Dissertation On

A STUDY ON THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FREE T3 AS A PROGNOSTIC INDICATOR

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FREE T3 AS A PROGNOSTIC INDICATOR**" submitted by **Dr.S.SABARISH** appearing for M.D. Branch I - General Medicine Degree examination in 2019 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of the TamilNadu Dr. M.G.R. Medical University, Chennai. I forward this to the TamilNadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled **"A STUDY ON THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FREE T3 AS A PROGNOSTIC INDICATOR"** is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2017 under the guidance and supervision of **Prof.Dr.P.VASANTHI., M.D.** The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ABBREVIATIONS

- NAFLD - Non Alcoholic Fatty Liver Disease
- PBC - Primary Biliary Cirrhosis
- PSC - Primary Sclerosing Cholangitis
- MPGN - Membrano Proliferative Glomerulo Nephritis
- HHT - Hereditary Hemorrhagic Telangiectasia
- PDGF - Platelet Derived Growth Factor
- MAP - Mean Arterial Pressure
- INR - International Normalized Ratio
- AST - Aspartate Amino Transferase
- ALT - Alanine Amino Transferase
- ALP - Alkaline phosphatase
- GGT - Gamma Glutamyl Transferase
- NT - Nucleotidase
- HCC - HepatoCellular Carcinoma
- TIPS - Transjugular Intrahepatic PortoSystemic Shunt
- RAAS - Renin Angiotensin Aldosterone System
- ADH - Anti Diuretic Hormone
- BRTO - Balloon Occluded Retrograde Transvenous Obliteration
- HPS - HepatoPulmonary Syndrome
- POPH - Porto Pulmonary Hypertension
- HRS - Hepato Renal Syndrome
- MELD - Model For End Stage Liver Disease

- BMI - Body Mass Index
- T3 - Tri Iodo thyronine
- T4 - Thyroxine
- TSH - Thyroid Stimulating Hormone

CONTENTS

INTRODUCTION

INTRODUCTION

Chronic liver disease refers to a disease of the liver characterized by progressive destruction associated with regeneration of the liver parenchyma ultimately resulting in fibrosis and cirrhosis. Chronic refers to disease process which lasts for over six months.[18]

Cirrhosis of liver is a histopathological diagnosis. It results in numerous complications such as

1. Ascites
2. Spontaneous bacterial peritonitis
3. Portal hypertension with variceal bleeding
4. Hepatic encephalopathy
5. Hepatorenal syndrome
6. Hepatopulmonary syndrome
7. Hepatocellular carcinoma
8. Coagulation disorder
9. Endocrine dysfunction

Endocrine dysfunction includes derangements in the functions of adrenal gland, disturbances in the gonadal axis, bone diseases and thyroid dysfunction[3].

Liver plays a pivotal role in thyroid hormone metabolism. It also produces thyroid hormone binding globulin, albumin that are essential for

binding thyroid hormones in circulation and delivering them to various body tissues. Chronic liver disease is associated with a low T3 syndrome.

Low T3 syndrome is characterized by low levels of T3, increased rT3 and decreased T3:T4 ratio. The reduced levels of T3 serves as an adaptive response to reduce the basal metabolic rate of hepatocytes and preserve liver function. T4 levels tend to be in the lower limits of normal range whereas TSH tends to remain in the normal range.

There appears to be an inverse correlation between the levels of T3 and the Child Pugh score and class. The levels of T3 are found to be significantly lower as the level of decompensation worsens. Thus serum free T3 levels can be used as a reliable prognostic marker in patients with cirrhosis. The levels of T3 tends to improve as the patient's liver function improves.

CHILD-TURCOTTE-PUGH CRITERIA

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

AIMS AND OBJECTIVES

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To study the thyroid function tests in decompensated chronic liver disease and to determine the importance of Free T3 levels as a prognostic indicator in patients with decompensated chronic liver disease.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DEFINITION

The term chronic liver disease in clinical context refers to the disease process of the liver that causes progressive destruction and regeneration of liver parenchyma that leads to cirrhosis and fibrosis. Chronicity denotes disease process which lasts over six months. It encompasses a wide spectrum of disease process which includes inflammation (chronic hepatitis), liver cirrhosis and hepatocellular carcinoma.[40]

Common causes of cirrhosis include:

1. Chronic viral hepatitis (hepatitis B and hepatitis c)
2. Alcoholic liver disease
3. Nonalcoholic fatty liver disease

The word cirrhosis is derived from the greek word ‘kirrhos” meaning “yellow/tawny” and the suffix “osis” meaning “condition”. The term was coined by Rene Laennec. The term cirrhosis refers to the final common pathway for the wide array of chronic liver diseases which results in replacement of the normal liver architecture by nodules. The rate of progression of chronic liver disease to cirrhosis varies from patient to patient.

It is irreversible in advanced stages where liver transplantation remains the only viable treatment option. Rarely, in early stages with treatment cirrhosis has been shown to be reversible. Cirrhosis makes the patients vulnerable to a

variety of complications and this is results in marked reduction in their life expectancy with a 10 year mortality of 34 to 66%, depending on the cause of cirrhosis.

ETIOLOGIES OF CIRRHOSIS

Viral
HBV
HCV
HDV

Autoimmune
Autoimmune hepatitis
PBC
PSC

Toxic
Alcohol
Arsenic

Metabolic
α_1-Antitrypsin deficiency
Galactosemia
Glycogen storage disease
Hemochromatosis
Nonalcoholic fatty liver disease and steatohepatitis
Wilson disease

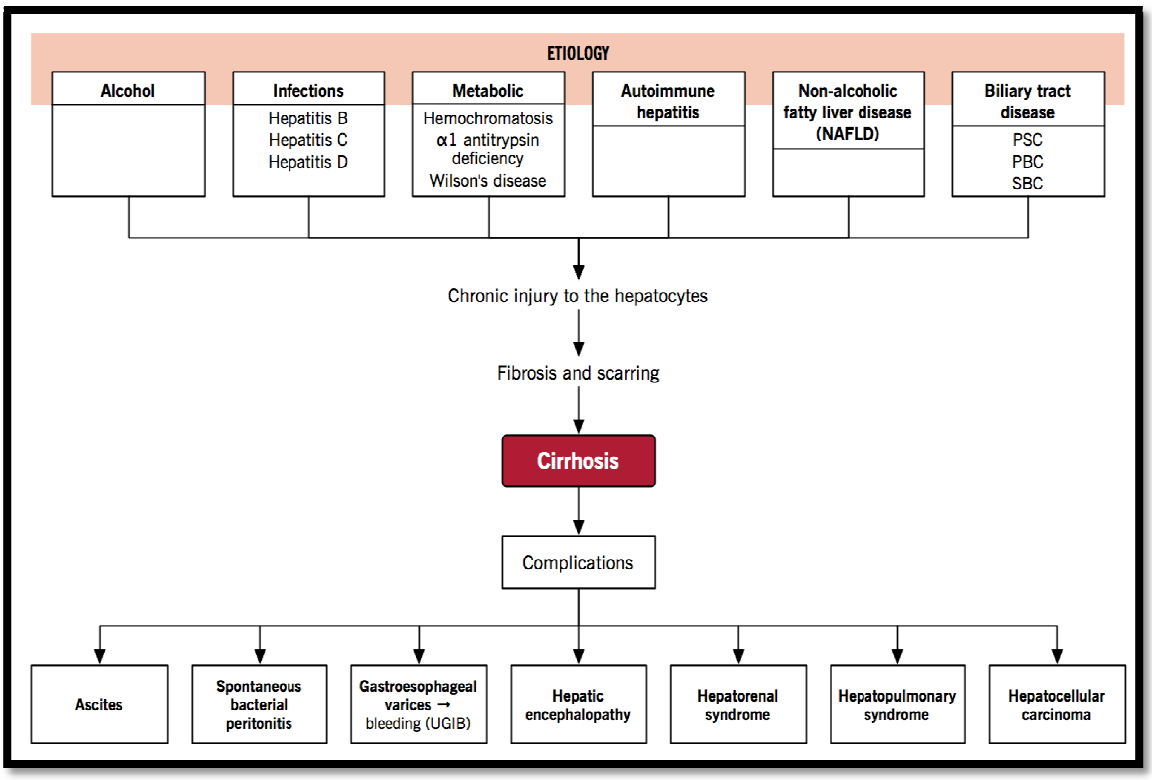
Biliary
Atresia
Stone
Tumor

Vascular
Budd-Chiari syndrome
Cardiac fibrosis

Genetic
CF
Lysosomal acid lipase deficiency

Iatrogenic
Biliary injury
Drugs: high-dose vitamin A, methotrexate

COMPLICATIONS OF CIRRHOSIS



PATHOGENESIS OF CIRRHOSIS

It is the final common result of various chronic liver diseases. Fibrosis is the precursor of cirrhosis. Various types of cells, cytokines and miRNA are involved in the initiation and progression of liver fibrosis and cirrhosis. Hepatic stellate cell activation is the main event in fibrosis. There is defenestration and capillarization of liver sinusoidal endothelial cells. The kupffer cells cause destruction of hepatocytes and activates hepatic stellate cells. Repeated cycles of apoptosis and regeneration of hepatocytes leads to established cirrhosis.

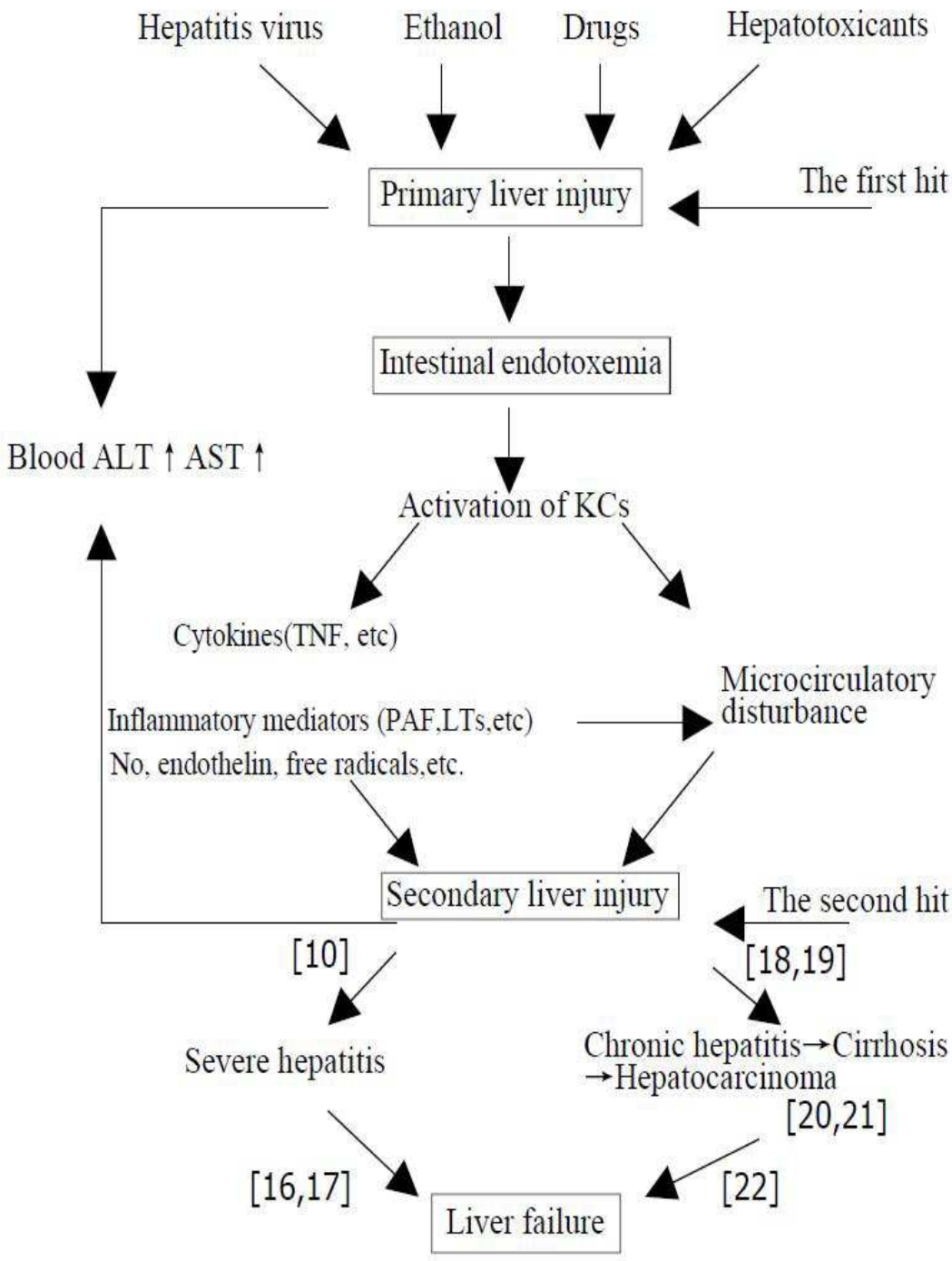
In recent decades NAFLD is emerging as a leading cause of chronic liver disease with prevalence as high as 30% in general population. Normally hepatic stellate cells resemble pericytes that lies in the abluminal side of

sinusoidal endothelial cell in the space of Disse. Stimulus for activation of hepatic stellate cells leads to transformation into a myofibroblast. This transformation is characterized by increased expression of smooth muscle actin, motility and contractility. The activated stellate cells lay down various forms of matrix proteins such as fibronectin, collagen 1. This matrix generation leads to further activation of HSCs and alteration in hepatic angioarchitecture. These pathways are mediated by kinase activation pathways that are mediated by PDGF, TGF-B and integrin.[18,40]

Other cell type implicated in cirrhosis include portal fibroblast. It resides closer to portal tract and is considered to be responsible for liver fibrosis that develops in portal based pathologies such as PBC and PSC. Epithelial injury in periportal region leads to transformation of portal fibroblasts to myofibroblasts. Cells other than myofibroblasts also play a pivotal role in pathogenesis of cirrhosis.Macrophages are also implicated in development of cirrhosis. They release inflammatory cytokines which cause HSC activation.

There are studies showing role of sinusoidal endothelial cells in fibrosis. They act through autocrine and paracrine signaling pathways that participate in angiogenesis. Angiogenesis in turn leads to fibrosis via paracrine release of HSC activating molecules. Inspite of involvement of multiple cell types in development of fibrosis, the hepatic stellate cells are most directly responsible for cirrhosis owing to its abundant capacity to produce matrix.

PATHOGENESIS OF CIRRHOSIS



CLINICAL FEATURES OF CIRRHOSIS

	Description	Cause
Jaundice[1–3]	Yellow discoloration of skin, cornea, and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >20 mg/L
Spider angiomata[9,10]	Central arteriole with tiny radiating vessels, mainly on trunk and face	Raised oestradiol, decreased oestradiol degradation in liver
Nodular liver[2]	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly[2]	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites[1–3,11]	Proteinaceous fluid in abdominal cavity, clinically detected when ≥1·5 L	Portal hypertension
Caput medusae[2]	Prominent veins radiating from umbilicus	Portal hypertension, reopening of umbilical vein that shunts blood from portal vein
Cruveilhier-Baumgarten syndrome[12]	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusae
Palmar erythema[1–3]	Erythema sparing central portion of the palm	Increased oestradiol, decreased oestradiol degradation in liver
White nails[13]	Horizontal white bands or proximal white nail plate	Hypoalbuminaemia
Hypertrophic osteoarthropathy/ finger clubbing[14]	Painful proliferative osteoarthropathy of long bones	Hypoxaemia due to right-to-left shunting, portopulmonary hypertension
Dupuytren's contracture[15]	Fibrosis and contraction of palmar fascia	Enhanced oxidative stress, increased inosine (alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern[16]	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to oestrone and oestradiol, reduced oestradiol degradation in liver
Hypogonadism[1–3]	Mainly in alcoholic cirrhosis and haemochromatosis	Direct toxic effect of alcohol or iron
Flapping tremor (asterixis)[1–3]	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus[17]	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting[1–3]	Occurs in >50% of patients with cirrhosis	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes[1–3]	Occurs in 15–30% of patients with cirrhosis	Disturbed glucose use or decreased insulin removal by the liver

Data from references 1–3, and 15 if not specified otherwise. *Usually absent in compensated cirrhosis; some findings only occur in a few cases.

Table 1: **Clinical features of cirrhosis***

CLINICAL AND PATHOLOGICAL ASSOCIATIONS

1: Gastrointestinal

The presence of splenomegaly and venous collaterals signifies portal hypertension. About 11% of patients with cirrhosis tend to have peptic ulceration. Duodenal ulcers are more frequent than gastric ulcers. Patients with cirrhosis tend to have greater prevalence of helicobacter pylori on serology.

Bacterial overgrowth occurs in about 30% of patients with cirrhosis and concomitant ascites. There is a positive correlation between administration of H2 blockers/PPIs and prevalence of bacterial overgrowth. The prevalence increases with age of the patient.

In patients with ascites there is an increased incidence of abdominal hernia. Surgical correction of hernia is usually deferred unless there is danger to life or in the presence of well compensated cirrhosis.

Pigment type gall stones are common in cirrhotics. Patients are poor candidates for surgical management of gall stones. Pancreatic calcifications and relapsing pancreatitis are usually associated with chronic liver disease. Parotid enlargement is usually noticed.

2: Renal

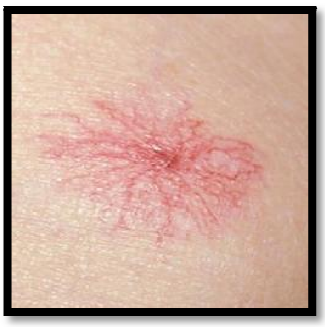
Hemodynamic alterations in cirrhosis predisposes the patient to Hepato Renal Syndrome. There is thickening of mesangial stalk along with capillary walls. Hepatitis C infection is associated with cryoglobulinemia and MPGN.

3:Foetor Hepaticus

The presence of dimethyl sulphide and ketones in alveolar air gives rise to a slightly fecal smell of breath which complicates severe hepatocellular disease and signifies existence of extensive collateral circulation. It can serve as a useful diagnostic sign in patients presenting with coma.

4:Vascular Spiders

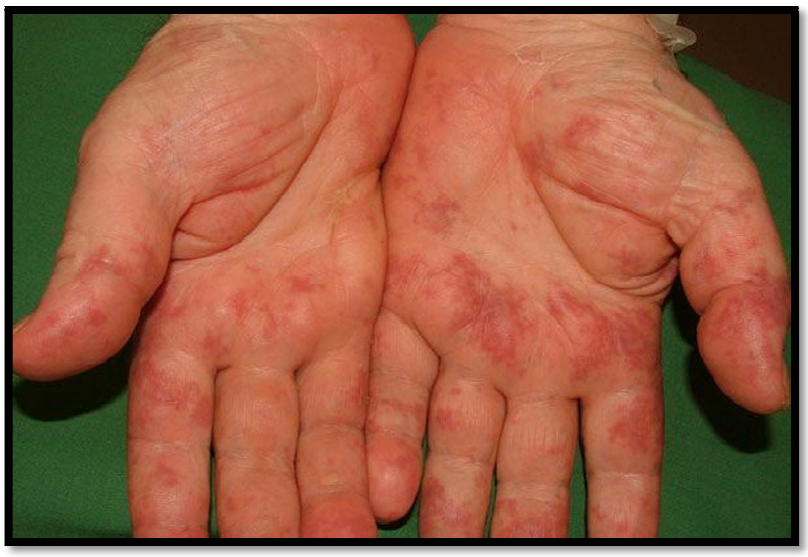
They are found in the vascular territory of superior vena cava in the necklace area, face, forearms and dorsum of hand. It consists of a central arteriole with numerous small vessels radiating from it resembling the legs of a spider. It blanches on applying pressure. They can be of prognostic value since they disappear as the hepatic function improves and tend to reappear as it worsens. The presence of multiple spider naevi along with clubbing of nails should invoke a suspicion of hepatopulmonary syndrome. The skin of cirrhotics resembles the silk threads in American dollar bills and hence the name paper money skin. There is appearance of white spots that develops in the arms and buttocks on cooling the skin. They represent the beginning of a spider naevi. Spider naevi can be present in other conditions like pregnancy, in young children. Other differentials include HHT, CREST syndrome, Campbell de Morgan’s spots, Venous star.



5: Palmar Erythema

A blanching erythematous rash can be observed in the thenar and hypothenar eminences with sparing of the centre of the palm. They are also appreciated in the soles. There can be associated throbbing pain and tingling of the hands. It is not a very common manifestation in cirrhotics.

The vascular spiders and palmar erythema occur as a result of excess estrogen in circulation that results in vasodilatation.



6:Leuconychia

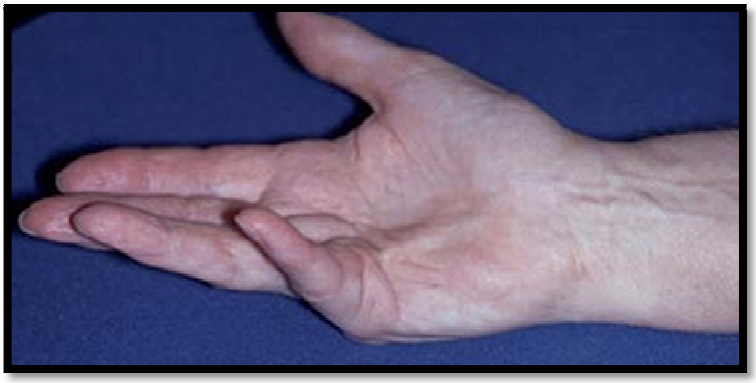
The presence of white finger nails are related to hypoalbuminemia

7:Clubbing

Clubbing though uncommon in cirrhosis, can be seen in cases of cystic fibrosis or hepato pulmonary syndrome. They are primarily due to platelet aggregation that passes peripherally through pulmonary AV shunts and causing release of PDGF.

8:Dupuytren's Contracture

It is seen in alcoholic cirrhosis as a result of thickening of the palmar fascia in the hand.



9:Malnutrition

Reduced intake of food with increased energy expenditure results in protein-calorie malnutrition and predicts shortened survival in cirrhotics. Patient experience reduced muscle mass and depleted fat stores with resultant muscle weakness and muscle wasting. Reduced hepatic bile salt production can give rise to steatorrhoea. Triceps skin fold thickness, BMI, mid arm muscle circumference can be used for bedside assessment of nutritional status

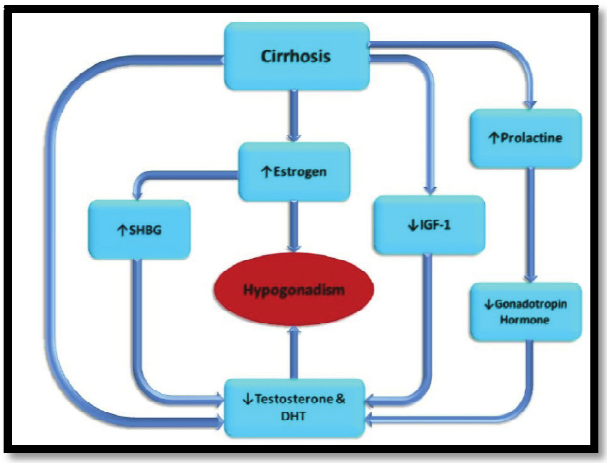
10:Hyperglycemia

Upto 80% of cirrhotics tend to develop impaired glucose tolerance with 10 – 20% developing diabetes.

11:Hypogonadism

Males tend to experience reduced libido and impotence with loss of secondary sexual characters and testicular atrophy. Females have ovulation failure, can develop infertility, irregular menstrual cycles. Tender gynaecomastia can develop in men as a result of drugs or alcohol induced enlargement of glandular elements of breast or in chronic autoimmune hepatitis. End organ sensitivities to sex hormones is altered in cirrhotics. Feminization can also signal primary liver cancer occasionally. Hypothalamic-pituitary dysfunction is also present.[3,5,15,18]

MECHANISM OF HYPOGONADISM IN CIRRHOSIS



12:Eye signs

The incidence of lid retraction and lid lag is significantly increased in cirrhotics compared to control population.

13:Muscle cramps

They correlate with presence of ascites, low MAP and plasma renin activity. They can be managed with oral quinine sulphate

14:Drug metabolism

There is reduced hepatic elimination of drugs with resultant increase in drug levels. This can be explained by reduced functional hepatic mass and shunting of blood past the liver. The dosage of drugs should be adjusted according to severity of the disease. There is also altered drug absorption, drug distribution, reduced protein binding, altered biliary secretion, enterohepatic circulation and unresponsiveness of target organs.

DIAGNOSIS OF CIRRHOSIS

Cirrhosis is a histological diagnosis. Constellation of clinical, biochemical and radiological features can give clues to a diagnosis of cirrhosis. Liver biopsy is not always needed to establish a diagnosis of cirrhosis. Markers of hepatic fibrosis from hematologic parameters, biochemical tests and serology are available to determine the extent of liver fibrosis.

LIVER FUNCTION TESTS

The battery of investigations that are useful in evaluating the functions of the liver include

1. Total bilirubin and direct bilirubin
2. Albumin
3. Prothrombin time/ INR
4. AST/ALT
5. ALP
6. GGTP/5’NT

The liver function tests can give an insight in establishing the etiology of the disease, differentiating the type of liver disorder, in assessing the severity of the disease as well as monitoring the disease progression and response to therapy.

I - TESTS BASED ON EXCRETORY FUNCTION

1. Serum bilirubin
2. Urine bilirubin
3. Urine and fecal urobilinogen
4. Urine bile salts
5. Dye excretion tests

II - TESTS BASED ON DETOXIFICATION FUNCTION

1. Determination of blood ammonia
2. Hippuric acid test

III - TESTS BASED ON SYNTHETIC FUNCTION

1. Plasma proteins
2. Prothrombin time

IV - TESTS BASED ON METABOLIC FUNCTION

1. Galactose tolerance test (carbohydrate metabolism)
2. Serum cholesterol (lipid metabolism)
3. Serum proteins and aminoaciduria (protein metabolism)

V - ENZYMES IN DIAGNOSIS OF LIVER DISEASE

1. Serum transaminases
2. Serum alkaline phosphatase

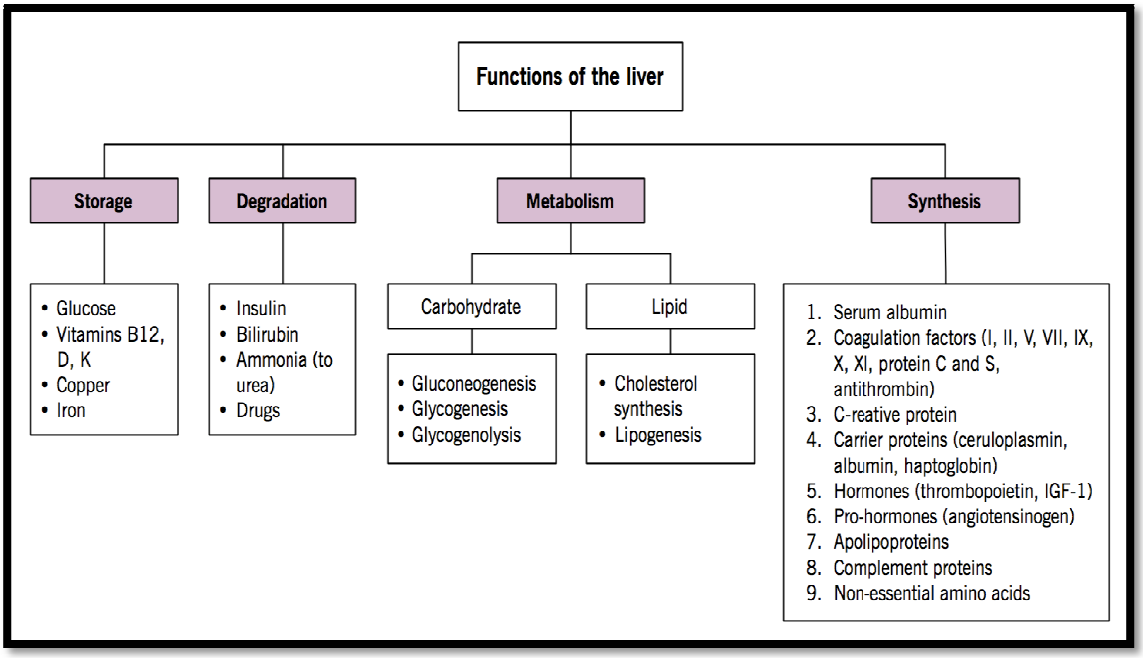
VI – TESTS TO DETECT HEPATIC FIBROSIS

1. Liver biopsy
2. Hyaluronan measurement
3. Fibrotest
4. Transient elastography and Magnetic resonance elastography

VII – QUANTITATIVE LIVER FUNCTION TESTS

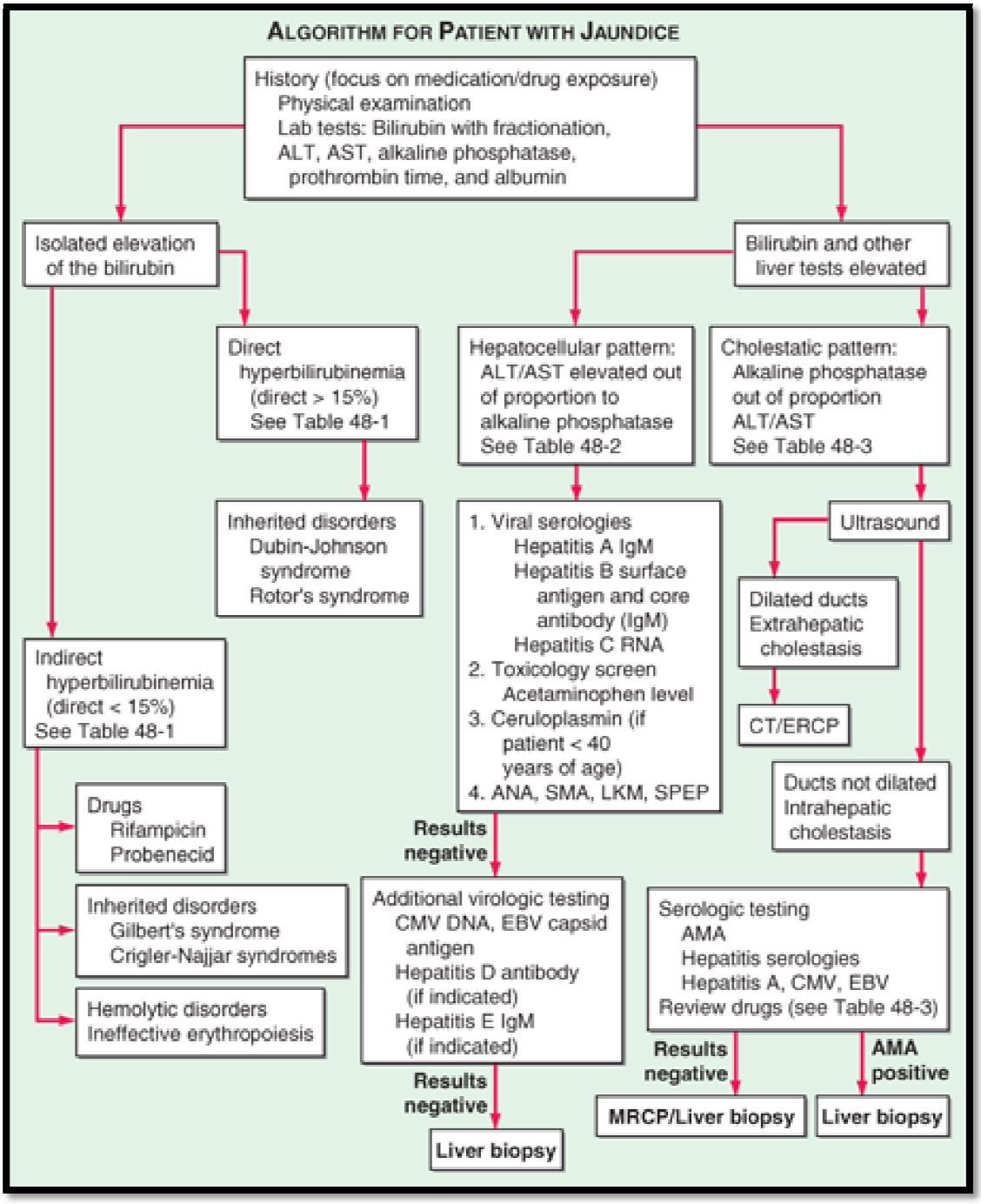
1. Indocyanin green clearance and caffeine clearance
2. Galactose elimination capacity and Lidocaine metabolite formation
3. Aminopyrine breath test

FUNCTIONS OF LIVER



Liver participates in storage, degradation of hormones, metabolism, synthesis. Derangement of liver function can manifest with functional abnormalities in anyone of these aspects. Laboratory investigations focused at these functions can throw light on the extent of liver damage, the probable etiology and the prognosis. Serial evaluation the liver function tests can help predict response to treatment and recovery from illness.

APPROACH TO A PATIENT WITH ELEVATED BILIRUBIN



CAUSES OF HYPERBILIRUBINEMIA

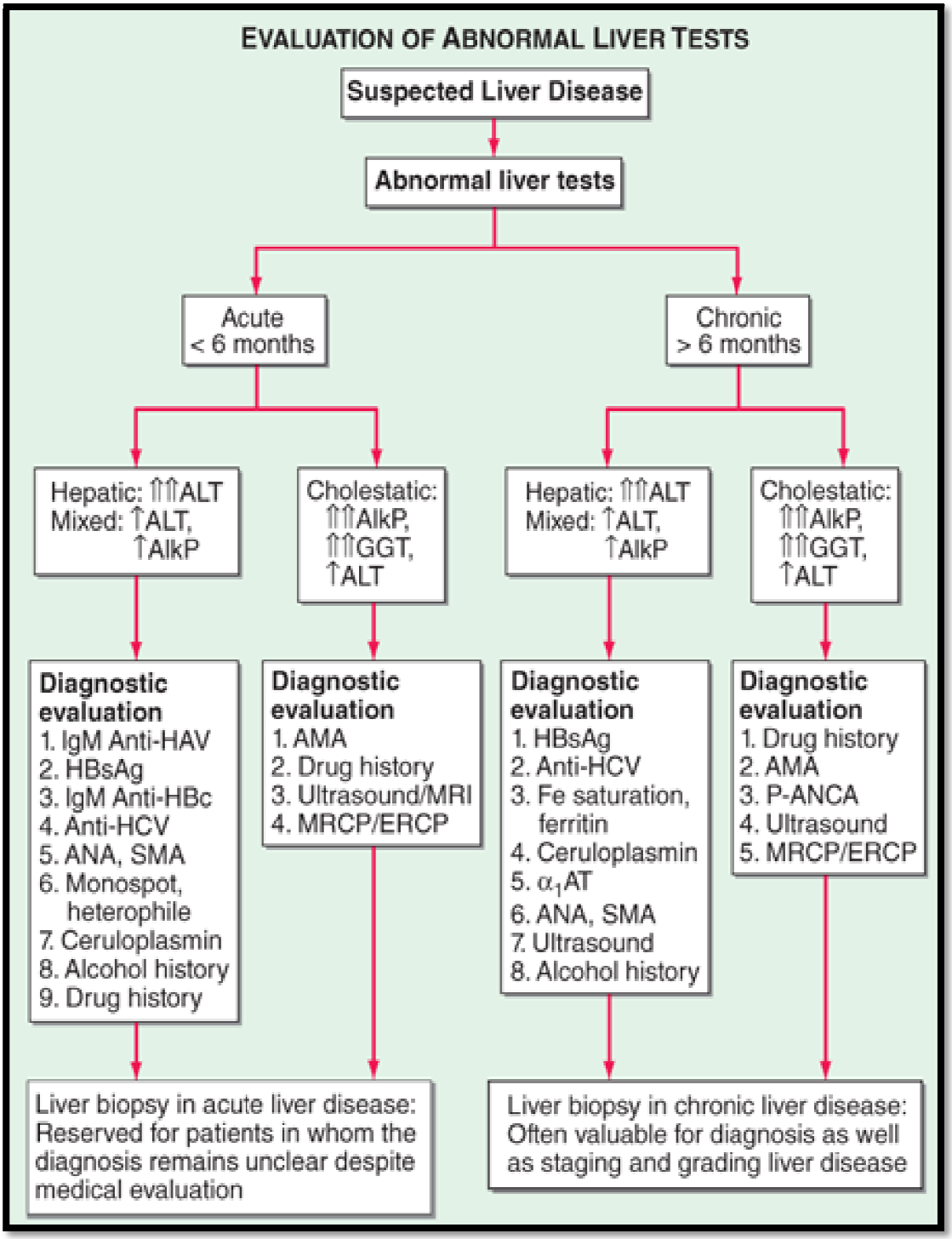
Unconjugated hyperbilirubinemia
Increased bilirubin production*
Extravascular hemolysis
Extravasation of blood into tissues
Intravascular hemolysis
Dyserythropoiesis
Wilson disease
Impaired hepatic bilirubin uptake
Heart failure
Portosystemic shunts
Some patients with Gilbert syndrome
Certain drugs¶ - rifampin, probenecid, flavaspadic acid, bunamiodyl
Impaired bilirubin conjugation
Crigler-Najjar syndrome types I and II
Gilbert syndrome
Neonates
Hyperthyroidism
Ethinyl estradiol
Liver diseases - chronic hepatitis, advanced cirrhosis
Conjugated hyperbilirubinemia
Defect of canalicular organic anion transport
Dubin-Johnson syndrome
Defect of sinusoidal reuptake of conjugated bilirubin
Rotor syndrome

Conjugated hyperbilirubinemia (continued)
Extrahepatic cholestasis (biliary obstruction)
Choledocholithiasis
Intrinsic and extrinsic tumors (eg, cholangiocarcinoma, pancreatic cancer)
Primary sclerosing cholangitis
AIDS cholangiopathy
Acute and chronic pancreatitis
Strictures after invasive procedures
Certain parasitic infections (eg, *Ascaris lumbricoides*, liver flukes)
Intrahepatic cholestasis
Viral hepatitis
Alcoholic hepatitis
Nonalcoholic steatohepatitis
Chronic hepatitis
Primary biliary cholangitis
Drugs and toxins (eg, alkylated steroids, chlorpromazine, herbal medications [eg, Jamaican bush tea], arsenic)
Sepsis and hypoperfusion states
Infiltrative diseases (eg, amyloidosis, lymphoma, sarcoidosis, tuberculosis)
Total parenteral nutrition
Postoperative cholestasis
Following organ transplantation
Hepatic crisis in sickle cell disease
Pregnancy
End-stage liver disease

CAUSES OF ELEVATED TRANSAMINASES

Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	**AST predominant (AST/ALT ≥1)**	
Drug-induced liver injury	Alcoholic hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency		Celiac disease
Congestive hepatopathy		Macro AST
Malignant infiltration of the liver		

INTERPRETATION OF ABNORMAL LFT



LFT PATTERNS IN HEPATOBILIARY DISORDERS

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU, ALT > AST	Normal to <3× normal elevation	Normal	Usually normal. If >5× above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT >2 suggests alcoholic hepatitis or cirrhosis	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation	Elevated, often >4× normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
(Obstructive jaundice)	Bilirubinuria	Rarely >500 IU		Normal	Normal
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation	Elevated, often >4× normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase		

Establishing a pattern of liver disease at the end of liver function testing can help the clinician in further evaluation of the disease process. These tests need to be repeated on several instances over days to week to embark upon a diagnostic pattern. The causes of derangement of liver function tests varies from region to region. Infectious diseases tend to cause more cases of chronic liver disease in developing nations when compared with developed nations. The most effective way to increase the specificity and sensitivity of the liver function testing is to combine a battery of investigations namely bilirubin, aminotransferases, prothrombin time, albumin, alkaline phosphatase along with judicious use of other investigations to establish the etiology.

NATURAL HISTORY OF THE DISEASE

Cirrhosis can be classified as either compensated or decompensated depending upon the development of complications.

Decompensation refers to the development of complications in the form of variceal hemorrhage, ascites, hepatic encephalopathy, jaundice or hepatocellular carcinoma. These complications are not present in compensated cirrhosis. 4 clinical stages of cirrhosis has been defined

Stage 1 – absence of both ascites and varices

Stage 2 – presence of varices without bleeding and absence of ascites

Stage 3 – ascites with or without esophageal varices

Stage 4 – variceal bleeding with or without ascites

The most common cause of death in cirrhosis is due to development of hepatic decompensation namely portal hypertension, HCC and sepsis. In case of compensated cirrhosis death occurs due to cardiovascular cause or stroke or malignancy or renal disease.

	Compensated Cirrhosis		Decompensated Cirrhosis	
Stage	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	No Varices No Ascites	Varices No Ascites	Ascites +/- Varices	Bleeding +/- Ascites
Death (at 1 Year)	1%	3%	20%	57%

I – ASCITES

The term ascites refers to the presence of free fluid within the peritoneal cavity. It can be caused due to cirrhotic or non cirrhotic causes. Cirrhosis remains the commonest cause of ascites. Non cirrhotic causes of ascites include peritoneal malignancy, cardiac failure and peritoneal tuberculosis.

Though there are different mechanisms of ascites formation presence of portal hypertension and renal sodium retention remains universal. It progresses through stages of diuretic responsiveness to dilutional hyponatremia, refractory ascites and can terminate in Hepato renal syndrome.

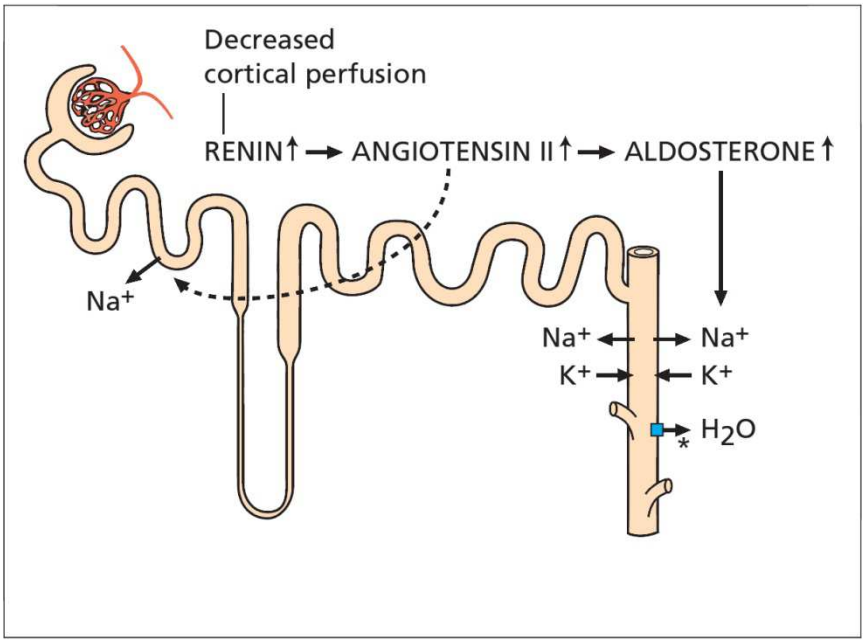
The transition from simple ascites to the stage of diuretic resistant ascites leads to decline in 1 year survival rate from 85% to 25%. The treatment of ascites is important in improving the quality of life, to avoid development of spontaneous bacterial peritonitis (SBP). Though newer treatments such as TIPS are being evaluated for treatment of refractory ascites Liver transplantation remains the ultimate therapy for ascites and should also always be considered when the patient presents for the first time with ascites.

Theories Of ascites formation:

The factor which initiates leakage of ascites into the peritoneal space is the sinusoidal hypertension. The regenerative nodules and fibrosis leads to hepatic venous outflow block and sinusoidal hypertension. The central event in the development of ascites is sodium and water retention which replenishes the intravascular volume and maintains the ascites formation.

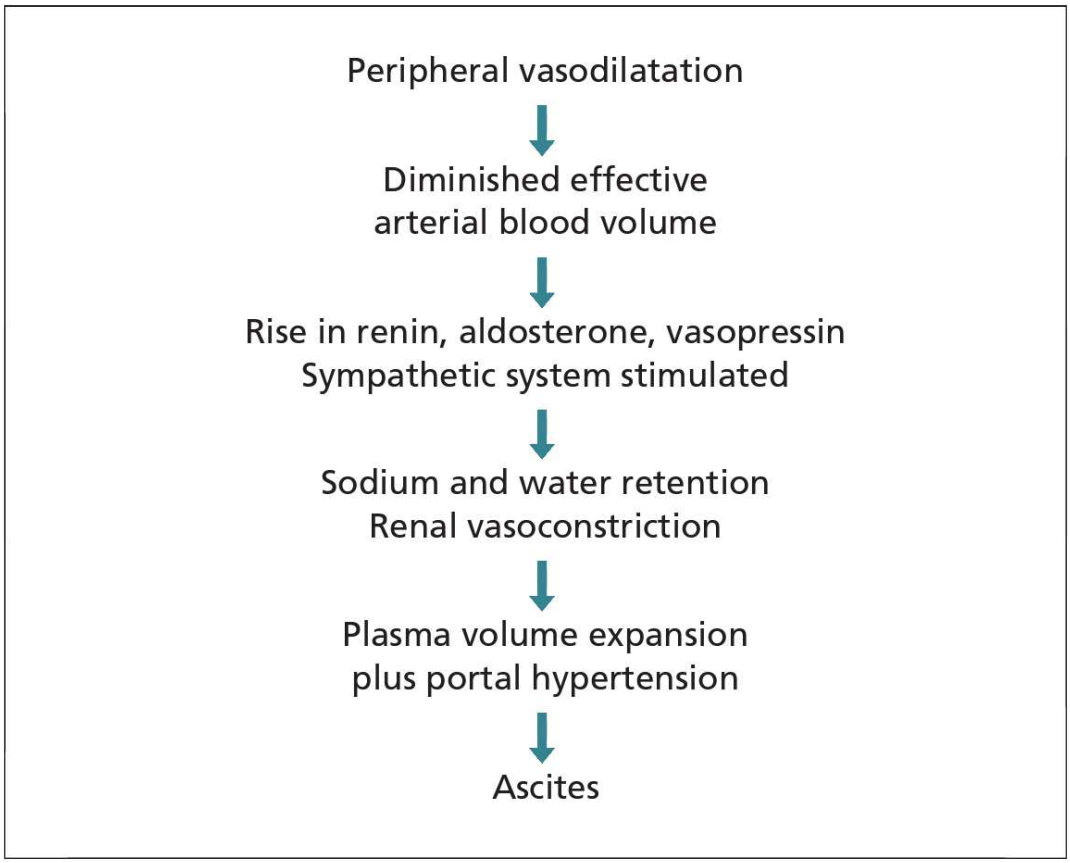
The development of ascites requires a minimal portal pressure gradient of 12mm Hg. Clinically significant portal hypertension refers to portal pressure gradient of 10mm Hg. Urinary sodium excretion is usually less than 5mmol/day. There is avid sodium retention even in the absence of ascites.

	Underfill/ peripheral arterial vasodilatation theory	Overfill theory
Primary event	Vascular	Renal
Secondary event	Renal	Vascular

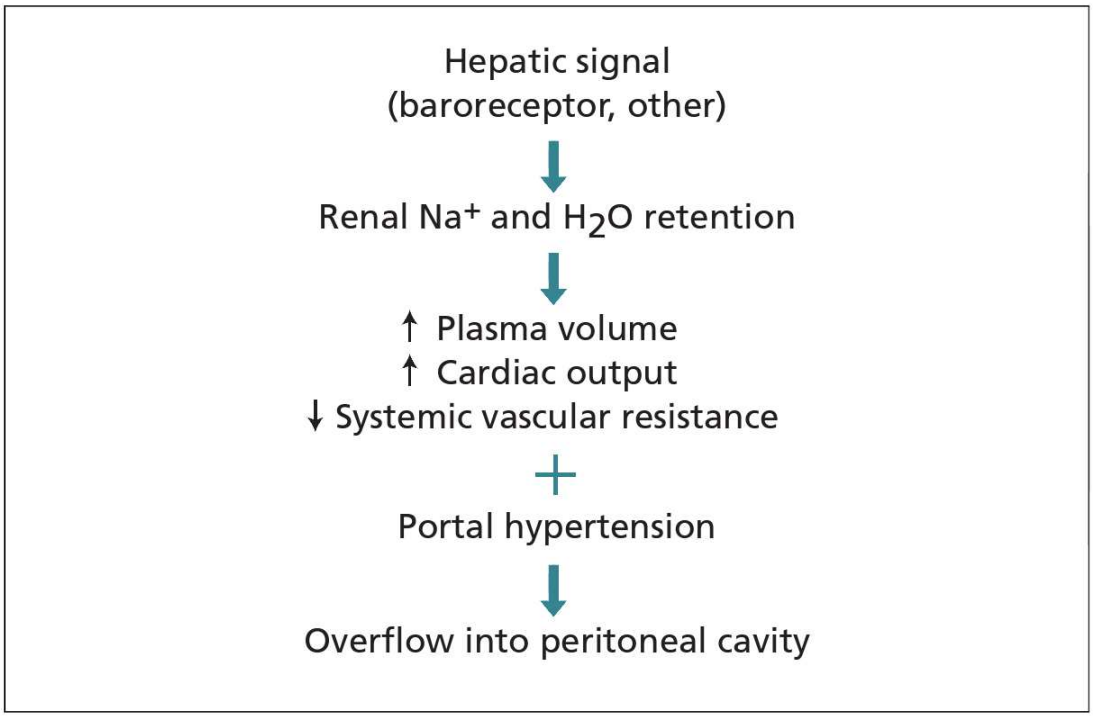


"Vasodilatation theory" is based upon the fact that altered hemodynamics in cirrhosis with arterial vasodilatation is the most likely cause of sodium retention. The vasodilatation is the result of excess production of nitric oxide (NO). other agents implicated in the peripheral vasodilatation includes carbon monoxide, adrenomedullin, endocannabinoids, prostacyclin, tumor necrosis factor alpha and urotensin. The arterial vasodilatation results in

reduced effective arterial blood volume and fall in systemic pressure which results in the activation of RAAS and sympathetic system. There is downstream release of aldosterone from adrenal gland. The aldosterone acts upon the renal tubules and results in reabsorption of sodium. Angiotensin 2 also leads to release of ADH and activation of adrenergic system.



"Overfill theory" is based upon the presence of renal sodium handling abnormalities in the absence of systemic vasodilatation or under filling. There is excess reabsorption of sodium and water which leads to expansion of plasma volume and increases cardiac output with a fall in systemic vascular resistance.



Ascites due to cirrhosis and elevated portal pressure gradient gives rise to a high SAAG (serum ascites albumin gradient) more than or equal to 1.1g/dl. The first line of management of ascites is salt restricted diet upto 2g/day. If this is ineffective then patient is started on oral diuretics. Frusemide and spironolactone are usually used. They can be titrated to achieve a maximum dose of 160mg for frusemide and 400mg for spironolactone. The term refractory ascites is given to free fluid in the abdomen despite optimal salt restriction and maximal dose of diuretics.

Refractory ascites can be managed with pharmacological agents such as midodrine or clonidine which acts by counteracting splanchnic vasodilatation. Beta blockers tend to reduce survival rates in patients with refractory ascites. It can also be managed with large volume paracentesis or TIPS. Large volume

paracentesis should be accompanied by albumin infusions to prevent circulatory dysfunction.

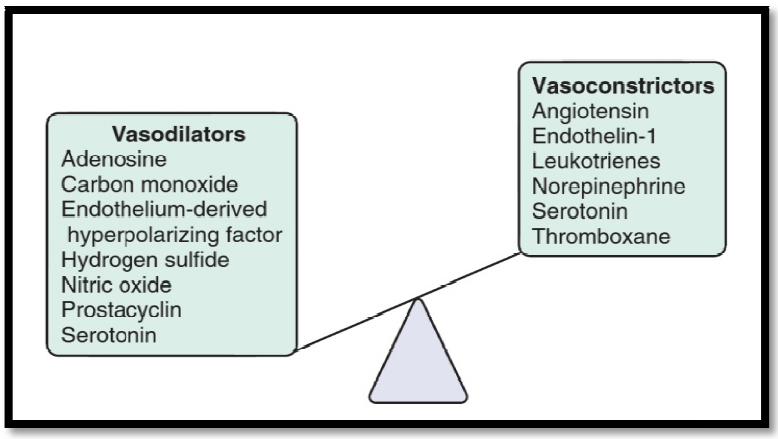
Complications of ascites include spontaneous bacterial peritonitis, hepatic hydrothorax and hepatorenal syndrome.

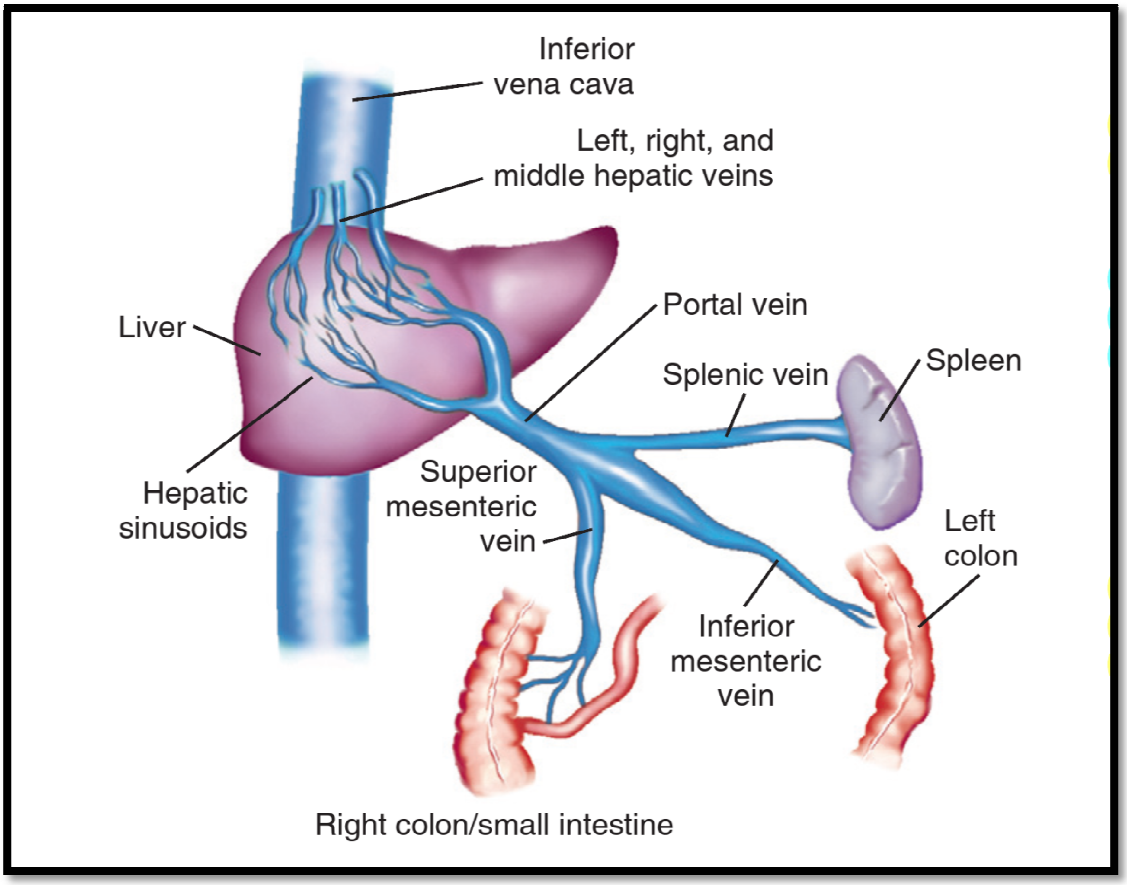
II – PORTAL HYPERTENSION

Capillary blood from the esophagus, stomach, small and large intestine, pancreas, gall bladder and spleen are carried via the portal venous system to the liver. It a high compliance and low pressure system. There is dual blood supply to the liver from mesenteric venous circulation (75%) and the remainder from hepatic artery. Liver consists of an inherent auto regulatory mechanism which helps in maintaining the total hepatic blood flow at a constant rate.

Portal hypertension arises as a result of change in portal resistance and change in portal blood flow. These changes can arise as a result of mechanical and vascular factors. Fibrosis and regenerative nodules constitute the mechanical factors. There are numerous mediators that result in intrahepatic vasoconstriction with splanchnic and peripheral vasodilatation.

Elevated portal pressure leads to development of porto-systemic collaterals. The flow pattern in collaterals is reversed and blood flows away from the liver towards the systemic circulation. The sites of collaterals include distal esophagus, proximal stomach, umbilicus, retroperitoneum, rectum.





There are four zones of venous drainage in the distal esophagus that is important to the understanding of the development of esophageal varices. This includes

1. The gastric zone – draining into short gastric and left gastric veins
2. The palisade zone – do not communicate with periesophageal veins

3. The perforating zone – connects esophageal submucosal veins and periesophageal veins
4. The truncal zone – longitudinal veins in lamina propria.

The palisade zone is most prone for bleeding since there is no perforating veins connecting the submucosal veins with periesophageal veins.[40]

Patients with intrahepatic cause of portal hypertension most commonly present with esophageal/gastric varices in continuity with esophageal varices. This requires a portal pressure gradient of 10mm Hg to develop. Increase in this gradient to 12mm Hg is required for the varices to bleed. Hepatic vein pressure gradient(HVPG) is an indirect method of measuring portal pressure. It is the difference between wedged hepatic venous pressure(WHVP) and free hepatic vein pressure(FHVP). It measures the gradient between portal vein and the intra abdominal inferior vena cava. 3 measurements are done in order to ensure reproducibility. Its uses include

1. Monitoring of portal pressure in patient taking drugs to prevent variceal bleeding
2. For prognostification
3. In clinical trials to asses drug efficacy
4. Risk of hepatic resection in patient with cirrhosis
5. To identify the cause of portal hypertension.

Other less common methods of assessing the pressure in the portal system includes splenic pulp pressure, portal vein pressure,endoscopic variceal pressure.

Type of Portal Hypertension	WHVP	FHVP	HVPG
Prehepatic	Normal	Normal	Normal
Presinusoidal	Normal	Normal	Normal
Sinusoidal	Increased	Normal	Increased
Postsinusoidal	Increased	Normal	Increased
Posthepatic Heart failure Budd-Chiari syndrome	Increased —	Increased Hepatic vein cannot be cannulated	Normal —

CLASSIFICATION OF PORTAL HYPERTENSION

- Prehepatic
  - Portal vein thrombosis
  - Splenic vein thrombosis
  - Massive splenomegaly (Banti's syndrome)
- Hepatic
  - Presinusoidal
    - Schistosomiasis
    - Congenital hepatic fibrosis
  - Sinusoidal
    - Cirrhosis—many causes
    - Alcoholic hepatitis
  - Postsinusoidal
    - Hepatic sinusoidal obstruction (venoocclusive syndrome)
- Posthepatic
  - Budd-Chiari syndrome
  - Inferior vena caval webs
  - Cardiac causes
    - Restrictive cardiomyopathy
    - Constrictive pericarditis
    - Severe congestive heart failure

Approximately one third of cirrhotics have varices and 5 to 15% of cirrhotics per year develop varices. One third of patients with varix develop bleeding. Portal hypertension is ameliorated by reducing the blood flow or decreasing intrahepatic resistance.

Pharmacologic agents act either by decreasing the splanchnic blood flow or by decreasing the intrahepatic vascular resistance.

1. Vasopressin analogs can be used for acute reduction of splanchnic blood flow. There can be systemic adverse effects resulting in vasoconstriction, negative inotropic/chronotropic effects on the myocardium. There is a possibility of increased afterload which can precipitate an episode of myocardial infarction. It can induce diuresis by acting on the kidney and can result in hyponatremia. Terlipressin can be used in combination with nitrates to reduce the systemic adverse effects.
2. Somatostatin and its analogs can cause reduction in portal blood pressure and reduce the collateral blood flow by inhibiting the release of glucagon. It can also bring about a decrease in portal pressure by reducing the splanchnic blood flow.
3. Beta blockers especially non selective beta blockers such as propranolol or nadolol are used. They cause decreased cardiac output, inhibits the mesenteric vasodilatation which brings about a decrease in portal blood flow. Measurement of HVPG can be done to asses the efficacy of beta blockers. Clinically a fall in heart rate can be used as a guide to titration of beta blockers. Beta blockers are detrimental in late stages of liver

disease and also in cases of refractory ascites it tends to increase the mortality.

4. Combined alpha and beta blockade. Carvedilol has non selective beta blockade along with a weak alpha receptor blocker activity. Carvedilol can cause hypotension and renal sodium retention. It has added antioxidant and anti proliferative properties. It reduces the incidence of rebleeding with significantly better adverse drug reaction profile. Increase in doses are heralded by the development of hypotension.
5. Nitrates result in venodilataion and brings down the portal pressure by reducing the portal venous blood flow. It is usually used in combination with a beta blocker to prevent episodes of rebleeding.
6. Other agents used are prazosin, losartan, simvastatin, ET blockers and NO donors.
7. Other treatment modalities include sclerotherapy, variceal ligation, detachable snares, balloon tamponade, stents, TIPS, BRTO.
8. Surgical treatment modalities can be either non shunt procedures (esophageal transection, devascularization)or portosystemic shunt procedures (selective shunts, partially selective shunts, portocaval shunts, mesenterico-left portal venous bypass).

BOX 92-2 Drugs Used in the Treatment of Portal Hypertension

Drugs That Decrease Portal Blood Flow

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

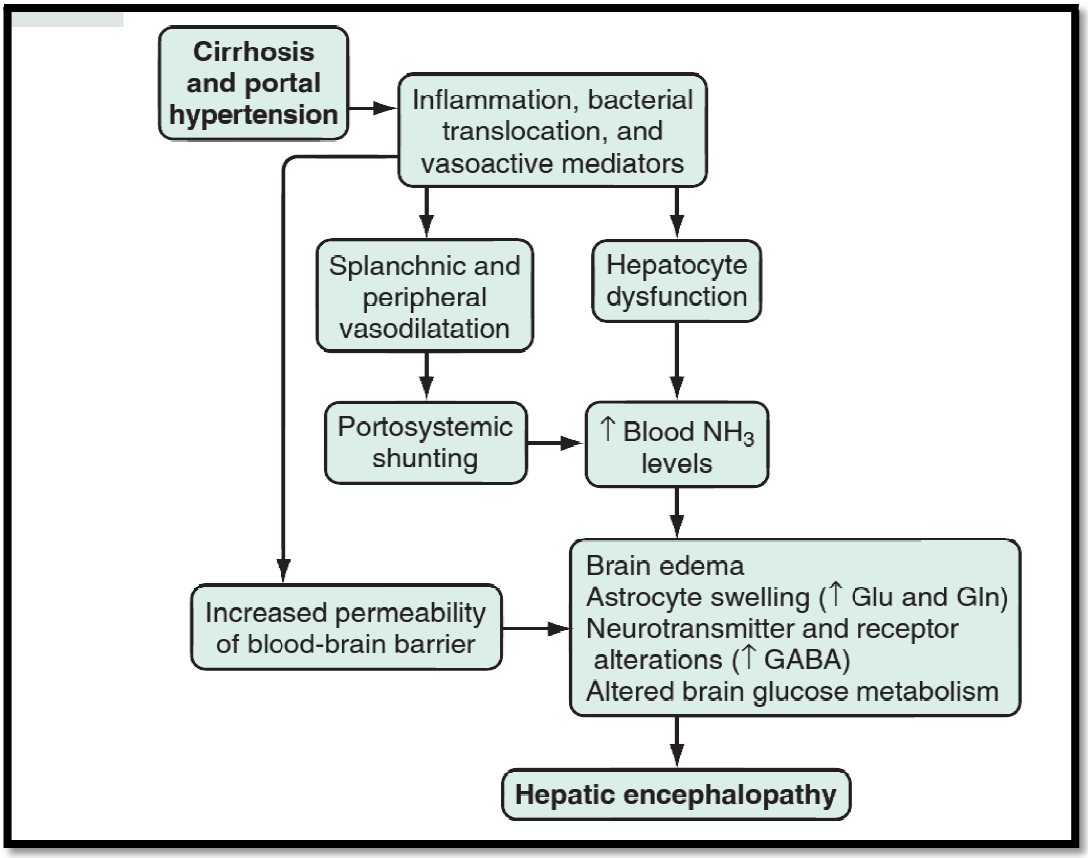
Drugs That Decrease Intrahepatic Resistance

α_1-Adrenergic blocking agents (e.g., prazosin)
Angiotensin receptor blocking agents
Nitrates

III – HEPATIC ENCEPHALOPATHY

It is a state of reversible neuropsychiatric symptoms that primarily results from accumulation of waste products especially ammonia by the liver. It has important implications on the patient survival. There can be either mild neurocognitive disturbance or frank coma. It is usually precipitated by an inciting event and elimination of the inciting event along with pharmacotherapy for removal of excess ammonia is the mainstay treatment. Liver transplantation can also reverse HE.

PATHOPHYSIOLOGY OF HEPATIC ENCEPHALOPATHY



There are 3 major categories of HE

1. Type A – associated with acute liver failure
2. Type B – associated with portosystemic shunts without liver disease
3. Type C – associated with chronic liver disease

Type C is the most common and can be further divided based on west haven criteria. Treatment of hepatic encephalopathy includes the use of non absorbable disaccharides (lactulose or lactitol).

GRADING OF HEPATIC ENCEPHALOPATHY

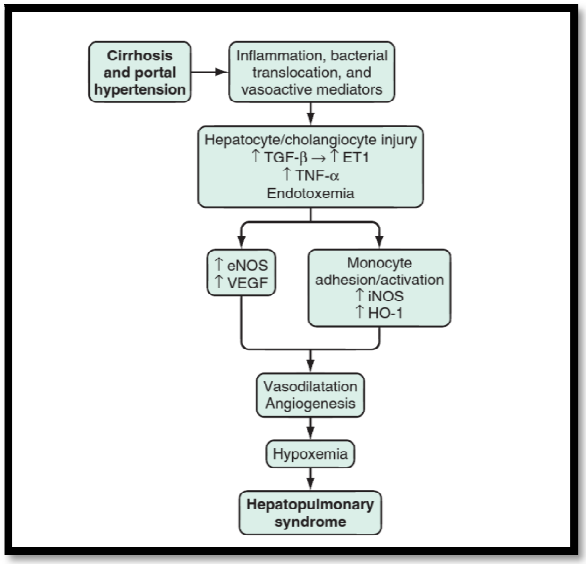
West Haven Criteria			SONIC			
Grade	**Intellectual Function**	**Neuromuscular Function**	**Classification**	**Mental Status**	**Special Tests**	**Asterixis**
0	Normal	Normal	Unimpaired	Not impaired	Normal	Absent
Minimal	Normal examination findings; subtle changes in work or driving	Minor abnormalities of visual perception or on psychometric or number tests	Covert HE	Not impaired	Abnormal	Absent
1	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination				
2	Changes in sleep-wake cycle, lethargy, mood and behavioral changes, cognitive dysfunction	Asterixis, ataxic gait, speech abnormalities (slow and slurred)	Overt HE	Impaired	Abnormal	Present (absent in coma)
3	Altered level of consciousness (somnolence), confusion, disorientation, and amnesia	Muscular rigidity, nystagmus, clonus, Babinski sign, hyporeflexia				
4	Stupor and coma	Oculocephalic reflex, unresponsiveness to noxious stimuli				

Oral antibiotics are also used to treat HE. The aim is to modify the intestinal bacterial flora and lowering of stool pH to promote excretion of ammonia. Rifaximin 550mg BD is widely used. Other agents include use of neomycin, metronidazole, vancomycin.

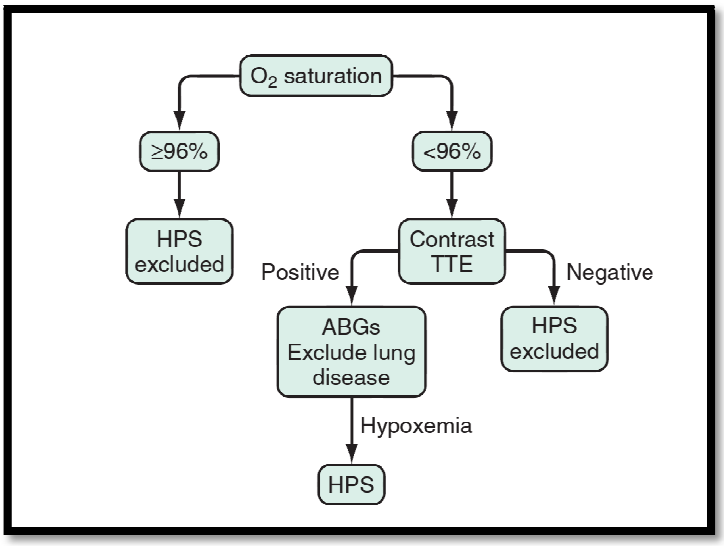
Sodium benzoate, sodium phenylbutyrate and sodium phenylacetate can enhance the excretion of ammonia in the urine. Zinc can also help in improvement of hepatic encephalopathy. MARS (molecular adsorbent recirculating system), albumin dialysis can also be tried. The role of LOLA has also been validated in many clinical trials and can alleviate the degree of hepatic encephalopathy.

IV – HEPATOPULMONARY SYNDROME AND PORTOPULMONARY HYPERTENSION

Hepatopulmonary syndrome results from alterations in the pulmonary microvasculature that leads to impaired gas exchange. POPH results from vasoconstriction and remodeling in resistance vessels. They indicate increased mortality rates in affected patients. HPS is associated with increased levels of NO in the pulmonary circulation that results in vasodilatation and angiogenesis in the pulmonary microvasculature. POPH histologically resembles other forms of pulmonary arterial hypertension. It is more common in women. The classic manifestations of HPS includes platypnea and orthodeoxia. Presence of clubbing and arterial hypoxemia in the absence of other cardiopulmonary disease should lead to a suspicion of HPS in patients with cirrhosis. The symptoms worsen over time. There is marked hypoxemia during sleep. IV contrast echocardiography can be used to detect presence of intrapulmonary shunting of blood.



POPH is characterized by exertional dyspnea. Physical examination can reveal signs suggesting pulmonary arterial hypertension. Presence of peripheral edema out of proportion to ascites should lead to suspicion of the presence of a superadded right ventricular dysfunction resulting from POPH. Initial echocardiographic evaluation suggesting right ventricular dysfunction should be subjected to pulmonary artery catheterization.



HPS reversed in upto 80% of patients with liver transplantation and is the treatment of choice. Liver transplantation is contraindicated in the presence of POPH because of the presence of right ventricular dysfunction. Pre treatment with medications to lower pulmonary vascular resistance can permit transplantation in such patients. Diuretics are used in POPH to reduce preload. Prostacyclin analogs, ET antagonist, PDE 5 inhibitors can be tried.

V – HEPATORENAL SYNDROME

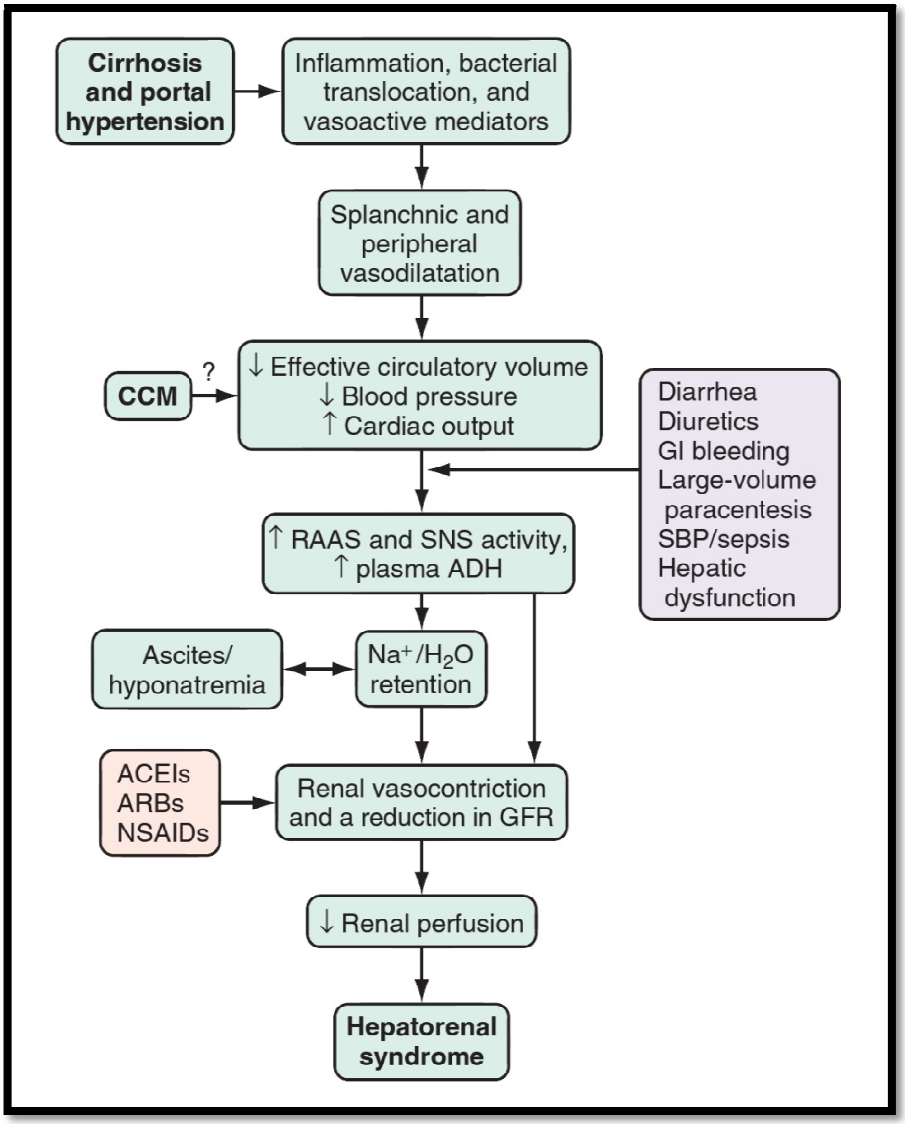
Hepatorenal syndrome is linked to the cascade of altered hemodynamics that is present in patients with cirrhosis of liver. There is intense renal vasoconstriction which leads on to development of renal failure with anatomically normal kidneys. It is essential to recognize and treat hepatorenal syndrome as it is linked to reduced survival in patients with established liver disease.

The 3 events which has been postulated in the initiation and progression of hepatorenal syndrome are

1. Splanchnic and systemic arterial vasodilatation
2. Renal vasoconstriction
3. Cardiac dysfunction

(continued)

PATHOPHYSIOLOGY OF HRS



The diagnosos of hepatorenal syndrome requires exclusion of other causes of renal dysfunction. The patients are asymptomatic from renal failure. The raising BUN can precipitate encephalopathy.

DIAGNOSTIC CRITERIA FOR HRS

Cirrhosis with ascites
Serum creatinine level ≥ 1.5 mg/dL (133 μmol/L)
No or insufficient improvement in serum creatinine level (remains ≥ 1.5 mg/dL) 48 hr after diuretic withdrawal and adequate volume expansion with IV albumin
Absence of shock
No evidence of recent use of nephrotoxic agents
Absence of intrinsic renal disease

There are two types of HRS

Type 1:

- Usually triggered by an inciting event
- SBP is the most common inciting event
- Rapidly progressive renal dysfunction
- Serum creatinine levels are usually above 2.5mg/dl

Type 2:

- Slower compared to type 1 HRS
- Usually observed in patients with severe diuretic resistant ascites
- Serum creatinine levels are usually less than 2.5mg/dl

CRITERIA FOR DIAGNOSIS OF KIDNEY DYSFUNCTION IN PATIENTS WITH CIRRHOSIS

Diagnosis	Criteria
Acute kidney injury	50% increase in the serum creatinine level from baseline in < 48 hours *OR* Rise of 0.3 mg/dL (26.4 μmol/L) in the serum creatinine level in < 48 hours
Chronic kidney disease	Glomerular filtration rate < 60 mL/min for > 3 months (using MDRD 6 formula)
Acute-on-chronic kidney disease	Glomerular filtration rate < 60 mL/min for > 3 months (using MDRD 6 formula) 50% increase in the serum creatinine level from baseline in < 48 hours or a rise of 0.3 mg/dL (26.4 μmol/L) in the serum creatinine level in < 48 hours

Management of HRS includes

- Correction of intravascular volume depletion
- Treating underlying infections
- Avoidance of nephrotoxic drugs
- Therapeutic options include medical therapy, TIPS and liver transplantation
- The therapies aim at reversing the systemic and splanchnic vasodilatation with vasoconstrictors and increasing the effective circulating volume with use of colloid followed by definitive treatment – liver transplantation

- Extracorporeal albumin dialysis with MARS, use of dopamine and use of non selective endothelin receptor antagonist have not demonstrated benefits on a large scale

MANAGEMENT OF HRS

- Measures to prevent variceal bleeding (e.g., beta blockers, band ligation)
- Pentoxifylline for severe alcoholic hepatitis
- Prevention of HRS
  - Avoid intravascular volume depletion (diuretics, lactulose, GI bleeding, large-volume paracentesis without adequate volume repletion)
  - Judicious management of nephrotoxins (ACEIs, ARBs, NSAIDs, antibiotics)
  - Prompt diagnosis and treatment of infections (SBP, sepsis)
  - SBP prophylaxis
- Treatment of HRS
  - Stop all nephrotoxic agents (ACEIs, ARBs, NSAIDs, diuretics)
  - Antibiotics for infections
  - IV albumin—bolus of 1 g/kg/day on presentation (maximum dose, 100 g daily). Continue at dose of 20-60 g daily as needed to maintain central venous pressure between 10 and 15 cm H_2O
  - Vasopressor therapy (in addition to albumin):
    - Terlipressin*—start at 1 mg IV every 4 hr and increase up to 2 mg IV every 4 hr if baseline serum creatinine level does not improve by 25% at day 3 of therapy
    - *OR*
    - Midodrine and octreotide—begin midodrine at 2.5-5 mg orally 3 times daily and increase to a maximum dose of 15 mg 3 times daily. Titrate to an MAP increase of at least 15 mm Hg; begin octreotide at 100 µg subcutaneously 3 times daily and increase to a maximum dose of 200 µg subcutaneously 3 times daily, or begin octreotide at a 25-µg IV bolus and continue at a rate of 25 µg/hr
    - *OR*
    - Norepinephrine—0.1-0.7 µg/kg/min as an IV infusion. Increase by 0.05 µg/kg/min every 4 hr and titrate to an MAP increase of at least 10 mm Hg
    - Duration of vasopressor treatment is generally a maximum of 2 weeks until reversal of hepatorenal syndrome or liver transplantation
- Evaluation of patient for liver transplantation

VI - COAGULATION DISORDERS

Loss of functional hepatocytes results in deficiency of procoagulant factors that are dependent on vitamin K (2,7,9,10), factor 5 and factor 11. There is a prolonged prothrombin time with increased risk of bleeding. This can be managed by transfusion of fresh frozen plasma, vitamin K and factor VIIa. INR is used in prediction of survival in cirrhotics by used of MELD scoring and also in prioritizing patients with liver disease for transplantation.

Presence of thrombocytopenia can indicate portal hyptertension leading on to hypersplenism. The platelet counts can also be decreased as a result of reduced thrombopoietin synthesis and bone marrow toxicity. There is also impaired platelet thrombin generation and as result there is impaired clot formation. However there is no direct increase in the risk of bleeding and hence routine transfusion of platelets are not indicated.

Cirrhosis leads on to dysfibrinogenimia that manifests either as hyper or hypofibrinolysis. There is also impaired production of endogenous anticoagulant proteins resulting in a state of hypercoagulability and risk of thrombosis. However there are no definite guidelines regarding the role of anticoagulation in preventing portal vein thrombosis in case of chronic liver disease.

Thromboelastography can asses components of clot formation, clot strength and stability. They can be used as a predictive tool in determining the risk of rebleeding from esophageal varices. Studies show that despite multiple coagulation abnormalities they tend to maintain a balanced homeostatic milieu.

VII – ENDOCRINE DYSFUNCTION

Cirrhosis is associated with numerous endocrine abnormalities such as[5]

1. Adrenal insufficiency
2. Gonadal dysfunction
3. Bone disease
4. Thyroid dysfunction

1. Adrenal insufficiency

Both compensated and decompensated liver disease is associated with a state of relative adrenal insufficiency. This results in greater hemodynamic instability with increased mortality. The proposed mechanisms of adrenal insufficiency in liver disease are as follows

- Inadequate hepatic cholesterol production resulting in insufficient release of adrenal cortisols during periods of stress.
- Adrenal insufficiency due to increased levels of endotoxins and circulating cytokines.

There is no sufficient data regarding the benefit of glucocorticoid supplementation in patients with liver disease.

2. Gonadal dysfunction

Cirrhotics tend to experience both central and peripheral hypogonadism. There is increase in levels of sex hormone binding globulin (SHBG) which binds testosterone and 17B – estradiol with relatively lower affinity for estrogens. There is relative increase in the levels of SHBG with reduced

synthesis of dehydroepiandrosterone sulfate which is the cause of the feminization syndrome seen in male patients with cirrhosis.[5,16,19]

Alcohol has direct effects on the leydig cells and also on the hypothalamo – pituitary – gonadal axis. This leads to a decrease in the serum levels of luteinizing hormone and reduced responsiveness to gonadotropin releasing hormone.

Spironolactone which is used in treatment of ascites in cirrhotics displaces androgen from its receptor and binding protein and also causes increased levels of estradiol with increased clearance of testosterone from the circulation thus leading to the development of painful gynecomastia. The role of testosterone supplementation in cirrhotics is not validated.[37]

3. Bone disease

There is increased risk of osteoporosis among the cirrhotics with the risk factor being presence of cholestasis, a maternal history of hip fracture, alcohol consumption, progression of liver disease, low BMI, glucocorticoid use for more than 3 months and age. Bone mineral density scan can be used as a screening tool to detect osteoporosis in cirrhotics especially in patients with primary biliary cirrhosis and primary sclerosing cholangitis and those who require treatment with glucocorticoids for more than 3 months. Calcium and vitamin D supplementation and use of bisphosphonates can improve bone mineral density without producing serious side effects.[41]

4. Thyroid disease.

Liver plays an important role in metabolism of thyroid hormones and also in producing circulating thyroid hormone binding globulin. Thyroid hormones are produced from a precursor glycoprotein Thyroglobulin (TG). The TG gets iodinated after secretion into the thyroid follicles. The TG gets iodinated on the tyrosine residues and are coupled via an ether linkage. There is reuptake of TG into the follicular cells and proteolysis with resultant release of T3 and T4.[18,39]

TSH is responsible for regulation of thyroid gland function. It exerts its action via TSH receptor which is a G protein coupled receptor. Other factors regulating thyroid hormone synthesis includes insulin like growth factor – I, epidermal growth factor, transforming growth factor B, endothelins and various cytokines.[18,39,40]

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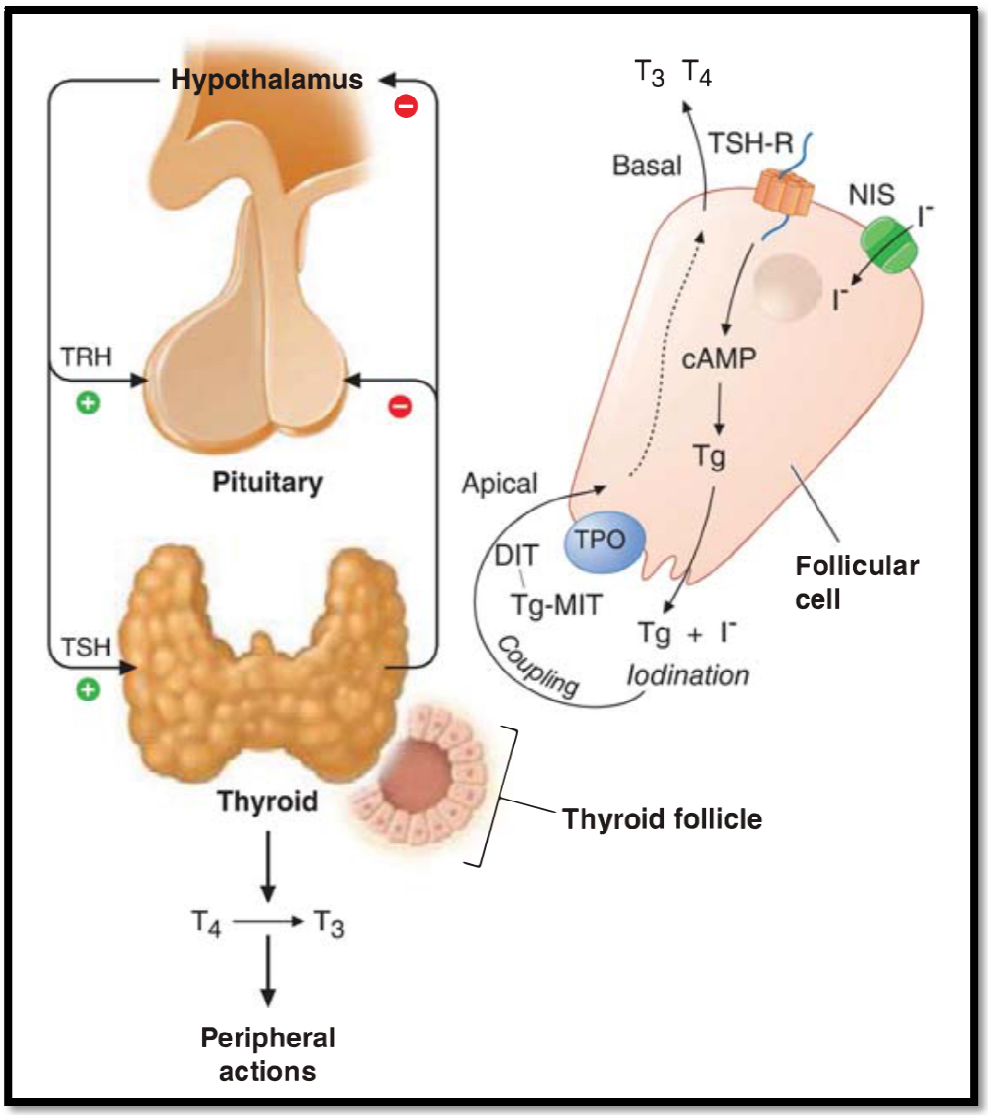


T4 is produced 20 times more than T3. They are bound to thyroxine binding globulin (TBG), Transthyretin (TTR), and albumin. Binding proteins increase the circulation pool of thyroid hormone, prolongs their half life and helps in delivery of thyroid hormones to various tissues.

TBG carries 80% of circulating pool of thyroid hormones with greater affinity for T4.

Albumin has relatively lower affinity for thyroid hormones and binds 10% of T4 and 30% of T3. TTR carries 10% T4 and very little T3. In toto approximately 99.98% of T4 and 99.7% T3 are protein bound.

PROPERTIES OF THYROID HORMONES

Hormone Property	T_4	T_3
Serum concentrations		
Total hormone	8 µg/dL	0.14 µg/dL
Fraction of total hormone in the unbound form	0.02%	0.3%
Unbound (free) hormone	$21 \times 10^{-12} M$	$6 \times 10^{-12} M$
Serum half-life	7 d	2 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 µg/d	32 µg/d
Intracellular hormone fraction	~20%	~70%
Relative metabolic potency	0.3	1
Receptor binding	$10^{-10} M$	$10^{-11} M$

T4 acts as precursor for T3. T4 is converted to T3 by the deiodinase enzymes. Type 1 deiodinase enzyme is located in thyroid gland, liver and kidneys. It has low affinity for T4. Type 2 deiodinase enzyme has higher affinity towards T4 and is found in pituitary gland, brain, brown fat and thyroid gland. Type 3 deiodinase enzyme is responsible for inactivation of T4 and T3 and is the most important source for rT3. Liver plays a pivotal role in metabolism and circulation of thyroid hormone by producing Thyroid binding globulin. It also plays an important role in producing T3 by action of the enzyme 5'deiodinase which is a selenium dependent enzyme and also produces rT3. Low free T3 syndrome is frequently found in patients with cirrhosis and it

is characterized by low levels of T3, increased rT3 and decreased T3:T4 ratio. The low levels of T3 is an adaptive response to reduce the basal metabolic rate of hepatocytes and preserve the liver function. Low T3 levels are also associated with low normal levels of fT4 and TSH levels in the normal or high normal range. There is an inverse correlation between the levels of T3 and the Child Pugh class and score. Loss of peripheral deiodination is the principal cause of decrease T3 levels.[2,3,10,22]

Poor nutrition has also been linked to the low levels of fT3 in circulation. Release of cytokines like IL6, alcohol consumption have also been linked to the low levels of fT3 in blood. Free T4 and TSH levels are not found to be significantly related to the Child Pugh class or scoring.[19,24,32]

A significant inverse correlation also exists between the levels of free T3 and MELD scoring. The levels of free T3 were significantly lower in decompensated cirrhosis in comparison to compensated cirrhosis. In conclusion serum free T3 levels can be used as a reliable prognostic indicator in patients with cirrhosis.[12,13]

MATERIALS AND METHODS

Study Centre : Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General hospital.

Study Design : Single centre observational prospective study.

Venue : Rajiv Gandhi Government General Hospital, Chennai.

Duration : Study conducted from June 2017 to November 2017.

Sample size was calculated using the formula **4*pq/d**, where **p** denotes the prevalence of the disease, **q = 1-p** and **d** denotes the error range. About 60 patients admitted to the medical wards with the diagnosis of decompensated chronic liver disease were chosen. A complete history was taken from the patients and the attenders including history of chronic kidney disease, previous history of treatment for hypo/hyperthyroidism, history of coronary artery disease. Basic blood investigations were done including a complete blood count, liver function test, pt/inr, renal function test, portal venous doppler, ultrasound abdomen and thyroid function test with measurement of serum free T3, free T4 and TSH.

A thorough physical examination was done and the degree of ascites and encephalopathy were quantified. Child Pugh score was calculated. Patients were treated as per established protocols.

Inclusion criteria:

Patients with a diagnosis of decompensated chronic liver disease admitted in medical wards.

Exclusion criteria:

Patients with cardiac failure, patients with chronic kidney disease, patients with pre existing thyroid dysfunction (hypo/hyperthyroidism) and patients who are terminally ill.

Statistical analysis plan:

Data analysed using statistical package – SPSS software

Consent:

Written informed consent was obtained from the participating patients/attenders.

Ethical committee approval:

Institutional Ethical Committee of Madras Medical College approved the study.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

Table 1 : Age groups in the study population

AGE_GROUP	FREQUENCY	PERCENT
30-40 YEARS	15	25.0
41-50 YEARS	29	48.3
ABOVE 50 YEARS	16	26.7
TOTAL	60	100.0

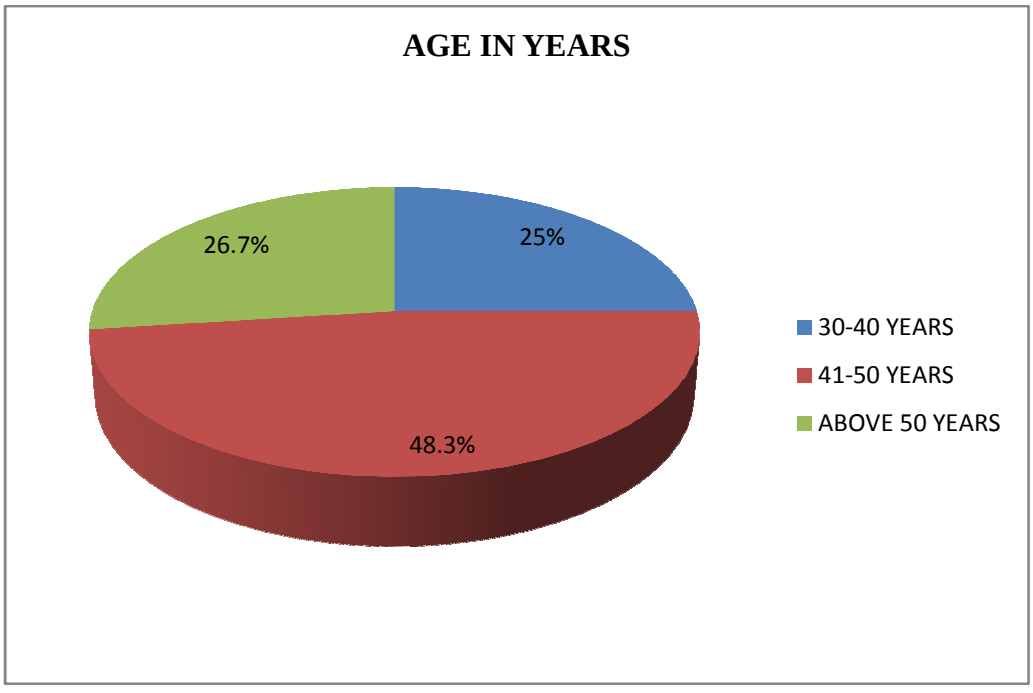


Table 2 : Gender distribution in the study population

GENDER	FREQUENCY	PERCENT
MALE	46	76.7
FEMALE	14	23.3
TOTAL	60	100.0

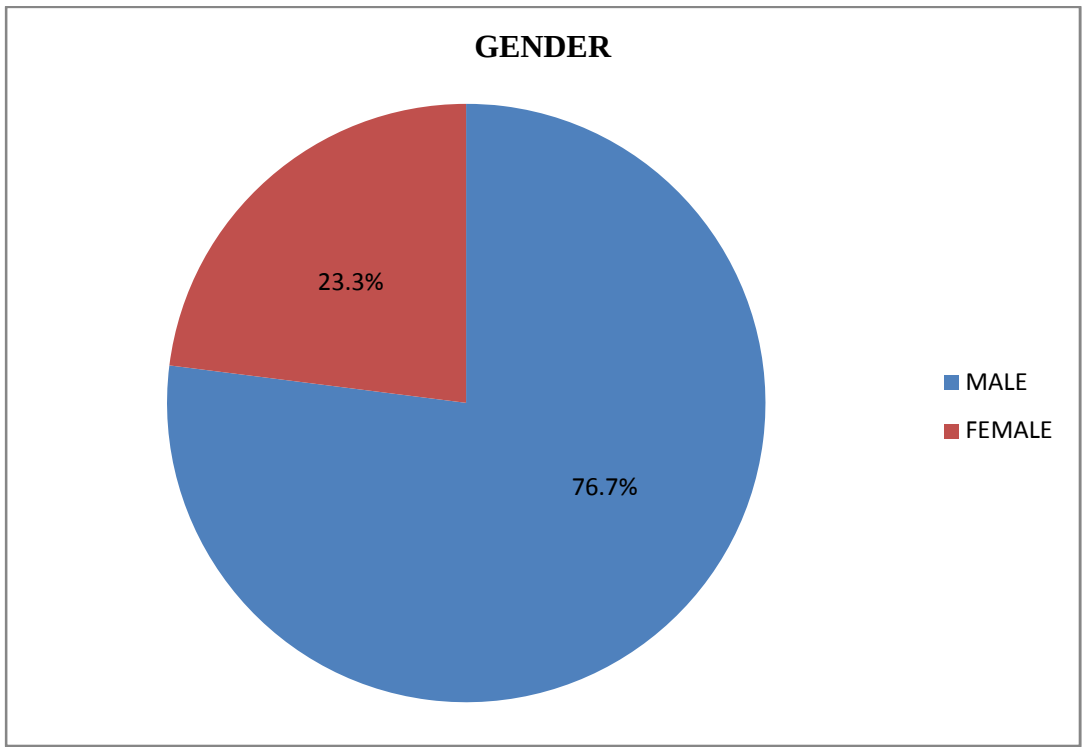


Table 3 : Ascites in the study population

ASCITES	FREQUENCY	PERCENT
ABSENT	20	33.3
MILD	25	41.7
TENSE	15	25.0
TOTAL	60	100.0

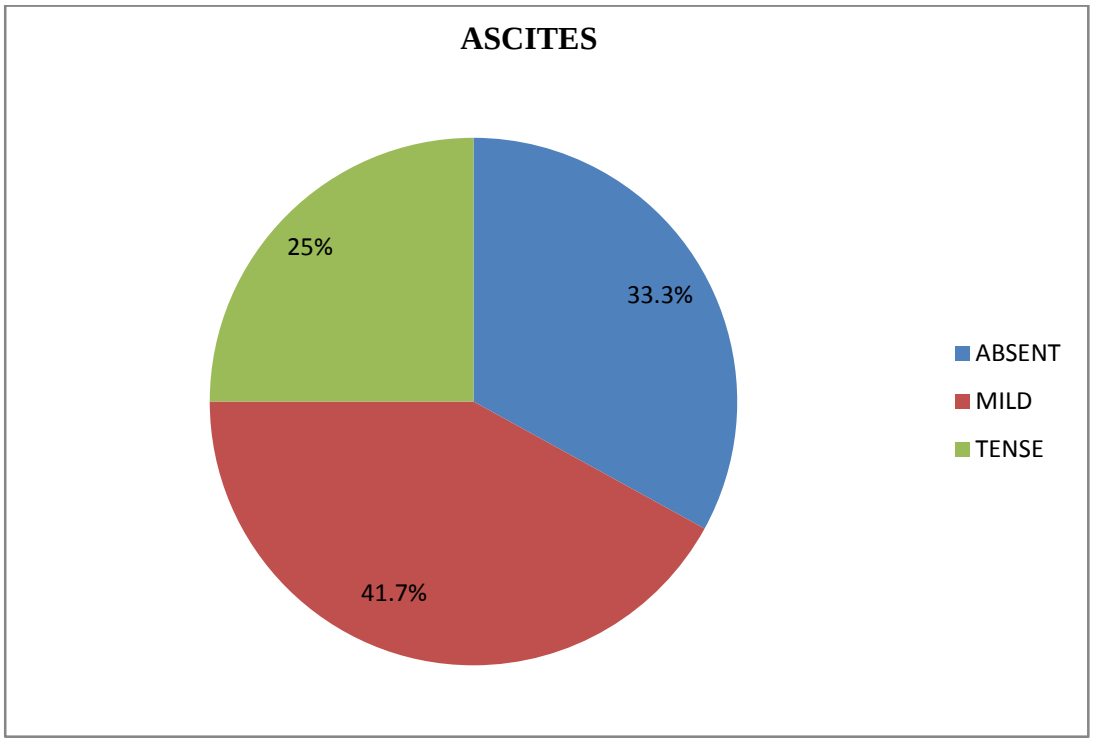


Table 4 : Encephalopathy in the study population

ENCEPHALOPATHY	FREQUENCY	PERCENT
ABSENT	31	51.7
GRADE 1	13	21.7
GRADE 2	10	16.7
GRADE 3	5	8.3
NONE	1	1.7
TOTAL	60	100.0

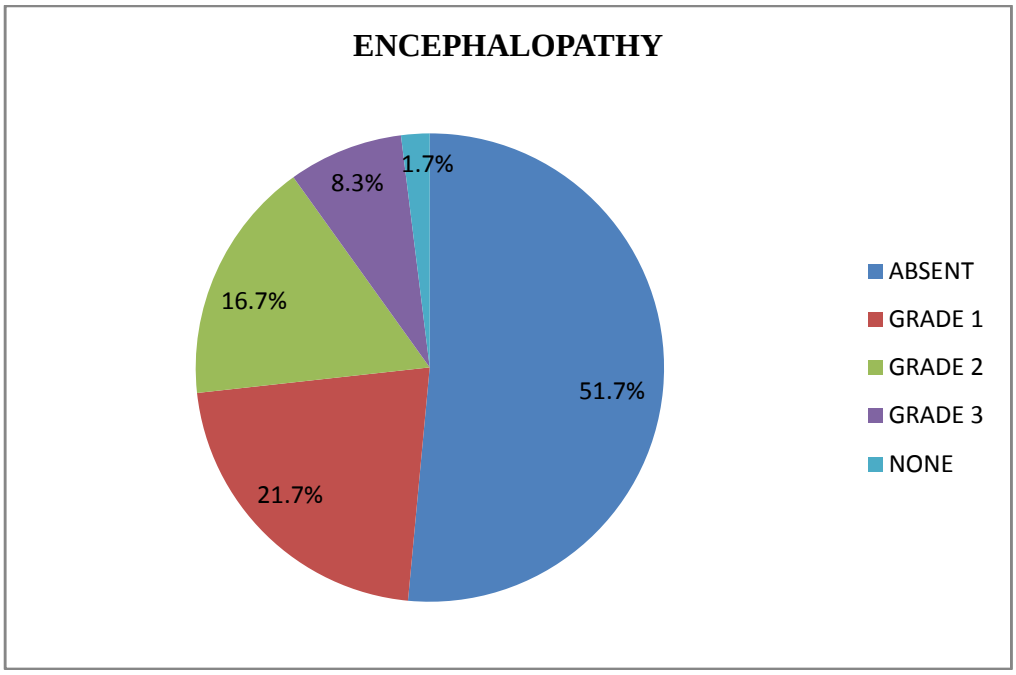


Table 5 : Child Pugh class in the study population

CHILD PUGH CLASS	FREQUENCY	PERCENT
A	7	11.7
B	20	33.3
C	33	55.0
TOTAL	60	100.0

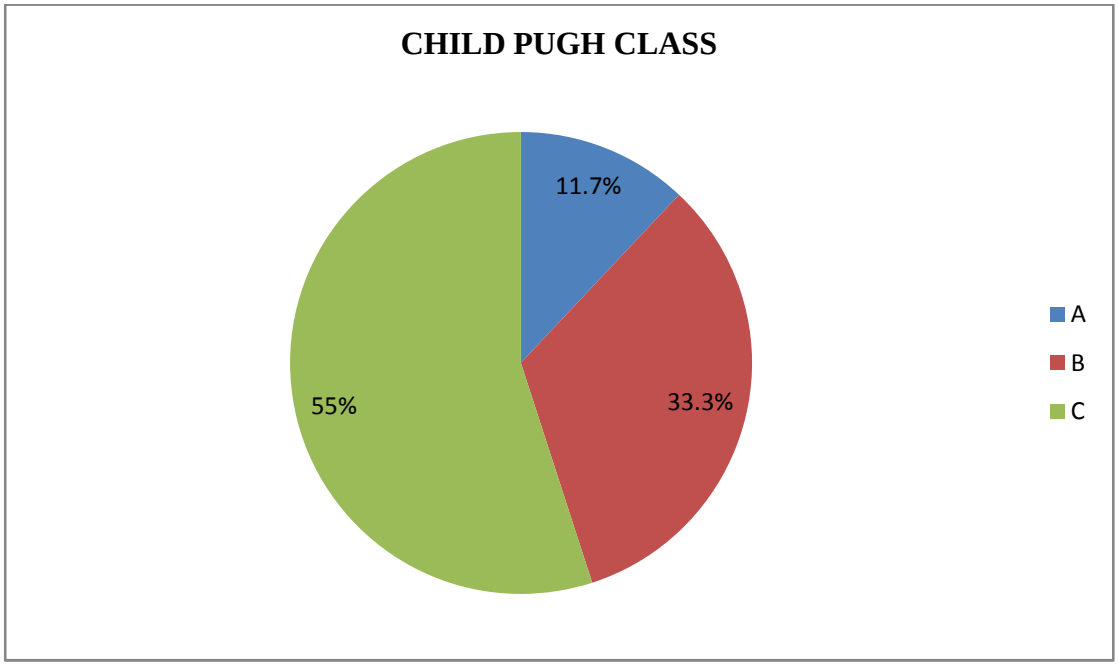
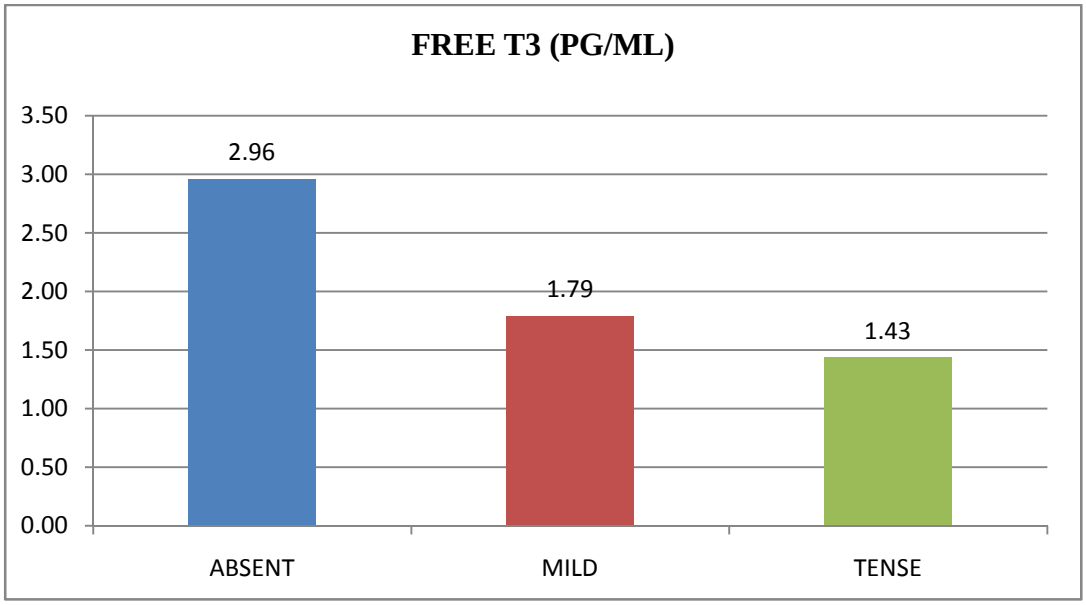


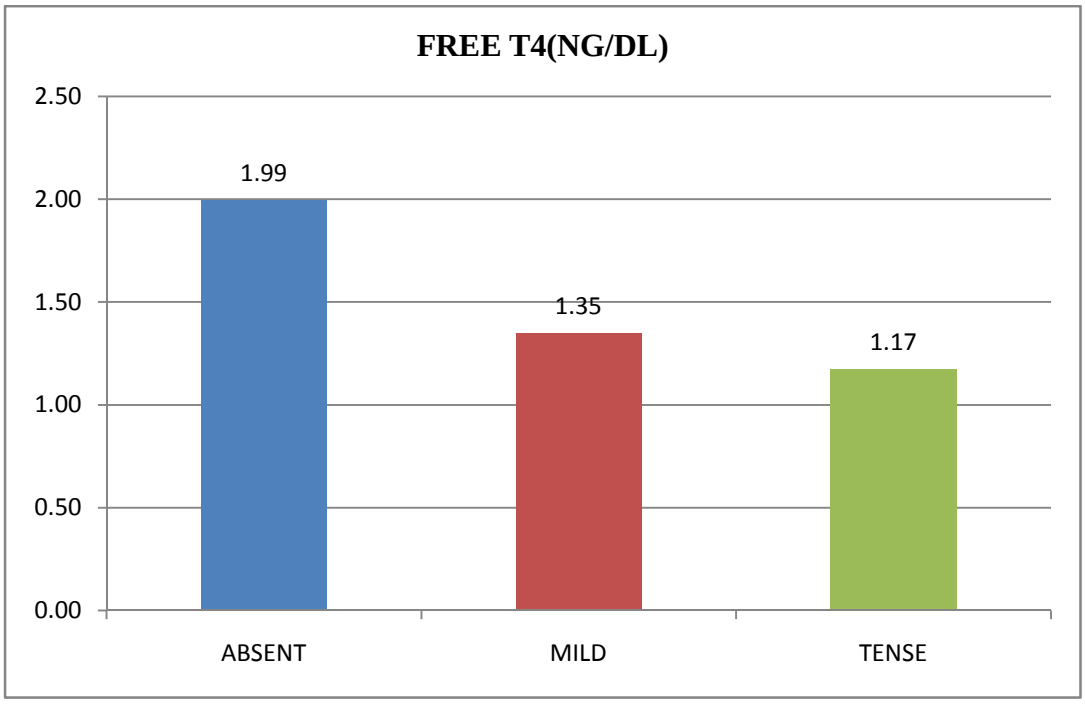
Table 6: Analysis of thyroid profile in patients with ascites in the study

DESCRIPTIVES										
ASCITES		N	MEAN	STD. DEVIATION	STD. ERROR	95% CONFIDENCE INTERVAL FOR MEAN		MINIMUM	MAXIMUM	F VALUE
						LOWER BOUND	UPPER BOUND			
FREE T3 (PG/ML)	ABSENT	20	2.9590	.41521	.09284	2.7647	3.1533	2.05	3.46	59.440**
	MILD	25	1.7924	.49224	.09845	1.5892	1.9956	1.22	3.22	
	TENSE	15	1.4340	.40597	.10482	1.2092	1.6588	1.08	2.34	
	TOTAL	60	2.0917	.77208	.09968	1.8922	2.2911	1.08	3.46	
FREE T4(NG/DL)	ABSENT	20	1.9930	.24938	.05576	1.8763	2.1097	1.32	2.36	60.459**
	MILD	25	1.3476	.25770	.05154	1.2412	1.4540	1.02	2.09	
	TENSE	15	1.1727	.19587	.05057	1.0642	1.2811	.86	1.54	
	TOTAL	60	1.5190	.41863	.05404	1.4109	1.6271	.86	2.36	
TSH(UIU/ML)	ABSENT	20	2.2086	.31146	.06964	2.0628	2.3544	1.90	2.91	37.976**
	MILD	25	2.8892	.41795	.08359	2.7167	3.0618	2.00	3.89	
	TENSE	15	3.3475	.44032	.11369	3.1037	3.5914	2.68	4.23	
	TOTAL	60	2.7769	.58815	.07593	2.6250	2.9289	1.90	4.23	

Free T3 levels in different clinical grades of ascites in the study



Free T4 levels in different clinical grades of ascites in the study



Serum TSH levels in different clinical grades of ascites in the study

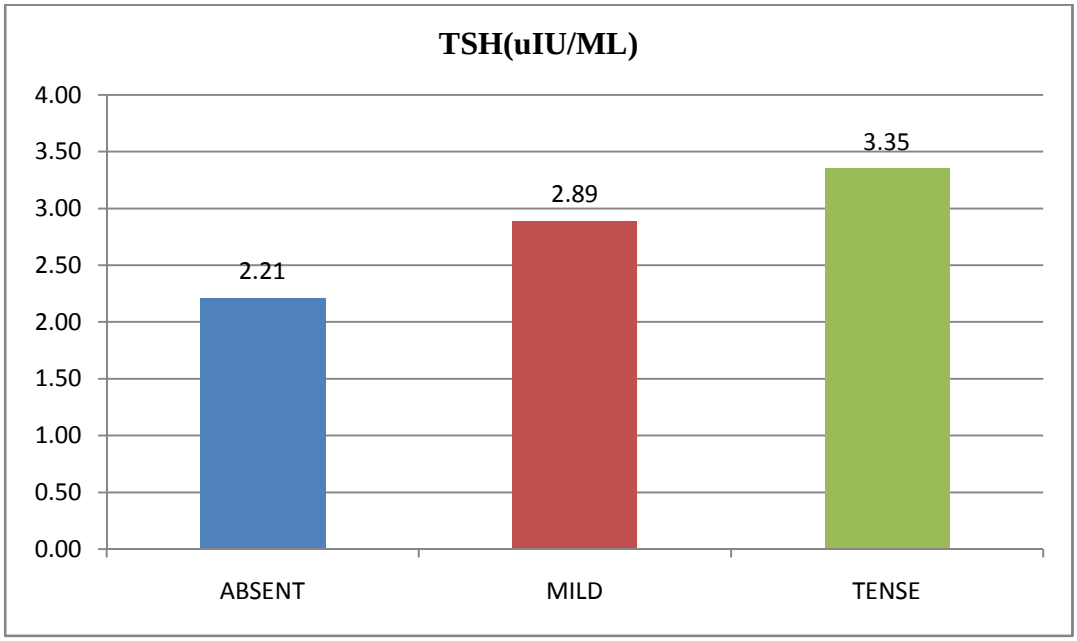


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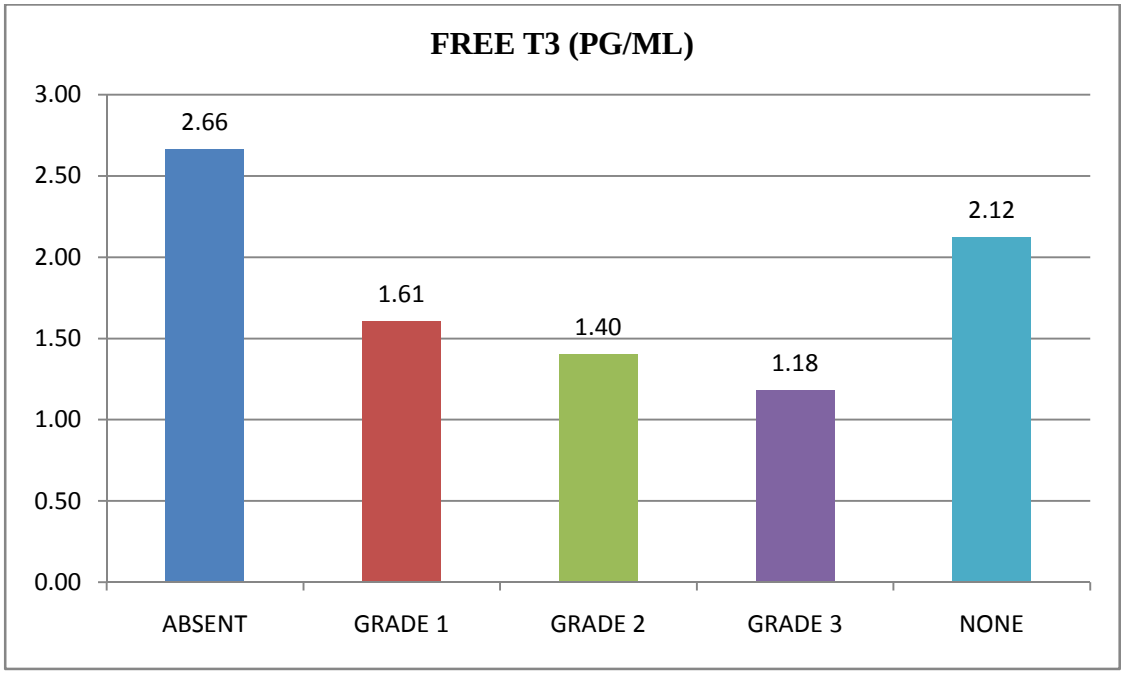
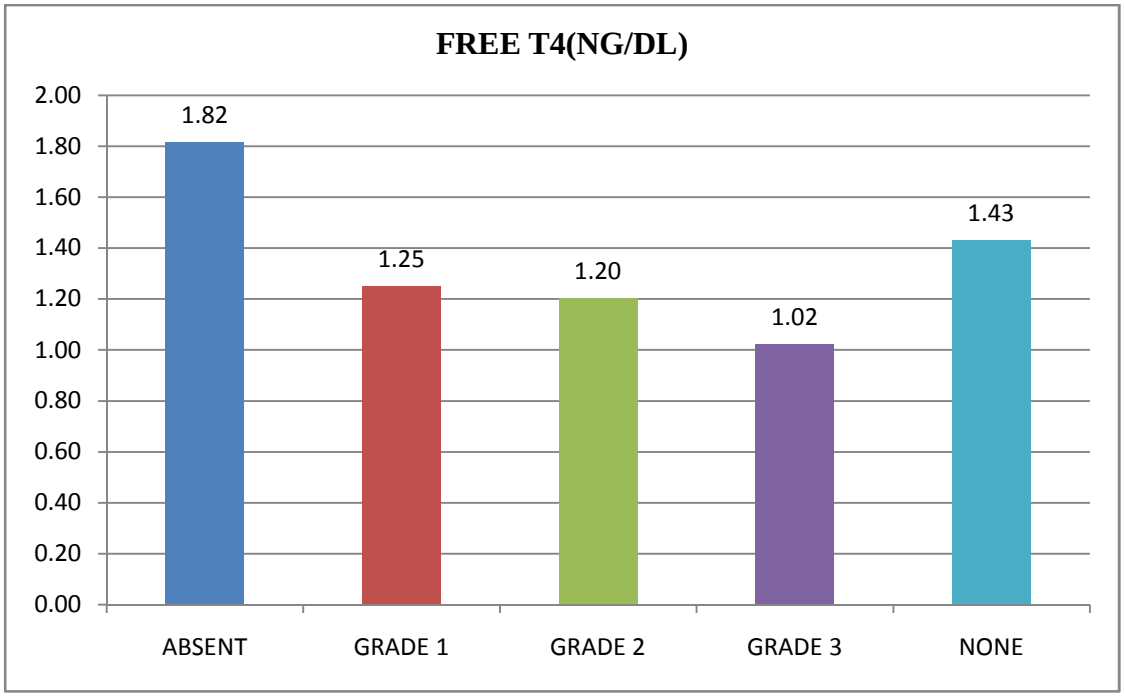
Table 7: Analysis of thyroid profile in patients with encephalopathy in the study

DESCRIPTIVES										
		N	MEAN	STD. DEVIATION	STD. ERROR	95% CONFIDENCE INTERVAL FOR MEAN		MINIMUM	MAXIMUM	
						LOWER BOUND	UPPER BOUND			
FREE T3 (PG/ML)	ABSENT	31	2.6639	.59487	.10684	2.4457	2.8821	1.62	3.46	23.338**
	GRADE 1	13	1.6069	.36447	.10109	1.3867	1.8272	1.12	2.43	
	GRADE 2	10	1.4010	.29920	.09462	1.1870	1.6150	1.22	2.22	
	GRADE 3	5	1.1800	.07616	.03406	1.0854	1.2746	1.08	1.26	
	NONE	1	2.1200	.	.	.	.	2.12	2.12	
	TOTAL	60	2.0917	.77208	.09968	1.8922	2.2911	1.08	3.46	
FREE T4(NG/DL)	ABSENT	31	1.8165	.35132	.06310	1.6876	1.9453	1.22	2.36	18.415**
	GRADE 1	13	1.2508	.20650	.05727	1.1260	1.3756	1.02	1.81	
	GRADE 2	10	1.2030	.13317	.04211	1.1077	1.2983	1.02	1.47	
	GRADE 3	5	1.0220	.10733	.04800	.8887	1.1553	.86	1.14	
	NONE	1	1.4300	.	.	.	.	1.43	1.43	
	TOTAL	60	1.5190	.41863	.05404	1.4109	1.6271	.86	2.36	
TSH(UIU/ML)	ABSENT	31	2.3985	.39918	.07169	2.2521	2.5450	1.90	3.13	19.395**
	GRADE 1	13	2.9868	.40830	.11324	2.7400	3.2335	2.03	3.46	
	GRADE 2	10	3.2128	.34886	.11032	2.9632	3.4624	2.73	3.89	
	GRADE 3	5	3.7698	.38413	.17179	3.2928	4.2468	3.41	4.23	
	NONE	1	2.4560	.	.	.	.	2.46	2.46	
	TOTAL	60	2.7769	.58815	.07593	2.6250	2.9289	1.90	4.23	

Free T3 levels in different grades of encephalopathy in the study



Free T4 levels in different grades of encephalopathy in the study



Serum TSH levels in different grades of encephalopathy in the study

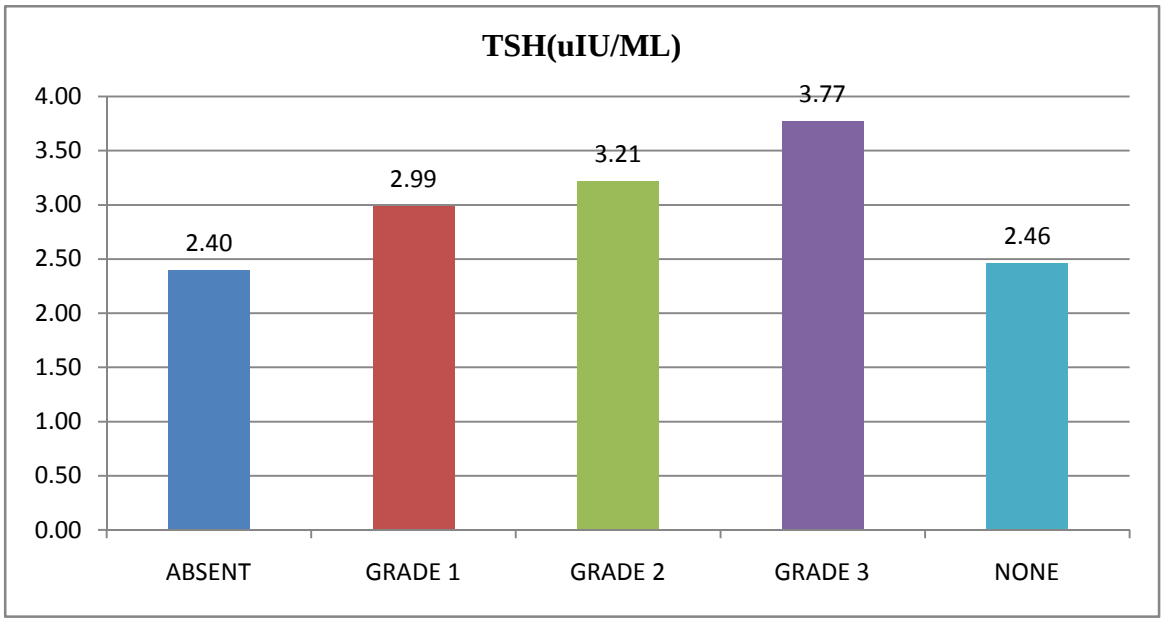


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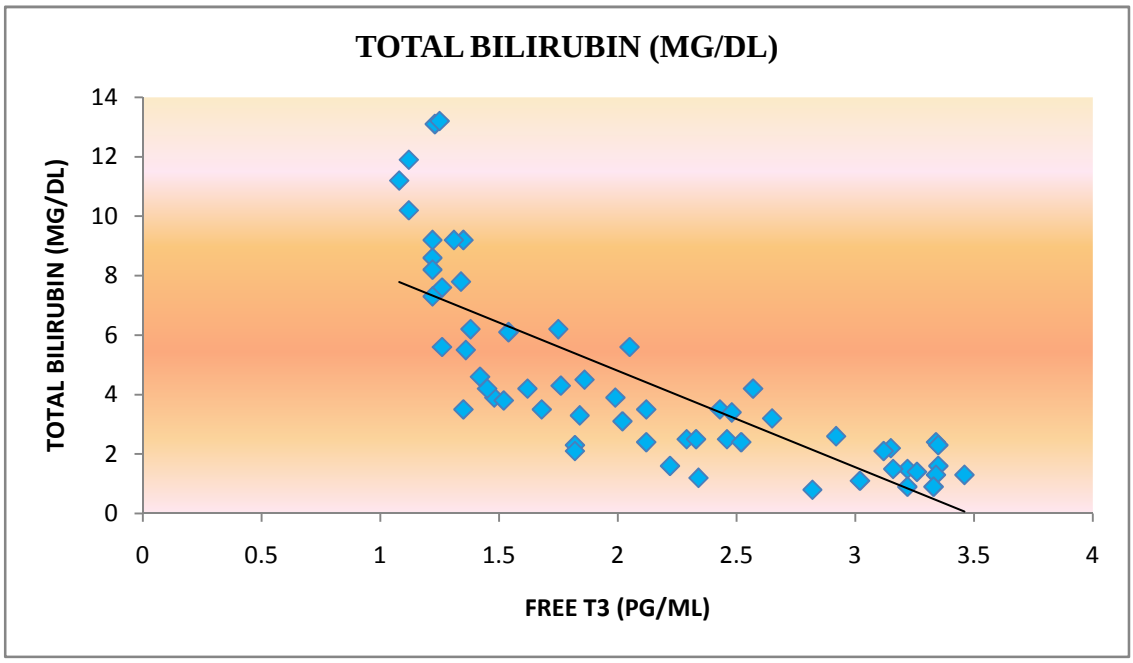
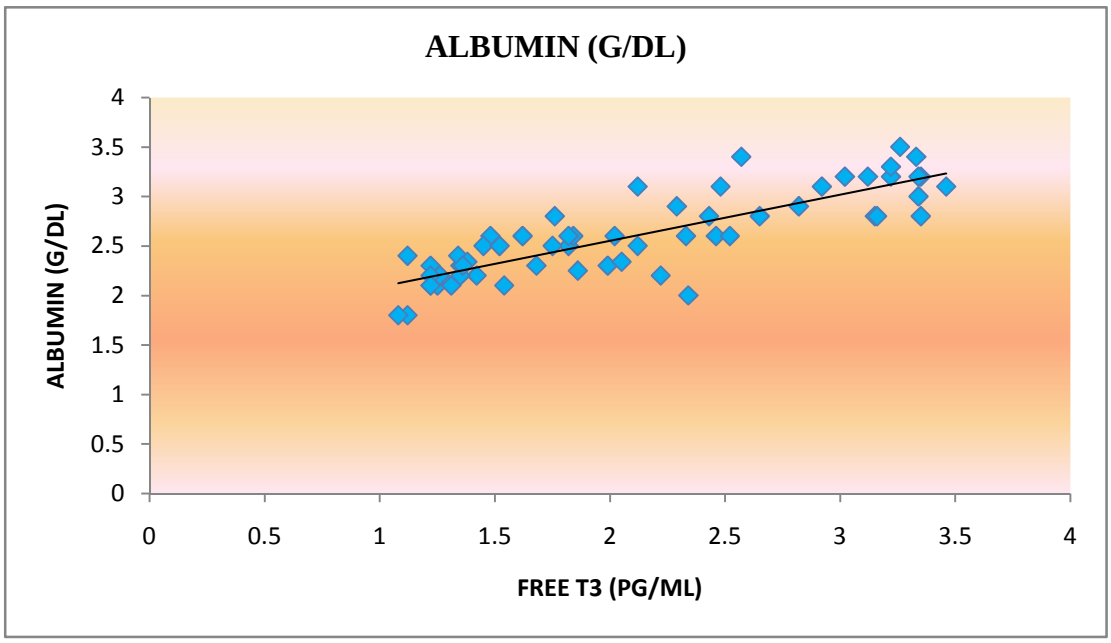
Table8: Analysis of thyroid profile and serum bilirubin, albumin and INR in the study

		FREE T3 (PG/ML)	FREE T4(NG/DL)	TSH(UIU/ML)
TOTAL BILIRUBIN (MG/DL)	PEARSON CORRELATION	-.777	-.729	.732
	SIG. (2-TAILED)	.000	.000	.000
	N	60	60	60
ALBUMIN (G/DL)	PEARSON CORRELATION	.840	.819	-.801
	SIG. (2-TAILED)	.000	.000	.000
	N	60	60	60
INR	PEARSON CORRELATION	-.825	-.777	.782
	SIG. (2-TAILED)	.000	.000	.000
	N	60	60	60
CHILD PUGH SCORE	PEARSON CORRELATION	-.964	-.923	.879
	SIG. (2-TAILED)	.000	.000	.000
	N	60	60	60

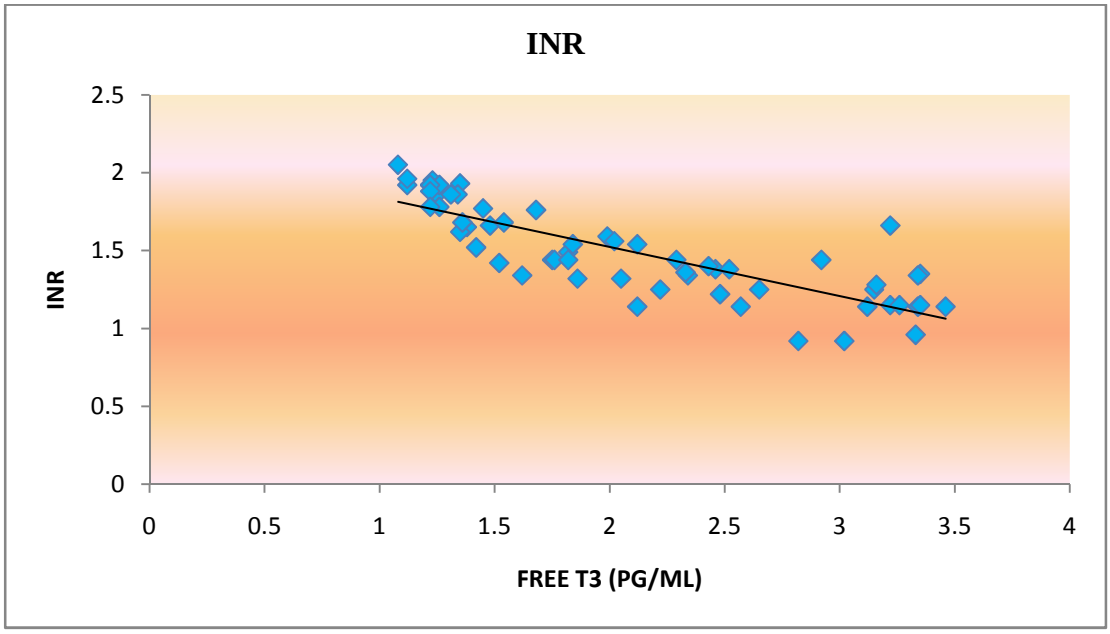
Correlation between Free T3 levels and Bilirubin levels in the study



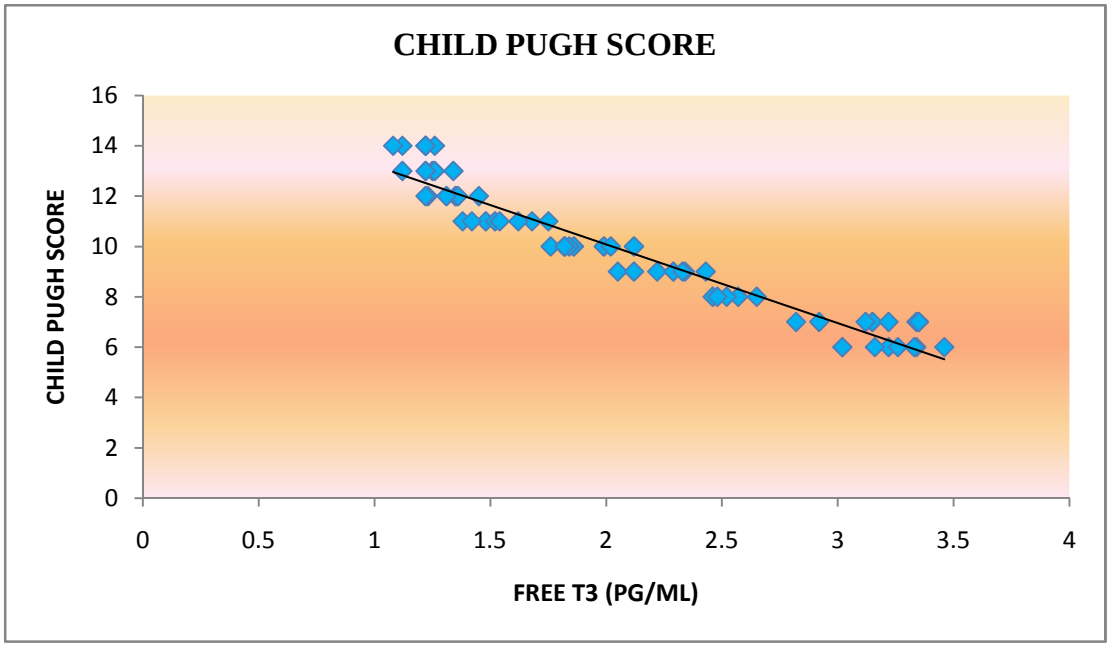
Correlation between Free T3 and Albumin levels in the study



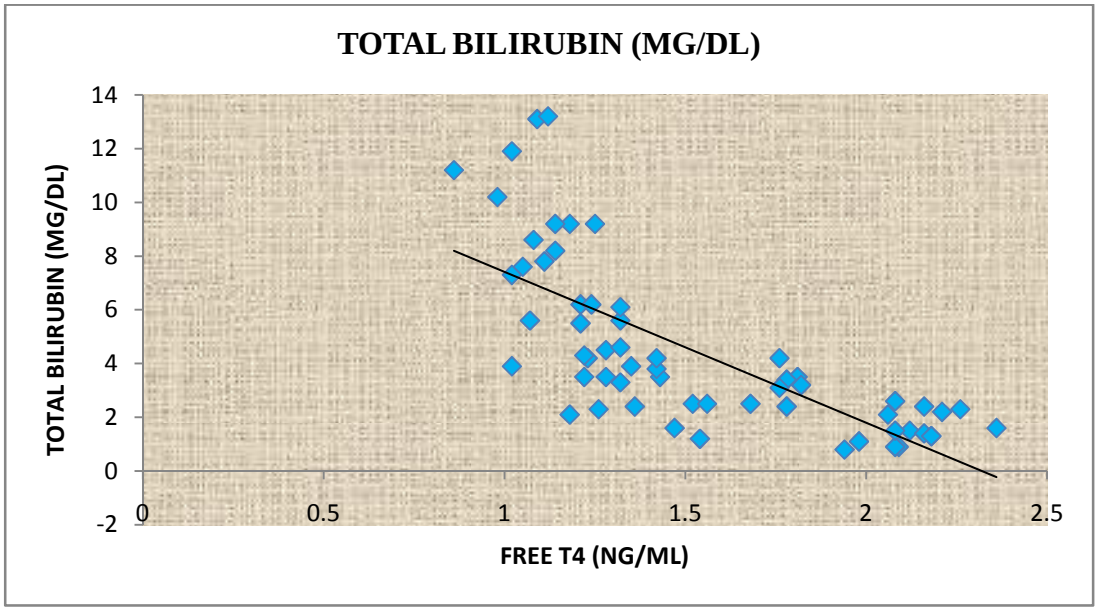
Correlation between Free T3 and INR levels in the study



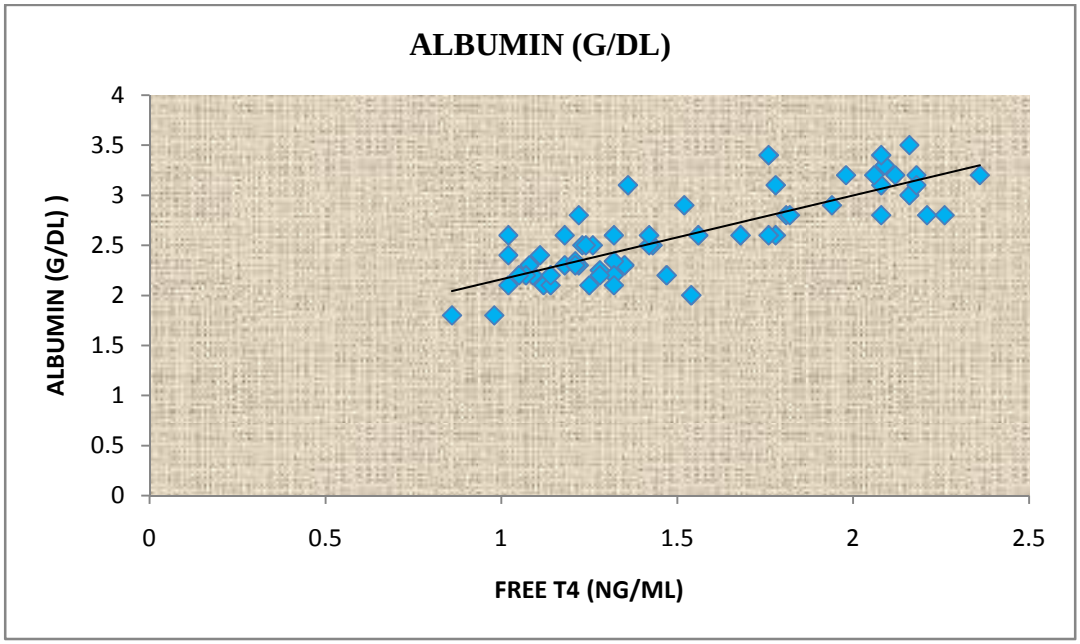
Correlation between Free T3 levels and the Child Pugh score in the study



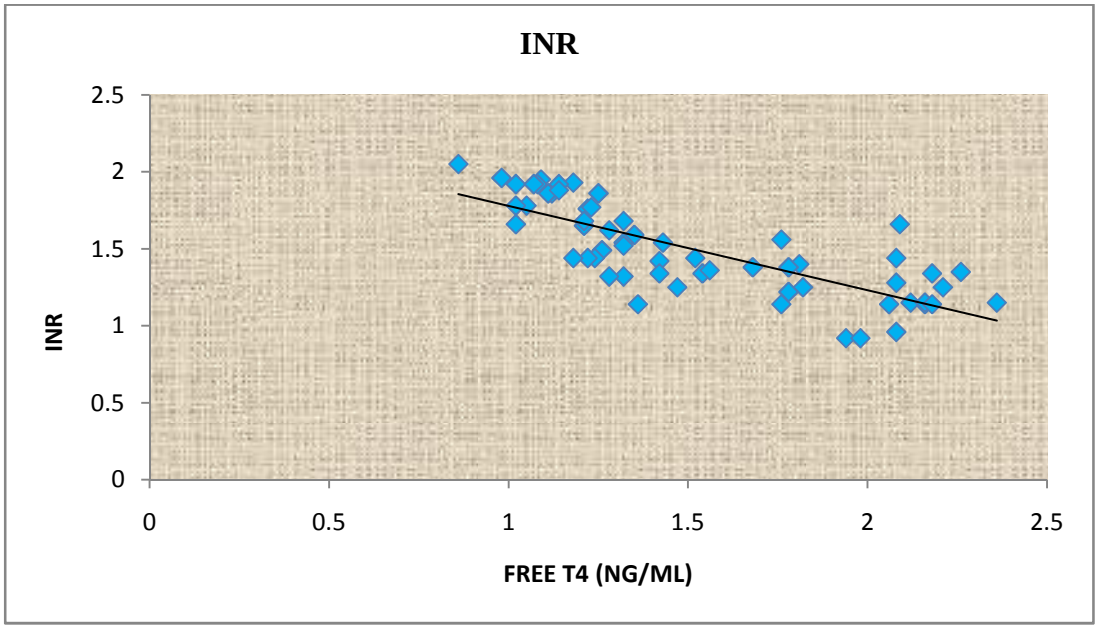
Correlation between Free T4 levels and Bilirubin levels in the study



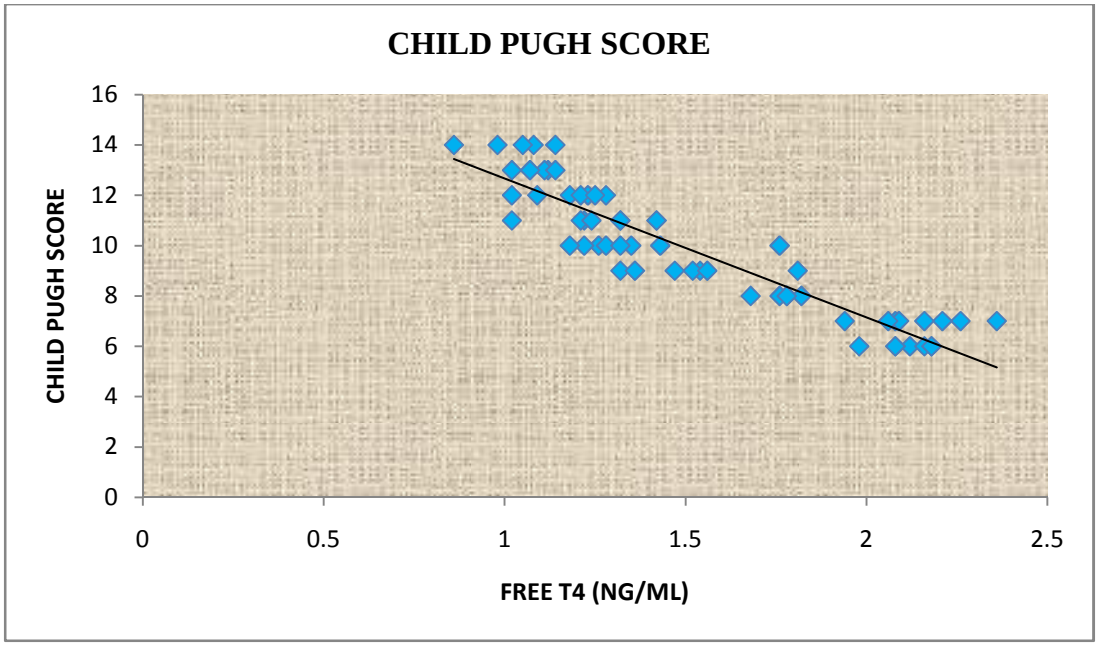
Correlation between Free T4 levels and Albumin levels in the study



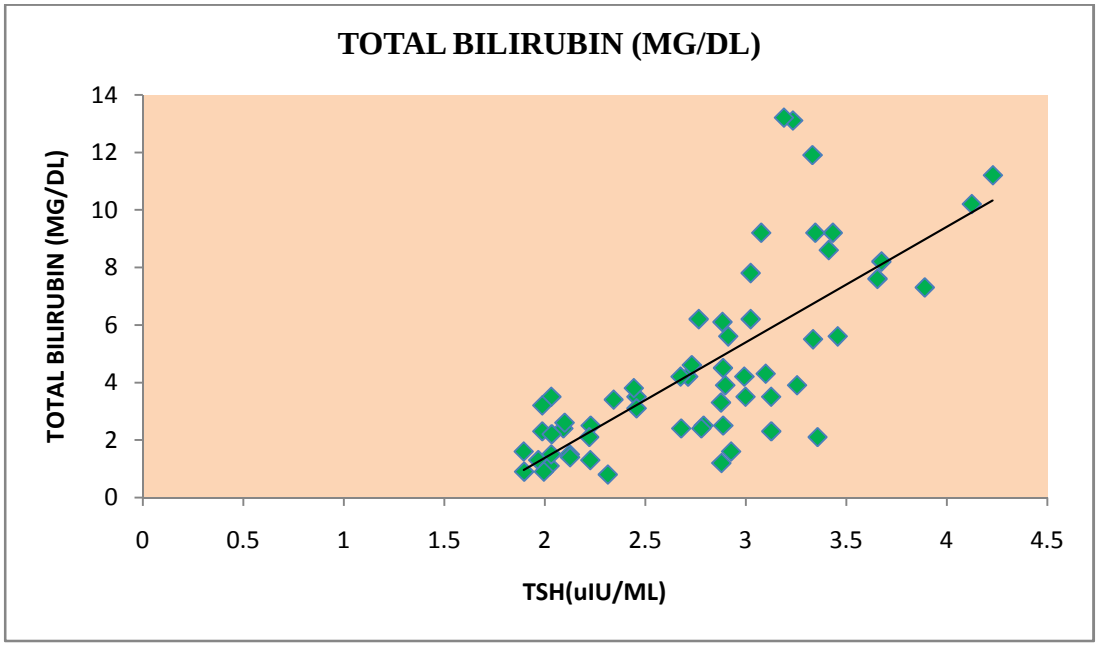
Correlation between Free T4 levels and INR in the study



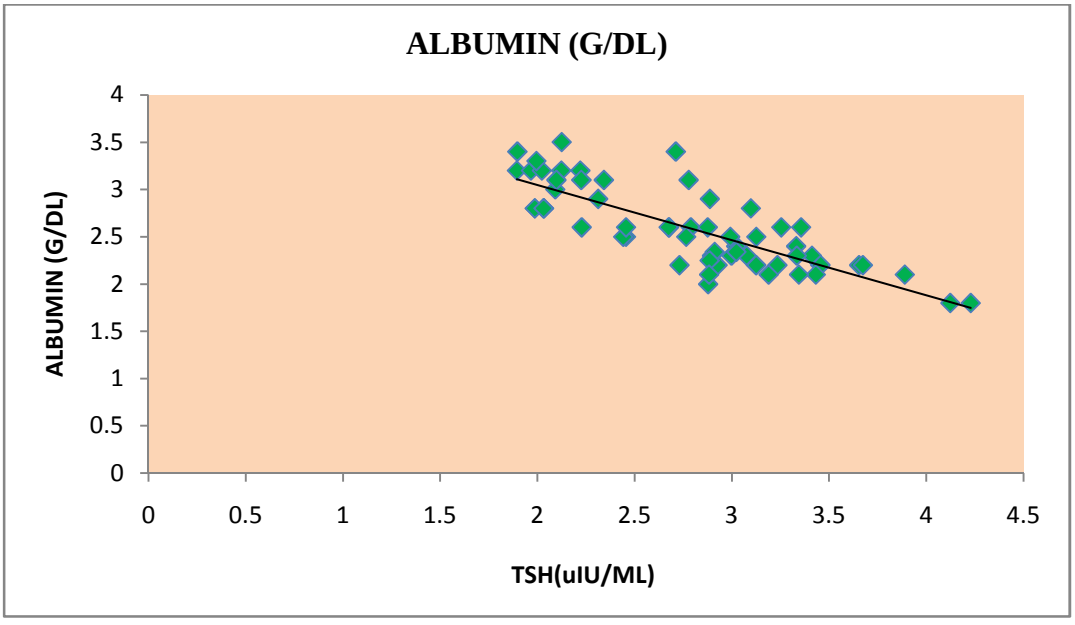
Correlation between Free T4 levels and Child Pugh score in the study



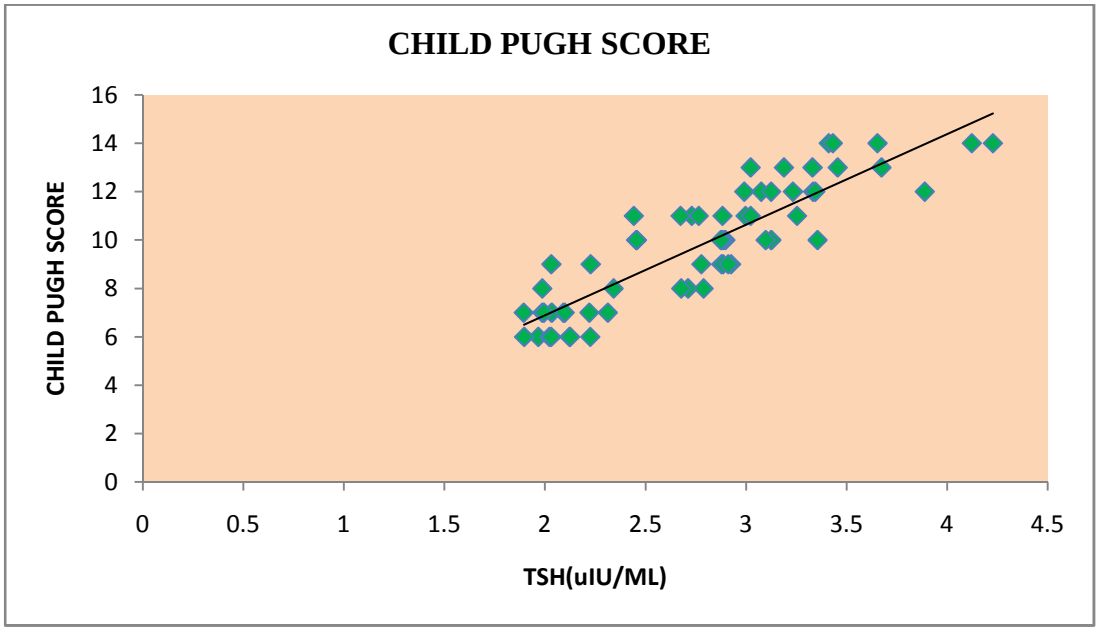
Correlation between serum TSH levels and Total Bilirubin in the study



Correlation between serum TSH levels and Albumin levels in the study



Correlation between serum TSH levels and Child Pugh score



Correlation between serum TSH levels and INR in the study

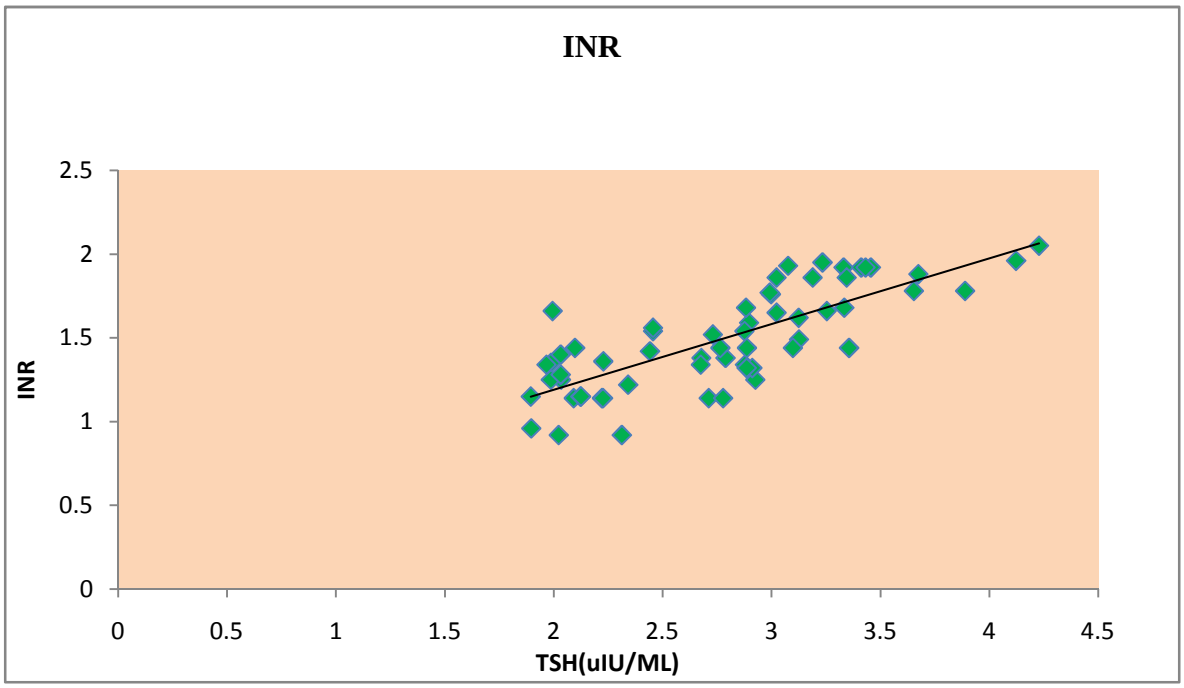
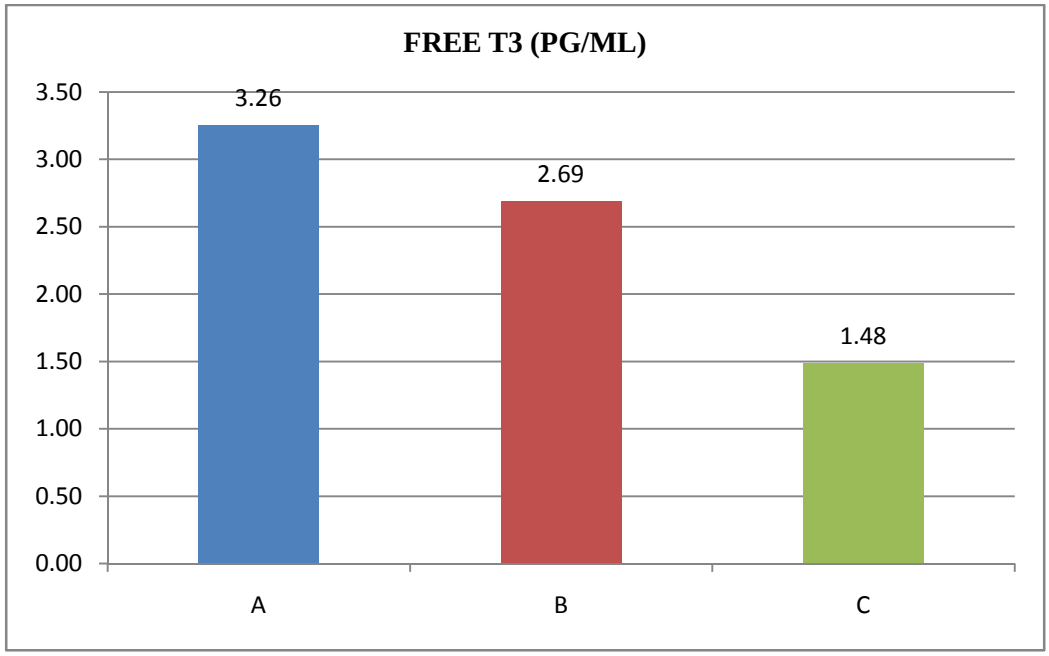


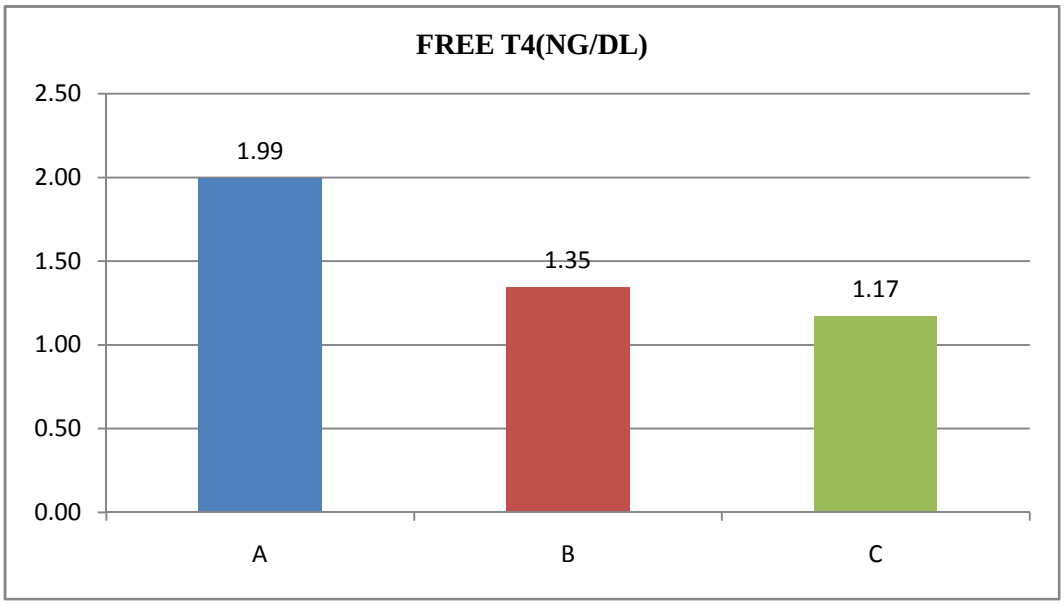
Table 9: Analysis of Thyroid profile and the Child Pugh classes in the study

DESCRIPTIVES										
CHILD PUGH CLASS		N	MEAN	STD. DEVIATION	STD. ERROR	95% CONFIDENCE INTERVAL FOR MEAN		MINIMUM	MAXIMUM	
						LOWER BOUND	UPPER BOUND			
FREE T3 (PG/ML)	A	7	3.2557	.14164	.05353	3.1247	3.3867	3.02	3.46	127.314**
	B	20	2.6865	.43635	.09757	2.4823	2.8907	2.05	3.35	
	C	33	1.4842	.29020	.05052	1.3813	1.5871	1.08	2.12	
	TOTAL	60	2.0917	.77208	.09968	1.8922	2.2911	1.08	3.46	
FREE T4 (NG/DL)	A	7	2.1114	.07198	.02721	2.0449	2.1780	1.98	2.18	78.986**
	B	20	1.8280	.30871	.06903	1.6835	1.9725	1.32	2.36	
	C	33	1.2061	.16769	.02919	1.1466	1.2655	.86	1.76	
	TOTAL	60	1.5190	.41863	.05404	1.4109	1.6271	.86	2.36	
TSH (UIU/ML)	A	7	2.0561	.11032	.04170	1.9541	2.1582	1.90	2.23	37.594**
	B	20	2.3892	.38108	.08521	2.2109	2.5675	1.90	2.93	
	C	33	3.1648	.43187	.07518	3.0117	3.3180	2.44	4.23	
	TOTAL	60	2.7769	.58815	.07593	2.6250	2.9289	1.90	4.23	

Free T3 levels and Child Pugh class in the study



Free T4 levels and Child Pugh class in the study



Serum TSH levels and Child Pugh class in the study

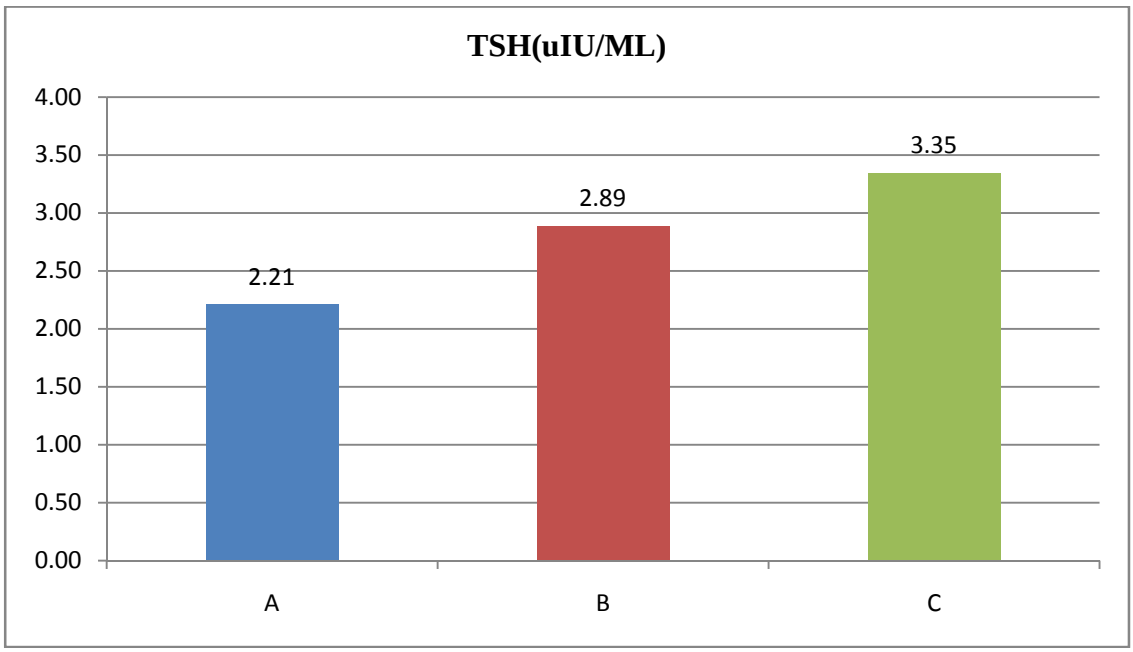


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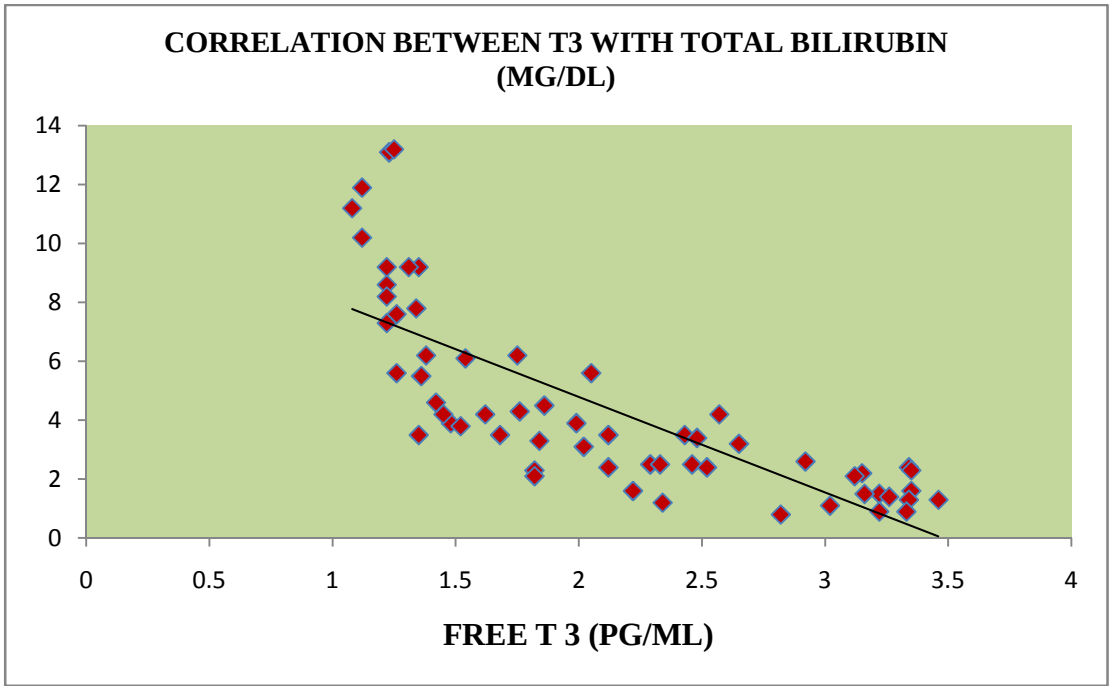
Table 10: Analysis of Free T3 levels and Bilirubin, Albumin,

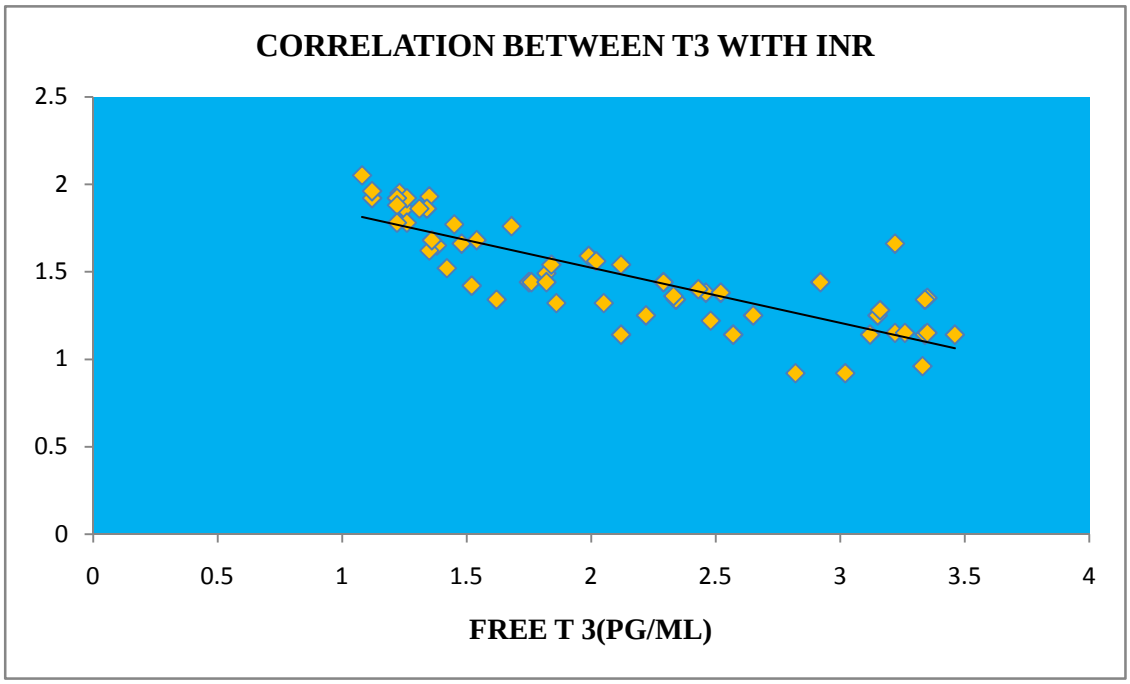
Child Pugh scores in the study

CORRELATIONS					
		INR	**TOTAL_BILIRUBIN_MGDL**	**ALBUMIN_GDL**	**CHILD_PUGH_SCORE**
FREE_T3_PGML	PEARSON CORRELATION	-.825**	-.777**	.840**	-.964**
	P VALUE	P<0.01	P<0.01	P<0.01	P<0.01
	N	60	60	60	60
**. CORRELATION IS SIGNIFICANT AT THE 0.01 LEVEL (2-TAILED).					

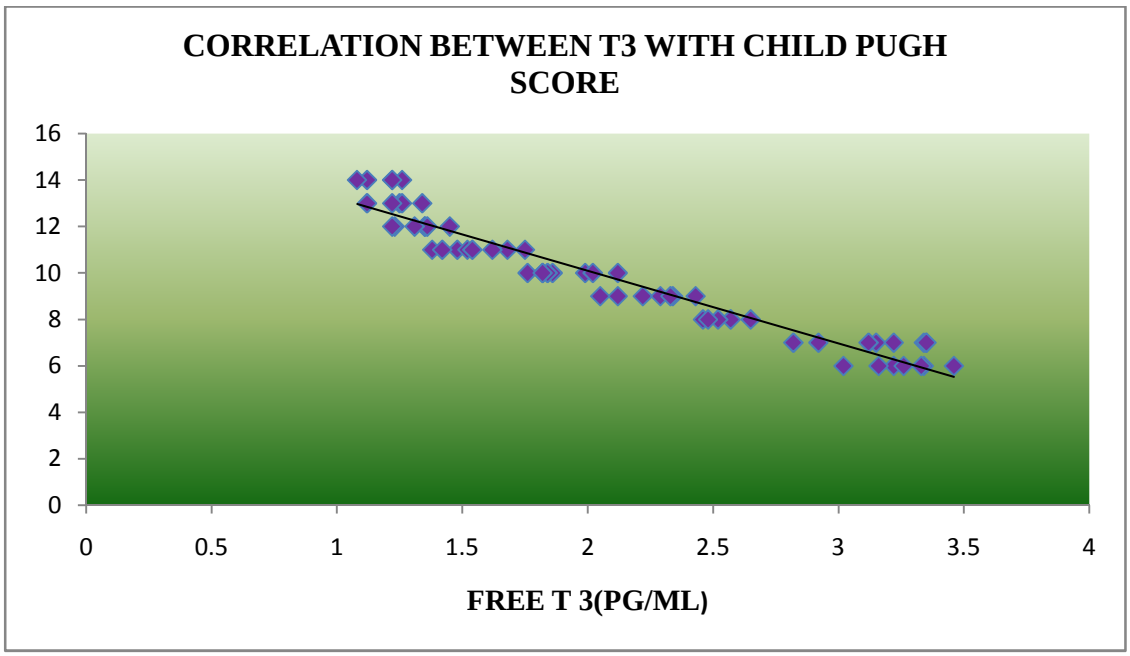
Correlation of Free T3 levels with total bilirubin in the study



Correlation of Free T3 levels with INR in the study



Correlation of Free T3 levels with the Child Pugh scores in the study



(Continued)

Table12: Distribution of Child Pugh class in the Age groups of the study

CROSSTAB						
			CHILD_PUGH_CLASS			TOTAL
			A	B	C	
AGE_GROUP	30-40 YEARS	COUNT	0	6	9	15
		% WITHIN CHILD_PUGH_CLASS	0.0%	30.0%	27.3%	25.0%
	41-50 YEARS	COUNT	3	11	15	29
		% WITHIN CHILD_PUGH_CLASS	42.9%	55.0%	45.5%	48.3%
	ABOVE 50 YEARS	COUNT	4	3	9	16
		% WITHIN CHILD_PUGH_CLASS	57.1%	15.0%	27.3%	26.7%
TOTAL		COUNT	7	20	33	60
		% WITHIN CHILD_PUGH_CLASS	100.0%	100.0%	100.0%	100.0%

PEARSON CHI-SQUARE=5.766 P= 0.217

Analysis of Child Pugh class in different age groups in the study

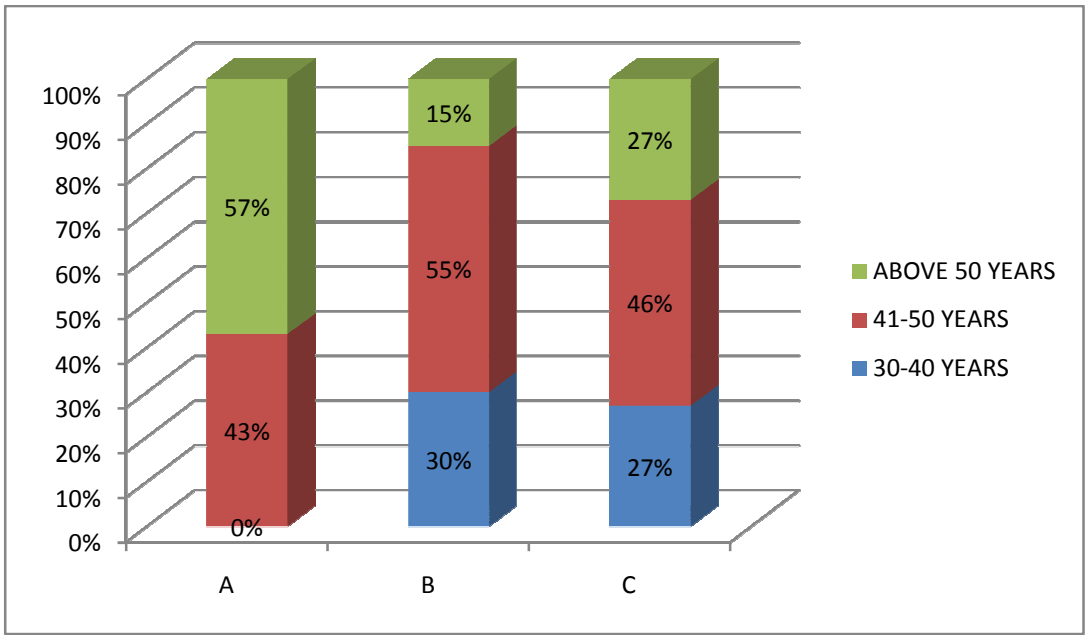


Table 13: Gender wise distribution of Child Pugh class in the study

CROSSTAB

			CHILD_PUGH_CLASS			TOTAL
			A	B	C	
SEX	MALE	COUNT	5	15	26	46
		% WITHIN CHILD_PUGH_CLASS	71.4%	75.0%	78.8%	76.7%
	FEMALE	COUNT	2	5	7	14
		% WITHIN CHILD_PUGH_CLASS	28.6%	25.0%	21.2%	23.3%
	TOTAL	COUNT	7	20	33	60
		% WITHIN CHILD_PUGH_CLASS	100.0%	100.0%	100.0%	100.0%

PEARSON CHI-SQUARE=0.221 P= 0.895

Analysis of Child Pugh class among the male and female genders in the study

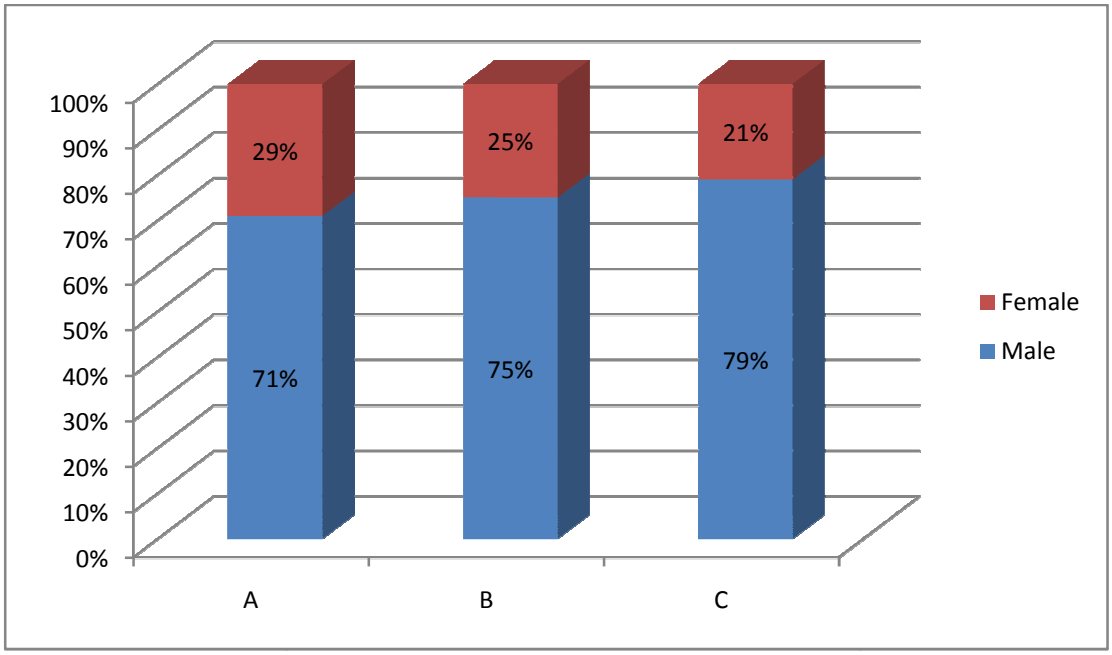


Table 14:Distribution of grades of ascites in among Child Pugh classes in the study

CROSSTAB

			CHILD_PUGH_CLASS			TOTAL
			A	B	C	
ASCITES	ABSENT	COUNT	7	13	0	20
		% WITHIN CHILD_PUGH_CLASS	100.0%	65.0%	0.0%	33.3%
	MILD	COUNT	0	5	20	25
		% WITHIN CHILD_PUGH_CLASS	0.0%	25.0%	60.6%	41.7%
	TENSE	COUNT	0	2	13	15
		% WITHIN CHILD_PUGH_CLASS	0.0%	10.0%	39.4%	25.0%
TOTAL		COUNT	7	20	33	60
		% WITHIN CHILD_PUGH_CLASS	100.0%	100.0%	100.0%	100.0%

PEARSON CHI-SQUARE=39.726** P<0.001

Analysis of different grades of Ascites and the Child Pugh class in the study

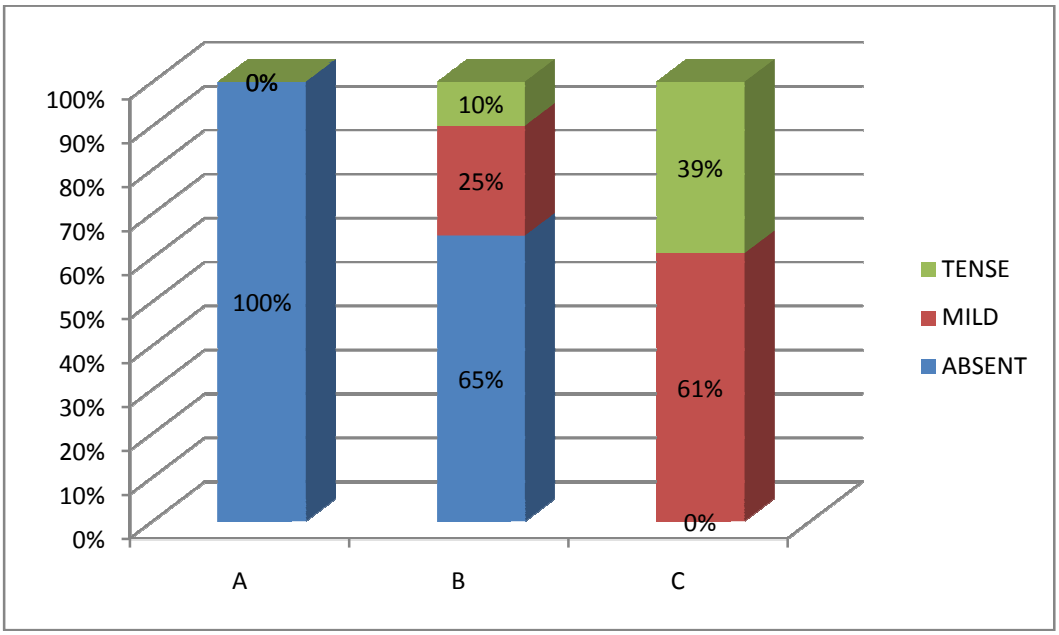
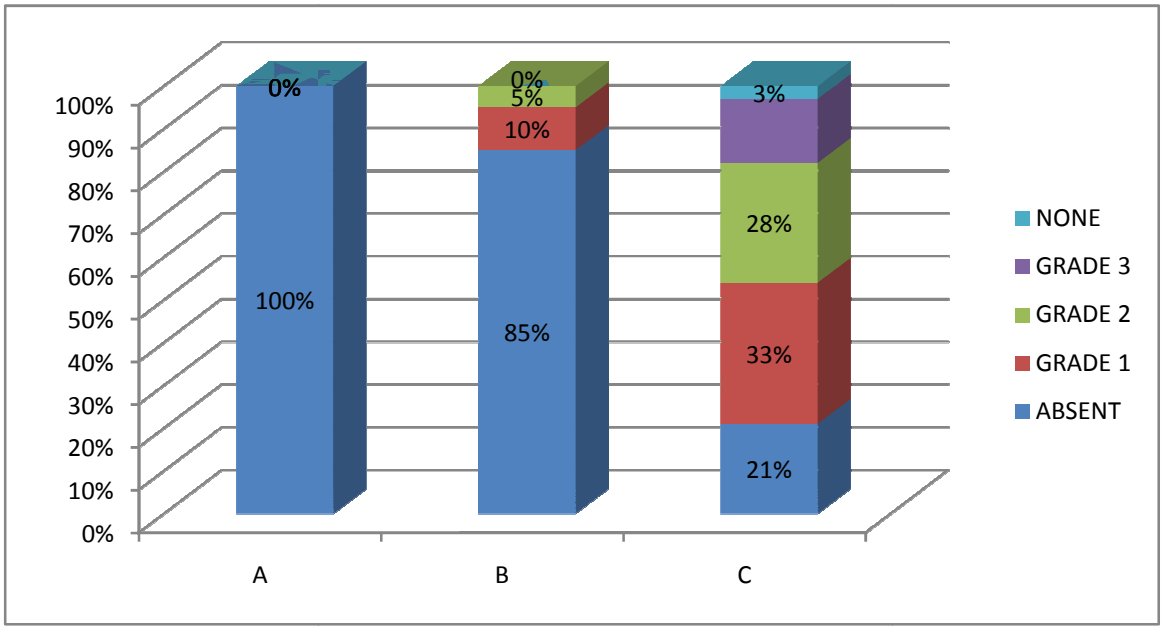


Table 15: Distribution of Encephalopathy in various Child Pugh class in the study

CROSSTAB						
			CHILD_PUGH_CLASS			TOTAL
			A	B	C	
ENCEPHALOPATHY	ABSENT	COUNT	7	17	7	31
		% WITHIN CHILD_PUGH_CLASS	100.0%	85.0%	21.2%	51.7%
	GRADE 1	COUNT	0	2	11	13
		% WITHIN CHILD_PUGH_CLASS	0.0%	10.0%	33.3%	21.7%
	GRADE 2	COUNT	0	1	9	10
		% WITHIN CHILD_PUGH_CLASS	0.0%	5.0%	27.3%	16.7%
	GRADE 3	COUNT	0	0	5	5
		% WITHIN CHILD_PUGH_CLASS	0.0%	0.0%	15.2%	8.3%
	NONE	COUNT	0	0	1	1
		% WITHIN CHILD_PUGH_CLASS	0.0%	0.0%	3.0%	1.7%
TOTAL		COUNT	7	20	33	60
		% WITHIN CHILD_PUGH_CLASS	100.0%	100.0%	100.0%	100.0%

PEARSON CHI-SQUARE=28.173** P<0.001

Analysis of grades of Encephalopathy in different Child Pugh class in the study



(Continued)

Table 11: Distribution of Free T3 levels and Bilirubin, Albumin and INR in the study

DESCRIPTIVES											
		N	MEAN	STD. DEVIATION	STD. ERROR	95% CONFIDENCE INTERVAL FOR MEAN		MIN.	MAX.		
						LOWER BOUND	UPPER BOUND			F VALUE	P VALUE
TOTAL_ BILIRUBIN_MGDL	A	7	4.2000	3.83580	1.44979	.6525	7.7475	.90	11.20	1.123	0.333
	B	20	3.7050	2.97170	.66449	2.3142	5.0958	1.10	13.10		
	C	32	5.0688	3.27753	.57939	3.8871	6.2504	.80	13.20		
	TOTAL	59	4.5034	3.25020	.42314	3.6564	5.3504	.80	13.20		
ALBUMIN_GDL	A	7	2.6000	.51962	.19640	2.1194	3.0806	1.80	3.30	0.393	0.677
	B	20	2.6425	.44876	.10035	2.4325	2.8525	2.00	3.50		
	C	32	2.5369	.38343	.06778	2.3986	2.6751	1.80	3.40		
	TOTAL	59	2.5802	.41822	.05445	2.4712	2.6892	1.80	3.50		
INR	A	7	1.5786	.31898	.12056	1.2836	1.8736	1.14	2.05	0.975	0.384
	B	20	1.4290	.27209	.06084	1.3017	1.5563	.92	1.95		
	C	32	1.5278	.30223	.05343	1.4188	1.6368	.92	1.96		
	TOTAL	59	1.5003	.29412	.03829	1.4237	1.5770	.92	2.05		
FREE_T3_PGML	A	7	2.0129	.87408	.33037	1.2045	2.8213	1.08	3.22	0.345	0.710
	B	20	2.2020	.73547	.16446	1.8578	2.5462	1.22	3.35		
	C	32	2.0250	.79618	.14075	1.7379	2.3121	1.12	3.46		
	TOTAL	59	2.0836	.77613	.10104	1.8813	2.2858	1.08	3.46		

DISCUSSION

DISCUSSION

The observational study done at MMC and RGGGH, Chennai during June 2017 to November 2017 in the Institute Of Internal Medicine studied thyroid dysfunction in patients with decompensated chronic liver disease. The correlation between the levels of free T3 in the serum and the Child Pugh score was analysed. A total of 60 inpatients admitted to the medical wards in RGGGH were enrolled in the study.

After getting informed consent from the patients or their relatives routine investigations were done which included complete blood hemogram, renal function tests, pt/apt and inr, liver function testing, portal venous Doppler, usg abdomen, thyroid profile with free T3, free T4 and TSH. After ensuring that patient did not have any confounding factors, the data was analysed for establishing the statistical significance of levels of serum T3 as a prognostic indicator in patients with decompensated liver disease.

Out of the 60 patients included in the study , 46 patients were male and 14 patients were female. 25% were in the 30 to 40 years age group, 48.3% were in the 41 to 50 years age group and 26.7% were in the above 50 years age group. The median age group was 45.2 years. Out of 60 patients, 33.3% had no ascites, 41.7% had mild ascites and 25% had tense ascites.

In the study population 51.7% patients had no encephalopathy, 21.7% patients had grade 1 hepatic encephalopathy, 16.7% had grade

2 encephalopathy, 8.3% patients had grade 3 encephalopathy. The grading was done according to the West Haven criteria.

The proportion of patients in Child Pugh class A were 11.7%, class B were 33.3% and class C were 55%.

It was observed that as the degree of ascites increases, the values of serum free T3 tend to decrease and become lesser than the normal. The levels of serum free T4 also shows a decreasing trend with the increase in degree of ascites. However the levels of free T4 tends to remain in the low normal range. Serum TSH tends to increases as the degree of ascites worsens but tends to remain in the high normal range.[19]

As far as the encephalopathy is concerned, the serum T3 levels shows a declining trend and tends to remain below the normal range as the degree of encephalopathy worsens. The levels of free T4 and TSH tend to remain within the normal range with levels of free T4 approaching a low normal level and levels of TSH reaching a high normal level with worsening degrees of hepatic encephalopathy.[17]

In case of hyperbilirubinemia the levels of free T3 decreases with increase in the serum bilirubin and falls below the normal, whereas the levels of free T4 and TSH tends to remain normal.

As the hypoalbuminemia worsens the level of serum free T3 falls below the normal, whereas the level of free T4 and TSH tends to remain fairly normal. As the coagulopathy in the study population worsens (measured by the INR) the levels of free T3 falls well below the normal level, with normal levels of T4 and TSH.

Person correlation was calculated to determine the degree of correlation between the levels of free t3 and variables in Child Pugh score and to analyse the statistical significance.

The pearson correlation between Free T3 and serum bilirubin was found to be - 0.777 with a p value of <0.01. The pearson correlation for INR and free T3 was found to be -0.825 with a p value <0.01. Similarly the pearson correlation was found to be -0.840 for serum albumin and free T3 with a p value of <0.01.

Finally the pearson correlation was applied for the total Child Pugh scores and serum free T3 levels which was -0.964 with a p value of <0.01. The statistical analysis of the data shows that a significant association exists between the Child Pugh score and free T3 levels in the serum of patients with decompensated chronic liver disease. [12,13,23,32]

This goes in line with the findings of the study published in june 2013 from Asian Institute of Gastroenterology, which was a retrospective study with one group of 310 cirrhotics (211 males and 99 females) between age 20 to 80 years and another group of healthy subjects aged 20 to 80 years (145 males and

105 females). The thyroid hormone levels were determined and possible relation between hypothyroidism and liver cirrhosis was looked for. After the analysis of their study results, it was found that cirrhotics had low levels of T3 with normal levels of T4 and TSH. The levels of freeT3 concentration seemed to have a good correlation with the state of the chronic liver disease and it also estimated the progress of liver disease.

Another study by Doctor Sudhir Kumar et al which enrolled 102 patients with cirrhosis (73 males and 29 females) analysed the thyroid abnormalities in chronic liver disease. The study concluded that lower T3 levels were associated with more severe liver injury and thyroid function testing should be carried out in all patients with cirrhosis to assess the severity and determine the prognosis.[42]

A Study by Doctor Sandeep Kharb et al published in Indian Journal of Endocrinology and Metabolism analysed the thyroid and gonadal dysfunction in patients with liver disease revealed significantly low T3 levels compared to the controls.[3]

The value of serum T3 falls below the normal range and decreases proportionately as the Child Pugh score increases, thus validating the role of measuring serum free T3 levels in patients with chronic liver disease and using it to assess prognosis with various levels of decompensation (as evidenced by worsening Child Pugh scores).

CONCLUSION

CONCLUSION

1. The mean age of patients admitted with decompensated chronic liver disease in the study population 45.2 years.
2. More than half of the patients belonged to Child Pugh class C.
3. Serum free T3 levels were found to have significant correlation with levels of albumin, bilirubin, INR in the study population.
4. Serum free T3 levels had a significant correlation with the Child Pugh score thus validating the use of measuring serum free T3 levels to assess the disease prognosis in patients with decompensated chronic liver disease.

LIMITATIONS

LIMITATIONS

1. It is a single centred study. We need multicentric study involving patients of different geographical areas to have a better analysis.
2. Liver biopsy/elastography was not done to confirm the diagnosis of cirrhosis.
3. Detailed thyroid profile with measurement of reverse T3, thyroglobulin were not carried out.
4. It is a cross sectional study, hence it cannot assess whether improvement of liver function with treatment is associated with an improvement in thyroid profile and serum free T3 levels.

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ANNEXURES

A STUDY ON THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATON OF FREE T3 AS A PROGNOSTIC INDICATOR

PROFORMA

NAME :

AGE :

SEX :

IP NO :

SYMPTOMS

FEVER

YELLOWISH DISCOLORATION OF EYES

ITCHING

H/S/O HYPO OR HYPER THYROIDISM (IF ANY)

ABDOMINAL DISTENTION

VOMITING BLOOD/PASSING BLACK TARRY STOOLS

ALTERED SENSORIUM

PAST HISTORY

K/C OF CAD/ CKD/ THYROID DYSFUNCTION

PERSONAL HISTORY

SMOKING OR ALCOHOL INTAKE.

GENERAL EXAMINATION

ASSESMENT OF LEVEL OF CONSCIOUNESS

ORIENTATION

MARKERS OF LIVER CELL FAILURE (IF ANY)

SYSTEMIC EXAMINATION

EXAMINATION OF UPPER GI TRACT

INSPECTION OF ABDOMEN

PALPATION OF ABDOMEN

PERCUSSION OF ABDOMEN

AUSCULTATION OF ABDOMEN

CVS :

RS :

CNS :

INVESTIGATIONS

CBC :

RFT :

LFT :

URINE R/E :

PT/APTT/INR :

VIRAL MARKERS :

THYROID FUNCTION TESTS :

CHILD PUGH SCORE

USG ABDOMEN

PORTAL VENOUS DOPPLER

ETHICAL COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
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CERTIFICATE OF APPROVAL

To

Dr.S.Sabarish
I Year PG in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.S.Sabarish,

The Institutional Ethics Committee has considered your request and approved your study titled **"THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FT3 AS A PROGNOSTIC INDICATOR" - NO.09052017**

The following members of Ethics Committee were present in the meeting hold on **02.05.2017** conducted at Madras Medical College, Chennai 3

1.Prof.Dr.C.Rajendran, MD.,	:Chairperson
2.Prof.R.Narayana Babu, MD.,DCH.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4.Prof.S.Suresh,MS.,Prof.of Surgery,MMC, Ch-3	: Member
5.Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
7.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
8.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PLAGIARISM SCREENSHOT

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Submitted By:	sabarishsankaran@gmail.com
Significance:	1 %

Sources included in the report:

https://www.healthline.com/health/decompensated-liver-disease

Instances where selected sources appear:

1

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A STUDY ON THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATON OF FREE T3 AS A PROGNOSTIC INDICATOR"** of the candidate **Dr.S.SABARISH** with registration Number **201611020** for the award of **M.D** in the branch of **GENERAL MEDICINE.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 2 percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

INFORMATION SHEET

We are conducting a study on **"THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FT3 AS A PROGNOSTIC INDICATOR.."** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co-operation to undergo relevant investigations as per need may be valuable to us. The purpose of this study is to ascertain the importance of thyroid function tests in assesing the prognosis in decompensated liver disease patients. We are selecting certain cases and if you are found eligible, we would like to perform extra tests and you will be subjected to thyroid function tests which in any way do not affect your final report or management. The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled. The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Investigator

Signature/thumb impression of the participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail : **THYROID FUNCTION TESTS IN DECOMPENSATED LIVER DISEASE AND IMPLICATION OF SERUM FREE T3 AS A PROGNOSTIC INDICATOR.**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

Patient may check (√) these circles

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. o ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. o ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. o ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. o ❑

e) I hereby consent to participate in this study. o ❑

f) I hereby give permission to undergo detailed clinical examination and relevant investigations as required. o ❑

Signature/thumb impression: Signature of the investigator:

Patient's Name and Address: Investigator's Name: **DR.S.SABARISH.**

MASTER CHART

SERIAL NO	AGE (YEARS)	SEX	TOTAL BILIRUBIN (MG/DL)	ALBUMIN (G/DL)	INR	ASCITES	ENCEPHALOPATHY	CHILD PUGH SCORE	CHILD PUGH CLASS	FREE T3 (PG/ML)	FREE T4(NG/DL)	TSH(uIU/ML)
1	37	MALE	4.2	3.4	1.14	ABSENT	ABSENT	8	B	2.57	1.76	2.712
2	50	FEMALE	1.6	2.2	1.25	MILD	GRADE 2	9	B	2.22	1.47	2.926
3	37	FEMALE	2.3	2.5	1.49	TENSE	ABSENT	10	C	1.82	1.26	3.126
4	70	FEMALE	0.8	2.9	0.92	MILD	ABSENT	7	B	2.82	1.94	2.313
5	41	MALE	3.9	2.6	1.66	MILD	GRADE 1	11	C	1.48	1.02	3.254
6	30	MALE	2.4	3	1.14	ABSENT	ABSENT	7	B	3.34	2.16	2.092
7	58	MALE	1.2	2	1.34	TENSE	ABSENT	9	B	2.34	1.54	2.878
8	46	FEMALE	2.5	2.9	1.44	TENSE	ABSENT	9	B	2.29	1.52	2.887
9	42	FEMALE	13.1	2.2	1.95	MILD	GRADE 2	12	C	1.23	1.09	3.234
10	51	MALE	13.2	2.1	1.86	TENSE	GRADE 2	13	C	1.25	1.12	3.189
11	42	MALE	9.2	2.3	1.93	MILD	GRADE 1	12	C	1.35	1.18	3.076
12	45	MALE	3.9	2.3	1.59	MILD	ABSENT	10	C	1.99	1.35	2.897

13	35	MALE	11.9	2.4	1.92	TENSE	GRADE 1	13	C	1.12	1.02	3.331
14	45	MALE	5.6	2.3	1.32	ABSENT	ABSENT	9	B	2.05	1.32	2.912
15	80	MALE	3.5	2.3	1.76	MILD	ABSENT	11	C	1.68	1.22	2.998
16	48	MALE	2.5	2.6	1.38	ABSENT	ABSENT	8	B	2.46	1.68	2.789
17	52	MALE	8.6	2.3	1.92	TENSE	GRADE 3	14	C	1.22	1.08	3.412
18	45	MALE	2.3	2.8	1.35	ABSENT	ABSENT	7	B	3.35	2.26	1.987
19	37	MALE	3.5	2.8	1.4	ABSENT	GRADE 1	9	B	2.43	1.81	2.032
20	40	MALE	4.5	2.2	1.32	MILD	ABSENT	10	C	1.86	1.28	2.886
21	52	MALE	1.5	3.2	1.15	ABSENT	ABSENT	6	A	3.22	2.12	2.123
22	45	MALE	7.8	2.4	1.86	TENSE	GRADE 2	13	C	1.34	1.11	3.023
23	48	FEMALE	4.2	2.5	1.77	MILD	GRADE 2	12	C	1.45	1.23	2.992
24	54	FEMALE	5.6	2.2	1.92	TENSE	GRADE 1	13	C	1.26	1.07	3.456
25	51	MALE	6.2	2.3	1.65	MILD	GRADE 1	11	C	1.38	1.21	3.023
26	48	MALE	3.3	2.6	1.54	MILD	ABSENT	10	C	1.84	1.32	2.876
27	39	FEMALE	7.6	2.2	1.78	TENSE	GRADE 3	14	C	1.26	1.05	3.654
28	47	MALE	3.5	2.5	1.54	MILD	NONE	10	C	2.12	1.43	2.456
29	48	MALE	2.2	2.8	1.25	ABSENT	ABSENT	7	B	3.15	2.21	2.034
30	47	MALE	1.6	3.2	1.15	ABSENT	ABSENT	7	B	3.35	2.36	1.895
31	42	MALE	4.6	2.2	1.52	MILD	GRADE 2	11	C	1.42	1.32	2.731
32	32	MALE	9.2	2.1	1.92	TENSE	GRADE 3	14	C	1.22	1.14	3.432
33	56	MALE	6.2	2.5	1.44	MILD	GRADE 1	11	C	1.75	1.24	2.765

34	30	MALE	2.4	2.6	1.38	ABSENT	ABSENT	8	B	2.52	1.78	2.678
35	64	FEMALE	3.2	2.8	1.25	ABSENT	ABSENT	8	B	2.65	1.82	1.987
36	32	MALE	2.5	2.6	1.36	MILD	ABSENT	9	B	2.33	1.56	2.228
37	45	MALE	1.4	3.5	1.15	ABSENT	ABSENT	6	A	3.26	2.16	2.125
38	42	MALE	3.5	2.2	1.62	TENSE	GRADE 2	12	C	1.35	1.28	3.125
39	51	MALE	3.8	2.5	1.42	MILD	GRADE 1	11	C	1.52	1.42	2.442
40	42	FEMALE	2.6	3.1	1.44	ABSENT	ABSENT	7	B	2.92	2.08	2.098
41	58	MALE	1.3	3.2	1.34	ABSENT	ABSENT	6	A	3.34	2.18	1.967
42	31	MALE	2.4	3.1	1.14	MILD	GRADE 1	9	B	2.12	1.36	2.778
43	64	FEMALE	1.1	3.2	0.92	ABSENT	ABSENT	6	A	3.02	1.98	2.023
44	43	MALE	0.9	3.3	1.66	MILD	ABSENT	7	B	3.22	2.09	1.995
45	37	MALE	4.3	2.8	1.44	MILD	GRADE 1	10	C	1.76	1.22	3.098
46	45	MALE	10.2	1.8	1.96	TENSE	GRADE 3	14	C	1.12	0.98	4.123
47	56	MALE	8.2	2.2	1.88	TENSE	GRADE 2	13	C	1.22	1.14	3.674
48	54	MALE	5.5	2.3	1.68	MILD	GRADE 1	12	C	1.36	1.21	3.334
49	44	FEMALE	4.2	2.6	1.34	TENSE	ABSENT	11	C	1.62	1.42	2.675
50	38	MALE	6.1	2.1	1.68	MILD	GRADE 1	11	C	1.54	1.32	2.883
51	42	MALE	3.4	3.1	1.22	ABSENT	ABSENT	8	B	2.48	1.78	2.342
52	50	MALE	2.1	3.2	1.14	ABSENT	ABSENT	7	B	3.12	2.06	2.221
53	44	MALE	7.3	2.1	1.78	MILD	GRADE 2	12	C	1.22	1.02	3.889
54	52	MALE	1.3	3.1	1.14	ABSENT	ABSENT	6	A	3.46	2.18	2.226

55	47	MALE	11.2	1.8	2.05	TENSE	GRADE 3	14	C	1.08	0.86	4.228
56	39	MALE	9.2	2.1	1.86	MILD	GRADE 2	12	C	1.31	1.25	3.345
57	45	MALE	0.9	3.4	0.96	ABSENT	ABSENT	6	A	3.33	2.08	1.897
58	48	FEMALE	1.5	2.8	1.28	ABSENT	ABSENT	6	A	3.16	2.08	2.032
59	46	FEMALE	2.1	2.6	1.44	MILD	GRADE 1	10	C	1.82	1.18	3.356
60	31	MALE	3.1	2.6	1.56	MILD	ABSENT	10	C	2.02	1.76	2.456