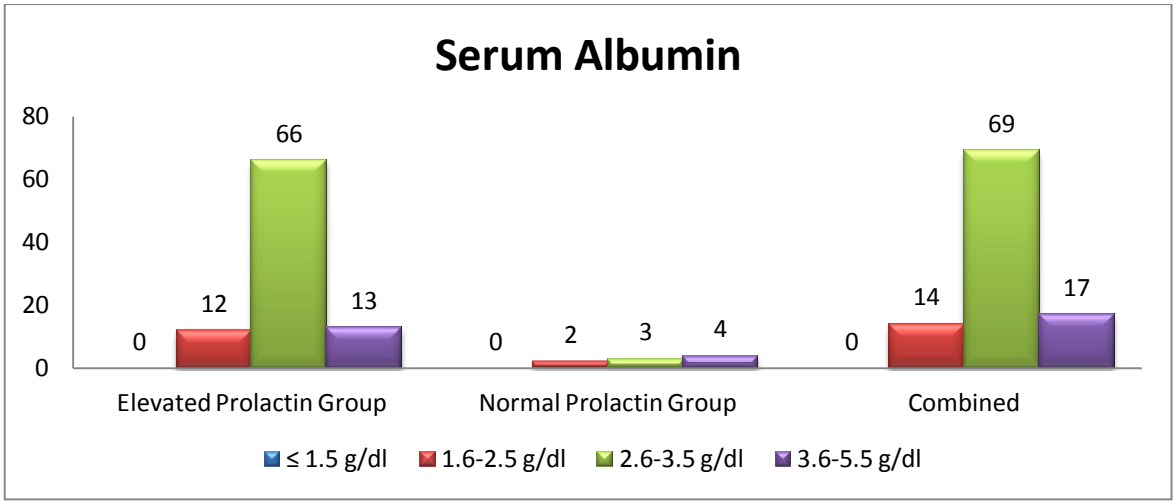
Fishers Exact Test

Among the study patients, there was a statistically significant difference in relation to gender status between elevated prolactin group (majority are males– 91.21%) and normal prolactin group (majority are females – 100.00%) with a p value of <0.05 as per fishers exact test. Therefore we reject the null hypothesis that there is no difference in gender status between the study groups

Discussion

The incidence of female gender was significantly less in elevated prolactin group compared to normal prolactin group by a percentage difference of 91.21 percentage points (91% lower). This difference is significant with a p-value of <0.0001 as per fishers exact test.

Serum Albumin



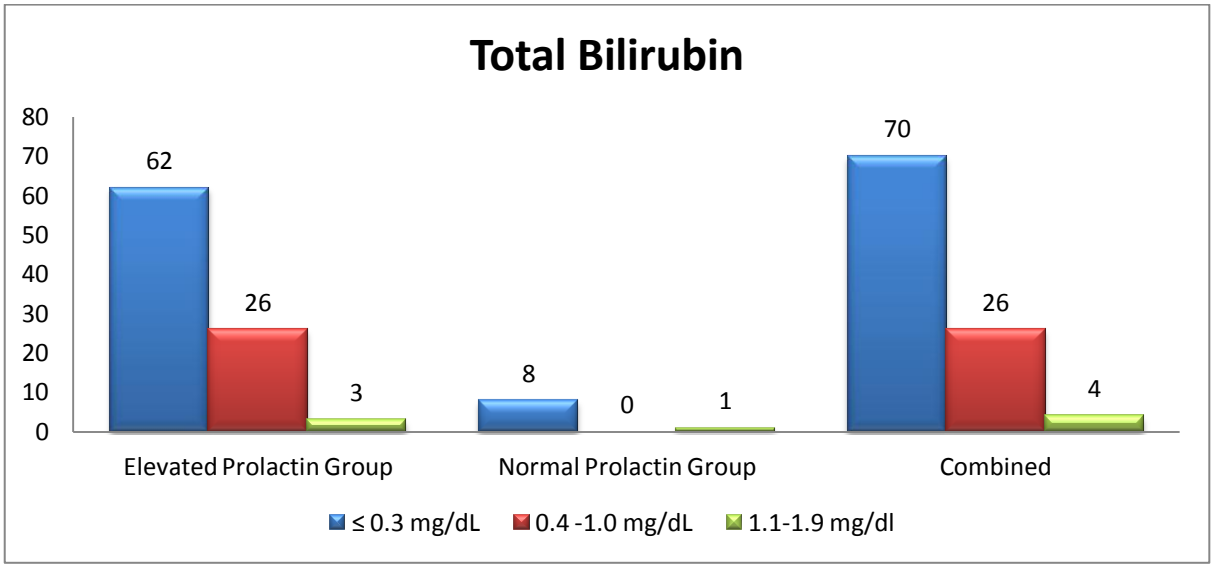
Serum Albumin	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
≤ 1.5 g/dl	0	0	0	0.00	0.00	0.00
1.6-2.5 g/dl	12	2	14	13.19	22.22	14.00
2.6-3.5 g/dl	66	3	69	72.53	33.33	69.00
3.6-5.5 g/dl	13	4	17	14.29	44.44	17.00
Total	91	9	100	100	100	100

Serum Albumin Distribution	Elevated Prolactin Group	Normal Prolactin Group	Combined
Mean	3.00	3.16	3.02
SD	0.50	0.61	0.51
P value			0.3843

Unpaired t Test

Among the study patients, there was no statistically significant difference in relation to serum albumin distribution between elevated prolactin group (mean=3.00, SD=0.50) and normal prolactin group (mean=3.16, SD=0.61) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in serum albumin distribution between the study groups

Total Bilirubin



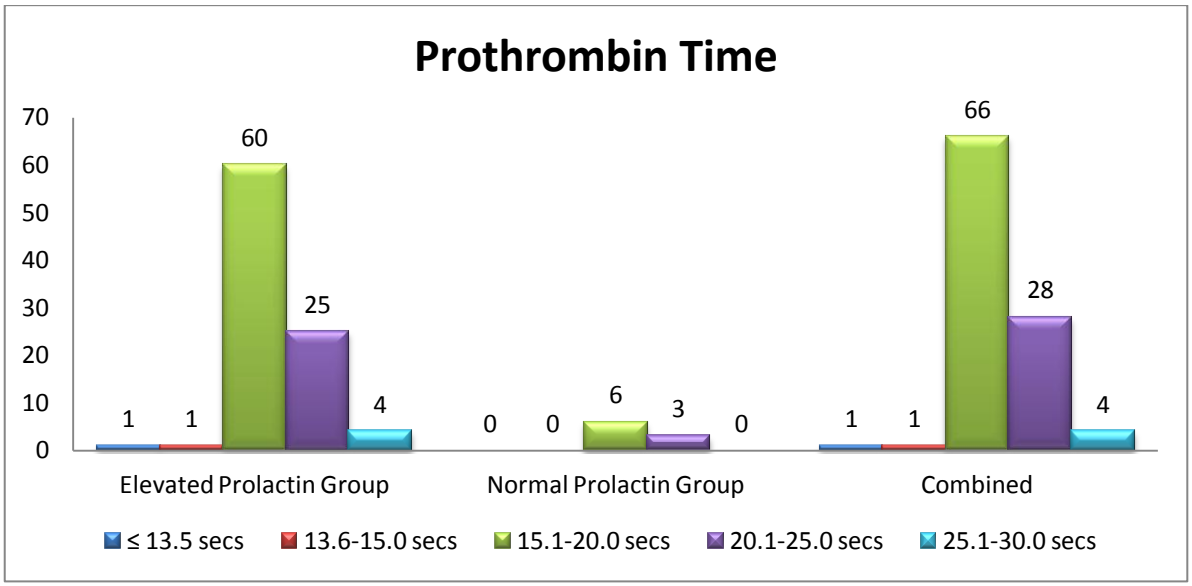
Total Bilirubin	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
≤ 0.3 mg/dL	62	8	70	68.13	88.89	70.00
0.4 -1.0 mg/dL	26	0	26	28.57	0.00	26.00
1.1-1.9 mg/dl	3	1	4	3.30	11.11	4.00
Total	91	9	100	100	100	100

Total Bilirubin Distribution	Elevated Prolactin Group	Normal Prolactin Group	Combined
Mean	1.48	1.51	1.49
SD	0.43	0.50	0.43
P value			0.8557

Unpaired t Test

Among the study patients, there was no statistically significant difference in relation to total bilirubin distribution between elevated prolactin group (mean=1.48, SD=0.43) and normal prolactin group (mean=1.51, SD=0.50) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in total bilirubin distribution between the study groups.

Prothrombin Time



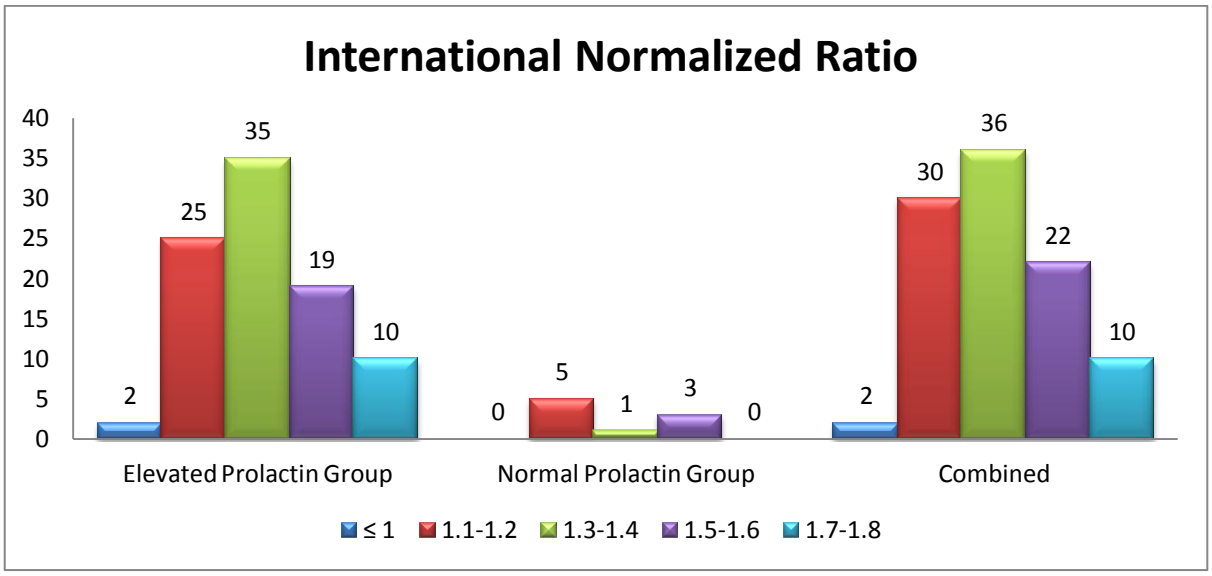
Prothrombin Time	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
≤ 13.5 secs	1	0	1	1.10	0.00	1.00
13.6-15.0 secs	1	0	1	1.10	0.00	1.00
15.1-20.0 secs	60	6	66	65.93	66.67	66.00
20.1-25.0 secs	25	3	28	27.47	33.33	28.00
25.1-30.0 secs	4	0	4	4.40	0.00	4.00
Total	91	9	100	100	100	100

Prothrombin Time Distribution	Elevated Prolactin Group	Normal Prolactin Group	Combined
Mean	19.64	18.78	19.56
SD	2.71	2.73	2.71
P value			0.3665

Unpaired t Test

Among the study patients, there was no statistically significant difference in relation to prothrombin time distribution between elevated prolactin group (mean=19.64, SD=2.71) and normal prolactin group (mean=18.78, SD=2.73) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in prothrombin time distribution between the study groups.

International Normalized Ratio

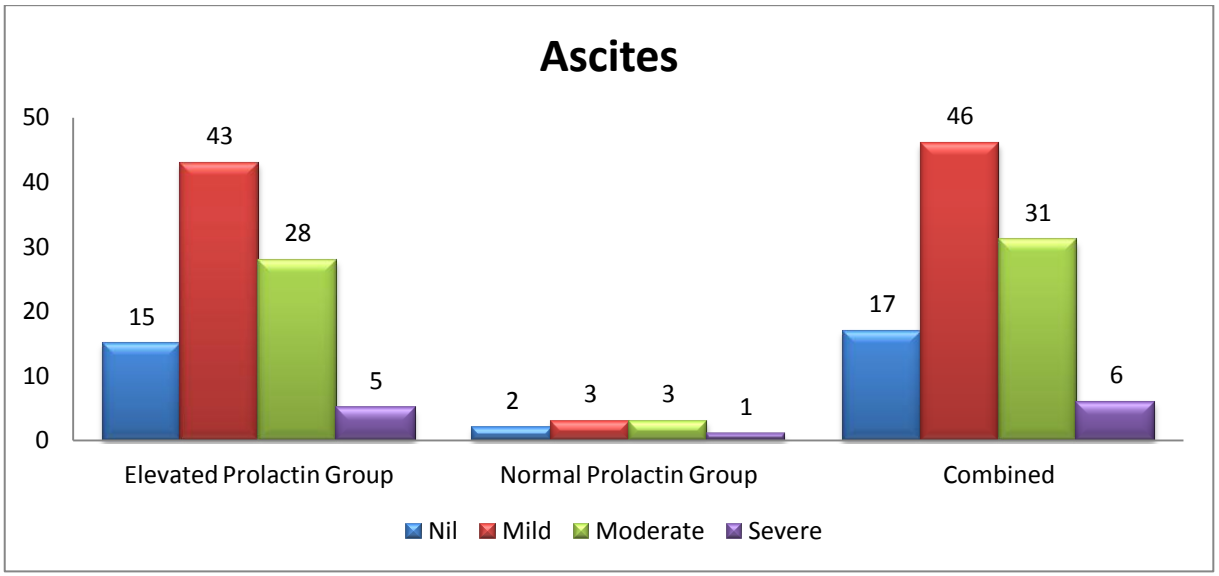


International Normalized Ratio	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
≤ 1	2	0	2	2.20	0.00	2.00
1.1-1.2	25	5	30	27.47	55.56	30.00
1.3-1.4	35	1	36	38.46	11.11	36.00
1.5-1.6	19	3	22	20.88	33.33	22.00
1.7-1.8	10	0	10	10.99	0.00	10.00
Total	91	9	100	100	100	100

International Normalized Ratio Distribution	Elevated Prolactin Group	Normal Prolactin Group	Combined
Mean	1.36	1.31	1.35
SD	0.20	0.19	0.20
P value			0.4956
Unpaired t Test			

Among the study patients, there was no statistically significant difference in relation to international normalized ratio distribution between elevated prolactin group (mean=1.36, SD=0.20) and normal prolactin group (mean=1.31, SD=0.19) with a p value of <0.05 as per unpaired t test. Therefore we fail to reject the null hypothesis that there is no difference in International Normalized Ratio distribution between the study groups.

Ascites



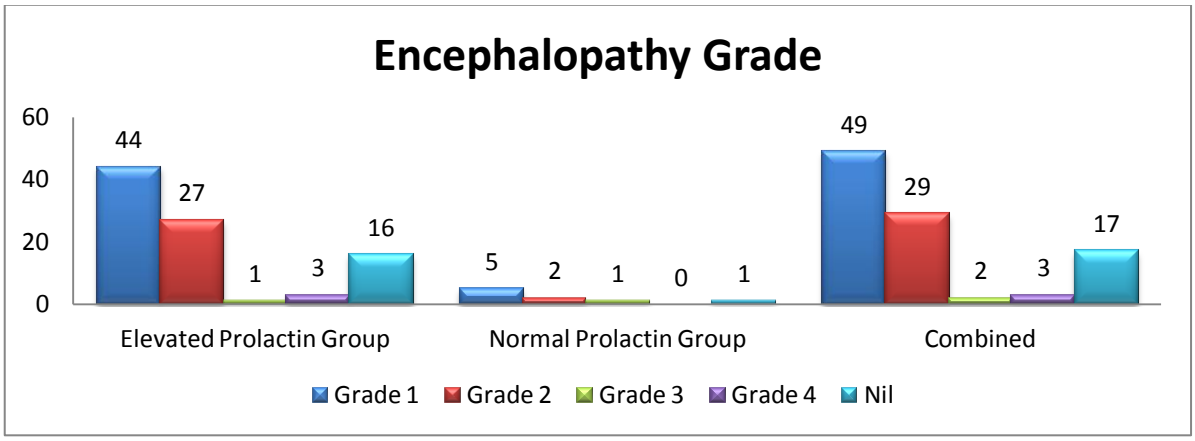
Ascites	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Nil	15	2	17	16.48	22.22	17.00
Mild	43	3	46	47.25	33.33	46.00
Moderate	28	3	31	30.77	33.33	31.00
Severe	5	1	6	5.49	11.11	6.00
Total	91	9	100	100	100	100

P value	0.6219

Fishers Exact Test

Among the study patients, there was no statistically significant difference in relation to ascites status between elevated prolactin group (majority had mild ascites– 47.25%) and normal prolactin group (majority had mild/moderate ascites– 33.33%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in gender status between the study groups.

Encephalopathy Grade



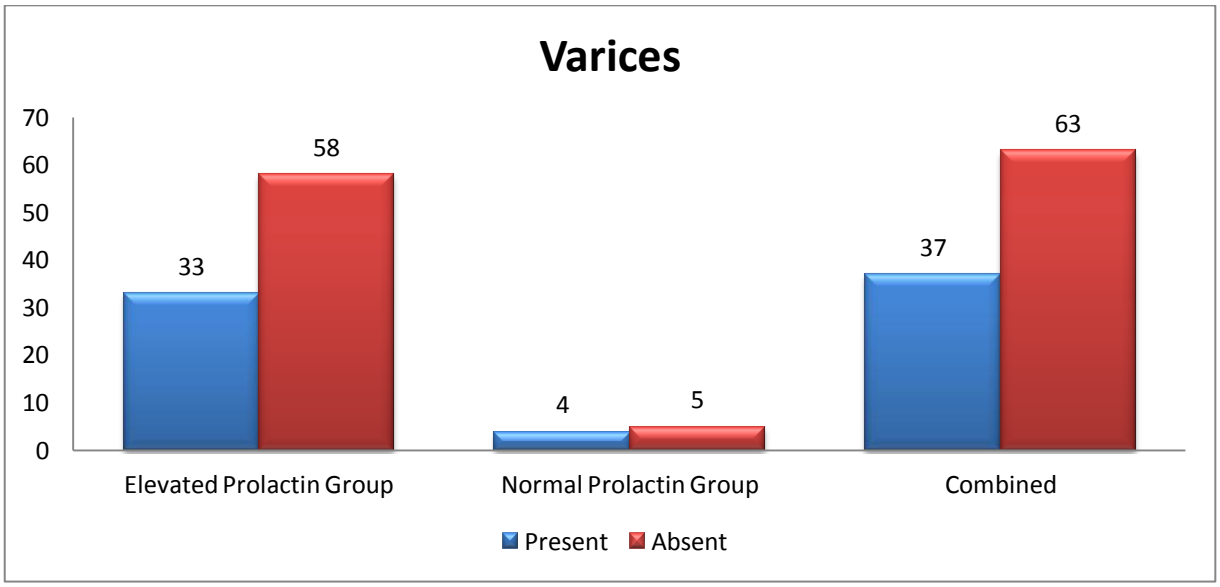
Encephalopathy Grade	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Grade 1	44	5	49	48.35	55.56	49.00
Grade 2	27	2	29	29.67	22.22	29.00
Grade 3	1	1	2	1.10	11.11	2.00
Grade 4	3	0	3	3.30	0.00	3.00
Nil	16	1	17	17.58	11.11	17.00

Total	91	9	100	100	100	100
P value				0.2791		

Fishers Exact Test

Among the study patients, there was no statistically significant difference in relation to encephalopathy grade status between elevated prolactin group (majority had grade 1 encephalopathy – 48.35%) and normal prolactin group (majority had grade 1 encephalopathy – 55.56%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in encephalopathy grade status between the study groups.

Varices

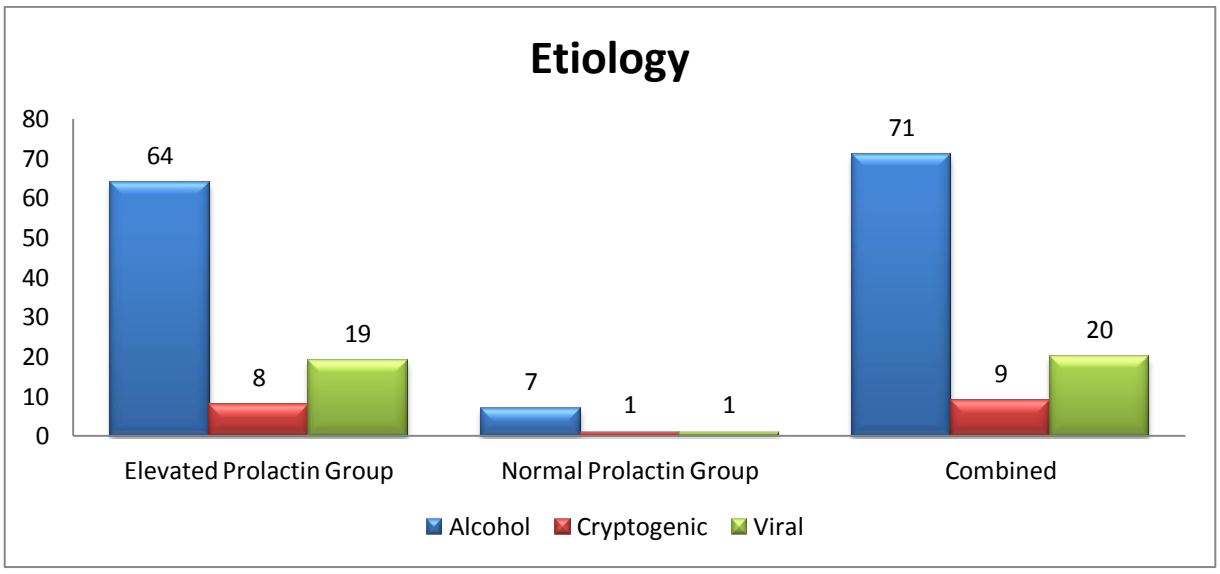


Varices	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Present	33	4	37	36.26	44.44	37.00
Absent	58	5	63	63.74	55.56	63.00
Total	91	9	100	100	100	100
P value				0.6277		

Fishers Exact Test

Among the study patients, there was no statistically significant difference in relation to varices status between elevated prolactin group (majority had absent varices– 63.74%) and normal prolactin group (majority had absent varices – 55.56%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in varices status between the study groups.

Etiology

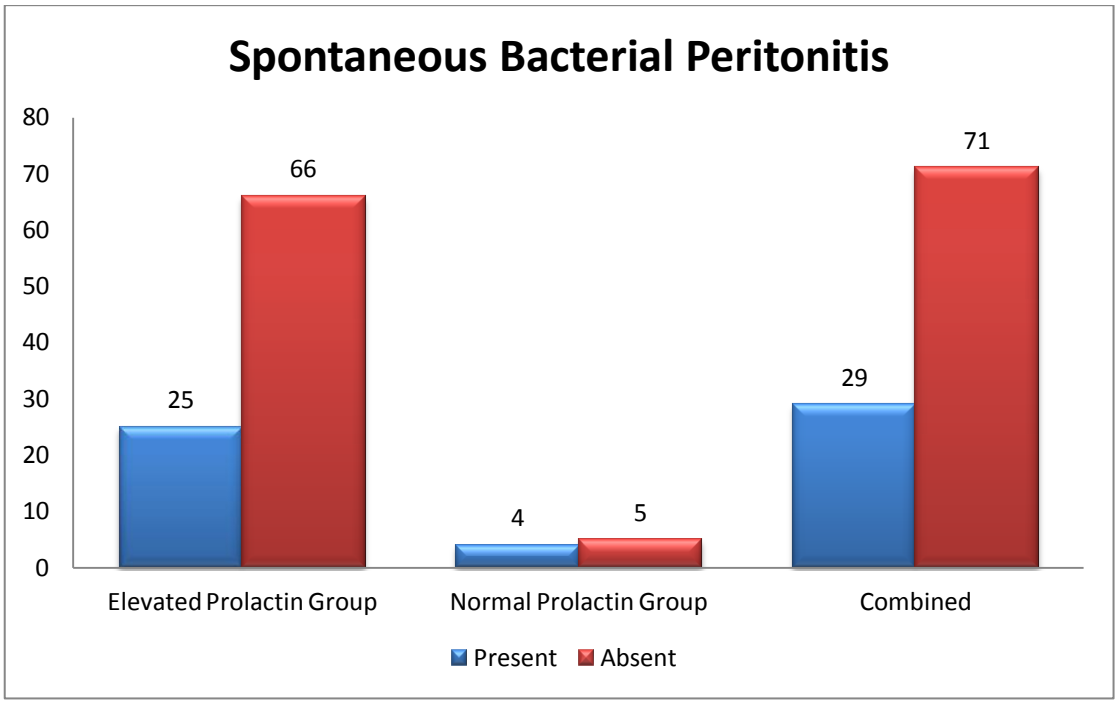


Etiology	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Alcohol	64	7	71	70.33	77.78	71.00
Cryptogenic	8	1	9	8.79	11.11	9.00
Viral	19	1	20	20.88	11.11	20.00
Total	91	9	100	100	100	100
P value				0.6385		

Fishers Exact Test

Among the study patients, there was no statistically significant difference in relation to etiology status between elevated prolactin group (majority had alcohol etiology– 70.33%) and normal prolactin group (majority had alcohol etiology – 77.78%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in etiology status between the study groups.

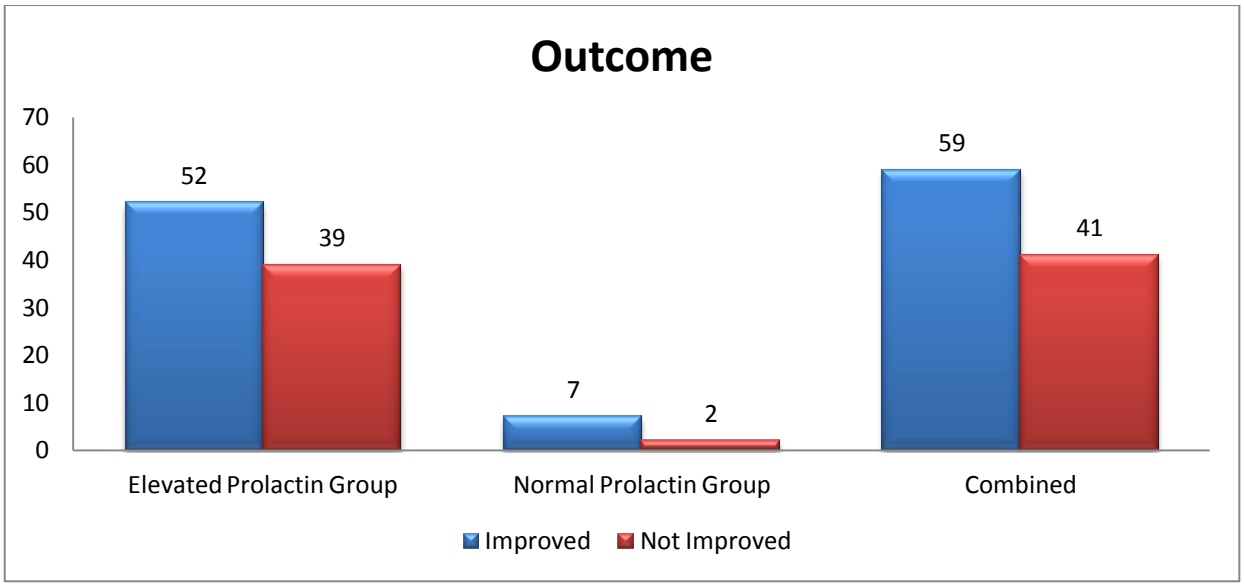
Spontaneous Bacterial Peritonitis



Spontaneous Bacterial Peritonitis	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Present	25	4	29	27.47	44.44	29.00
Absent	66	5	71	72.53	55.56	71.00
Total	91	9	100	100	100	100
P value				0.2844		
Fishers Exact Test						

Among the study patients, there was no statistically significant difference in relation to spontaneous bacterial peritonitis status between elevated prolactin group (majority had no SBP – 72.53%) and normal prolactin group (majority had no SBP – 55.56%) with a p value of <0.05 as per fishers exact test. Therefore we fail to reject the null hypothesis that there is no difference in spontaneous bacterial peritonitis status between the study groups.

Outcome



Outcome	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Improved	52	7	59	57.14	77.78	59.00
Not Improved	39	2	41	42.86	22.22	41.00
Total	91	9	100	100	100	100
P value				0.0366		

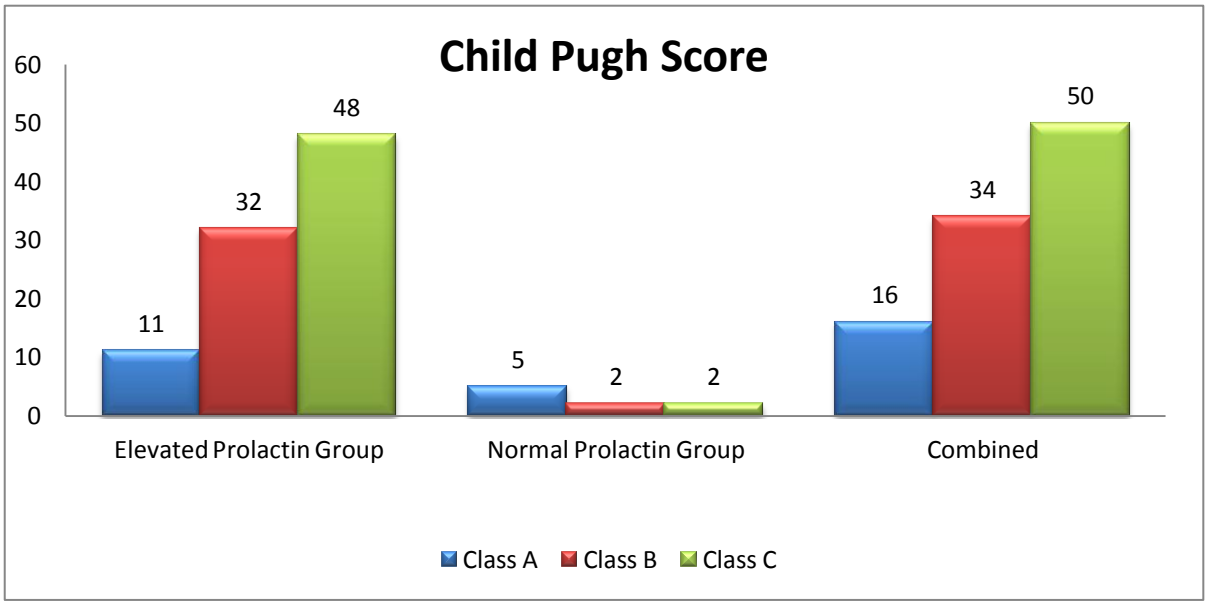
Fishers Exact Test

Among the study patients, there was a statistically significant difference in relation to outcome status between elevated prolactin group (majority improved– 57.14%) and normal prolactin group (majority improved – 77.78%) with a p value of <0.05 as per fishers exact test. Therefore we reject the null hypothesis that there is no difference in outcome status between the study groups

Discussion

The incidence of not improved outcome was significantly more in elevated prolactin group compared to normal prolactin group by a percentage difference of 20.63 percentage points (48% higher). This difference is significant with a p-value of 0.0366 as per fishers exact test.

Child Pugh Score



Child Pugh Score	Elevated Prolactin Group	Normal Prolactin Group	Combined	Elevated Prolactin Group (%)	Normal Prolactin Group (%)	Combined (%)
Class A	11	5	16	12.09	55.56	16.00
Class B	32	2	34	35.16	22.22	34.00
Class C	48	2	50	52.75	22.22	50.00
Total	91	9	100	100	100	100
P value				0.0078		

Fishers Exact Test

Among the study patients, there was a statistically significant difference in relation to child pugh score status between elevated prolactin group (majority were class B – 35.16%) and normal prolactin group (majority were Class A – 55.56%) with a p value of <0.05 as per fishers exact test. Therefore we reject the null hypothesis that there is no difference in child pugh score status between the study groups

Discussion

The incidence of class A child pugh score which signifies 100% 1 year survival and 85% 2 year survival was significantly less in elevated prolactin group compared to normal prolactin group by a percentage difference of 43.47 percentage points (78% lower).

The incidence of class C child pugh score which signifies 45% 1 year survival and 35% 2 year survival was significantly more in elevated prolactin group compared to normal prolactin group by a percentage difference of 30.53 percentage points (58% higher).

This difference is significant with a p-value of 0.0078 as per fishers exact test.

CONCLUSION

The conclusions obtained from the study

Male cirrhotic patients have elevated serum prolactin level 11.38 times more than female cirrhotic patients

Cirrhotic patients with elevated prolactin level are associated with poor prognosis

Patients belonging to class A child pugh scoring have low levels of prolactin compared to class C child pugh.

LIMITATIONS OF THE STUDY

Small sample size

Other variables which determine the outcome to be considered.

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PROFORMA

NAME : AGE:

SEX:

ADDRESS: CONTACT NO:

COMPLAINTS:

HISTORY

ALCOHOLISM YES NO DURATION:

HEAD INJURY YES NO

HYPOTHYROIDISM YES NO

KIDNEY DISEASE YES NO

CRANIAL SURGERY YES NO

H/O MEDICATION -

RELEVANT CLINICAL EXAMINATION:

PALLOR: ICTERUS: PAROTID ENLARGEMENT:

CLUBBING: PEDAL EDEMA:

ABDOMINAL GIRTH:

SPIDER NAEVI:

GYNAECOMASTIA: FLAPS:

DUPYTRENS CONTRACTURE: PALMAR ERYTHEMA

SYSTEMIC EXAMINATION:

ABDOMEN :

CARDIOVASCULAR:

RESPIRATORY:

CNS:

LABORATORY INVESTIGATION

HB: TC: PLATELET:

LFT: RFT:

SAAG: PT : INR:

HBsAG ANTI HCV:

SERUM PROLACTIN:

U/S ABDOMEN: ASCITIC FLUID ANALYSIS:

OGD SCOPY:

SCORING SYSTEM :

CHILD PUGH GRADING:

WEST HAVEN STAGING:

COMMENT:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD PUGH SCORING IN CIRRHOSIS

AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

A STUDY TO CORRELATE SERUM PROLACTIN AND CHILD PUGH SCORING IN CIRRHOSIS

AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:	கையொப்பம் / விரல்
ரேகை:	
ஆராய்ச்சியாளராக	கையொப்பம் மற்றும் தேதி

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work	: A Study to correlate Serum Protection and Child Pugh Scoring in Cirrhosis.
Principal Investigator	: Dr. T K Rajasekara Pandian
Designation	: PG, MD (General Medicine)
Department	: Department of General Medicine Government Stanley Medical College, Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.03.2016 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

S.N	AGE	SEX	S.PROLACTIN	S.ALB	S.BIL	PT	INR	ASCITES	HE	C.P. SCORE	VARICES	ETIOLOGY	OUTCOME	SBP
1	45	MALE	30	3.5	1.1	16 SEC	1.1	MILD	GRADE -1	CLASS -B	ABSENT	VIRAL	IMPROVED	ABSENT
2	30	MALE	22	3.2	1.9	18 SEC	1.2	NONE	NONE	CLASS -A	ABSENT	ALCOHOL	IMPROVED	ABSENT
3	62	MALE	31	3	3.3	19 SEC	1.3	MILD	GRADE -1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
4	46	MALE	38	3.3	3.2	17 SEC	1.2	MODERATE	GRADE- 2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	ABSENT
5	50	MALE	27	3.6	1.3	14 SEC	1	NONE	NONE	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
6	38	MALE	23	3.8	1.5	12 SEC	0.8	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
7	42	MALE	35	2.9	1.8	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	NOT IMPROVED	ABSENT
8	43	MALE	34	2.8	1.6	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	IMPROVED	PRESENT
9	50	MALE	39	2.3	1.4	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	ABSENT
10	45	MALE	37	2.9	1.6	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
11	60	MALE	29	3.2	1	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
12	45	MALE	28	3.1	1.2	19 SEC	1.3	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
13	47	MALE	35	2	1.3	24 SEC	1.7	SEVERE	GRADE-3	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
14	44	FEMALE	39	2.6	1.8	21 SEC	1.5	SEVERE	GRADE-4	CLASS-C	PRESENT	CRYTOGENIC	NOT IMPROVED	PRESENT
15	43	MALE	40	2.8	2	20 SEC	1.4	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
16	50	MALE	30	3	1.6	19 SEC	1.3	NONE	NONE	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
17	33	MALE	39	3.2	1.9	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
18	30	MALE	28	3.5	1.4	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
19	49	MALE	27	4.1	1.5	16 SEC	1.1	MILD	GRADE-1	CLASS-B	ABSENT	VIRAL	IMPROVED	ABSENT
20	63	MALE	25	3.9	1.2	16 SEC	1.1	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
21	65	MALE	36	2.6	1	19 SEC	1.3	SEVERE	GRADE-4	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
22	54	MALE	27	2.9	1.9	17 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
23	49	MALE	40	2.7	2.2	19 SEC	1.3	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	ABSENT
24	50	MALE	26	2.8	1.8	19 SEC	1.3	MODERATE	GRADE-2	CLASS-B	PRESENT	CRYTOGENIC	IMPROVED	PRESENT
25	65	MALE	31	2.2	1.7	22 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	PRESENT
26	55	MALE	28	3	1.6	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
27	51	MALE	26	2.8	1.3	17 SEC	1.2	MODERATE	GRADE-2	CLASS-B	PRESENT	VIRAL	IMPROVED	ABSENT
28	60	MALE	29	2.7	1.2	22 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
29	50	FEMALE	23	2.2	1.5	23 SEC	1.6	MODERATE	GRADE-2	CLASS-B	PRESENT	ALCOHOL	IMPROVED	PRESENT
30	47	MALE	24	2.8	1.9	18 SEC	1.2	MODERATE	GRADE-2	CLASS-B	PRESENT	ALCOHOL	IMPROVED	PRESENT
31	48	MALE	34	2.9	1.4	20 SEC	1.4	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	NOT IMPROVED	ABSENT
32	78	MALE	23	3	1.4	19 SEC	1.3	NONE	NONE	CLASS -B	ABSENT	ALCOHOL	IMPROVED	ABSENT
33	34	MALE	27	3.5	1.3	16 SEC	1.1	MILD	GRADE-1	CLASS-B	ABSENT	VIRAL	IMPROVED	ABSENT
34	58	MALE	22	3.8	1.2	16 SEC	1.1	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
35	58	FEMALE	26	3.7	1.3	17 SEC	1.2	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
36	45	MALE	28	3.3	1	19 SEC	1.3	NONE	NONE	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
37	57	FEMALE	28	3.4	2.8	17 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	CRYTOGENIC	IMPROVED	ABSENT
38	53	MALE	30	3.1	1.6	19 SEC	1.3	MODERATE	GRADE-2	CLASS-B	PRESENT	ALCOHOL	IMPROVED	ABSENT
39	44	MALE	39	2.6	1.4	24 SEC	1.7	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
40	57	MALE	34	2.9	1.5	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	ABSENT
41	53	MALE	26	3.9	1.3	17 SEC	1.2	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
42	44	MALE	36	2.8	1.4	22 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	NOT IMPROVED	ABSENT
43	55	MALE	37	2	1.5	26 SEC	1.8	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
44	43	MALE	29	3	1.6	19 SEC	1.3	NONE	NONE	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
45	42	MALE	25	3.5	1.7	18 SEC	1.2	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
46	46	MALE	26	3.8	1.8	17 SEC	1.2	NONE	NONE	CLASS-A	ABSENT	CRYTOGENIC	IMPROVED	ABSENT
47	47	FEMALE	38	2.9	1.9	20 SEC	1.4	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
48	46	MALE	35	2.7	2	21 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
49	55	MALE	35	2.8	1.2	22 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	NOT IMPROVED	ABSENT
50	48	MALE	35	2.2	1.4	26 SEC	1.8	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
51	37	MALE	36	3	1.6	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
52	50	FEMALE	40	2.8	1.7	22 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	IMPROVED	ABSENT
53	46	MALE	28	2.6	0.9	23 SEC	1.6	MODERATE	GRADE-2	CLASS-B	PRESENT	ALCOHOL	IMPROVED	PRESENT
54	53	MALE	36	2.2	1	26 SEC	1.8	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
55	42	MALE	37	2.9	1.1	21 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	IMPROVED	PRESENT
56	62	MALE	37	2.7	1.3	21 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	NOT IMPROVED	ABSENT
57	34	MALE	27	3.9	1.2	16 SEC	1.1	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
58	48	FEMALE	37	2.9	1	21 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
59	42	MALE	36	2.8	3.2	21 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	IMPROVED	PRESENT
60	55	MALE	39	2.2	1.6	26 SEC	1.8	MODERATE	GRADE-2	CLASS-C	PRESENT	CRYTOGENIC	NOT IMPROVED	PRESENT
61	62	MALE	28	3	1.4	19 SEC	1.3	NONE	NONE	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
62	55	MALE	40	2.8	1.3	21 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
63	62	FEMALE	39	2.7	1.2	21 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	VIRAL	IMPROVED	ABSENT
64	55	MALE	35	2.2	1.1	22 SEC	1.5	MILD	GRADE-1	CLASS-C	ABSENT	CRYTOGENIC	NOT IMPROVED	ABSENT
65	44	MALE	27	3	1.3	20 SEC	1.4	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
66	61	MALE	26	3.5	1.4	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
67	45	FEMALE	28	3.8	1.5	16 SEC	1.1	NONE	NONE	CLASS-A	ABSENT	VIRAL	IMPROVED	ABSENT
68	41	MALE	25	4	1.3	16 SEC	1.1	NONE	NONE	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
69	53	FEMALE	29	3.6	1.2	17 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
70	52	MALE	28	3.2	1.1	19 SEC	1.3	MILD	GRADE-1	CLASS-B	ABSENT	VIRAL	IMPROVED	ABSENT
71	47	MALE	28	2.8	1.3	23 SEC	1.6	MODERATE	GRADE-2	CLASS-B	PRESENT	ALCOHOL	IMPROVED	PRESENT
72	41	MALE	33	2.2	1.4	24 SEC	1.7	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
73	49	FEMALE	34	2.9	1.5	23 SEC	1.6	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	IMPROVED	PRESENT
74	52	MALE	26	3.7	1.2	17 SEC	1.2	MILD	GRADE-1	CLASS-A	ABSENT	ALCOHOL	IMPROVED	ABSENT
75	45	MALE	28	3.3	1.3	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
76	48	MALE	28	3.8	1.1	16 SEC	1.1	MILD	GRADE-1	CLASS-B	ABSENT	CRYTOGENIC	IMPROVED	ABSENT
77	42	FEMALE	28	3.7	1.1	16 SEC	1.1	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT

78	40	MALE	32	3	1	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	IMPROVED	ABSENT
79	44	FEMALE	31	2.5	1.9	24 SEC	1.7	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	ABSENT
80	54	FEMALE	29	2.7	1.5	22 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	IMPROVED	PRESENT
81	58	MALE	28	2.8	1.4	21 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	PRESENT
82	57	MALE	30	3	1.2	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
83	64	FEMALE	29	2.5	1.3	21 SEC	1.5	SEVERE	GRADE-3	CLASS -C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
84	59	MALE	29	2.8	1.4	20 SEC	1.4	SEVERE	GRADE-4	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
85	53	MALE	29	3.2	1.3	19 SEC	1.3	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	PRESENT
86	56	MALE	29	2	1.4	24 SEC	1.7	SEVERE	GRADE-4	CLASS -C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
87	58	MALE	30	2.9	2	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
88	53	MALE	32	3.3	1.3	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
89	55	FEMALE	34	3.4	1.3	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	CRYTOGENIC	NOT IMPROVED	ABSENT
90	56	MALE	28	3.5	1.5	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
91	64	MALE	27	3.8	1.6	16 SEC	1.1	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
92	66	MALE	31	3.3	1.2	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
93	67	MALE	29	3.4	1.4	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
94	66	MALE	28	3.2	1.5	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	ALCOHOL	NOT IMPROVED	ABSENT
95	56	MALE	27	3.1	1.4	19 SEC	1.3	MILD	GRADE-1	CLASS-C	ABSENT	CRYPTOGENIC	NOT IMPROVED	ABSENT
96	54	MALE	25	3.6	1.3	18 SEC	1.2	MILD	GRADE-1	CLASS-B	ABSENT	ALCOHOL	IMPROVED	ABSENT
97	55	FEMALE	27	2.8	1.4	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT
98	49	MALE	26	2	1.3	25 SEC	1.7	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	IMPROVED	PRESENT
99	64	MALE	29	2.7	1.2	20 SEC	1.4	MODERATE	GRADE-2	CLASS-C	PRESENT	VIRAL	NOT IMPROVED	PRESENT
100	52	MALE	30	2.6	1.1	21 SEC	1.5	MODERATE	GRADE-2	CLASS-C	PRESENT	ALCOHOL	NOT IMPROVED	PRESENT

ABBREIVATIONS

1. CBC - COMPLETE BLOOD COUNT
2. TC – TOTAL COUNT
3. RFT - RENAL FUNCTION TEST
4. LFT – LIVER FUNCTION TEST
5. T.B – TOTAL BILIRUBIN
6. D.B – DIRECT BILURUBIN
7. SAP – SERUM ALKALINE PHOSPATASE
8. AST – ASPARTATE TRANSAMINASE
9. ALT – ALANINE TANSAMINASE
10. PT – PROTHROMBIN TIME
11. INR – INTERNATIONAL NORMALISED RATIO
12. OGD SCOPY – OESOPHAGO GASTRODUODENOSCOPY
13. HBsAg – SURFACE ANTIGEN OF HEPATITIS B
14. ANTI HCV – ANTIBODY FOR HEPATITIS C
15. USG – ULTRASOUND
16. SAAG – SERUM ASCITIC ALBUMIN GRADIENT
17. CT - COMPUTED TOMOGRAPHY
18. MRI - MAGNETIC RESONANCE IMAGING