Dissertation on

"THE ROLE OF RENAL RESISTIVE INDEX IN ASSESSING THE EARLY RENAL DYSFUNCTION OF CIRRHOSIS"

Submitted in partial fulfilment for the Degree of

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INSTITUTE OF INTERNAL MEDICINE

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THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY

CHENNAI – 600003

APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitled "**THE ROLE OF RENAL RESISTIVE INDEX IN ASSESSING THE EARLY RENAL DYSFUNCTION OF CIRRHOSIS"** is a bonafide original work done by **Dr.NIVETHITHA KARTHIKA L,** in partial fulfilment of the requirements for M.D.GENERAL MEDICINE BRANCH – I examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2016, under my guidance and supervision in 2015

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CONTENTS

ABBREVATIONS

ALT	-	ALANINE TRANSAMINASE
ADQI	-	ACUTE DIALYSIS QUALITY INITIATIVE
ANA	-	ANTI NUCLEAR ANTIBODY
AST	-	ASPARTATE TRANSAMINASE
CPC	-	CHILD PUGH CLASSIFICATION
CTGF	-	CONNECTIVE TISSUE GROWTH FACTOR
CTP	-	CHILD TURCOT PUGH
EDV	-	END DIASTOLIC VELOCITY
GGT	-	GAMMA GLUTAMYL TRANSFERASE
UGI	-	UPPER GASTROINTESTINAL
HVPG	-	HEPATIC VENOUS PRESSURE GRADIENT
HPS	-	HEPATOPULMONARY SYNDROME
HRS	-	HEPATORENAL SYNDROME
IAC	-	INTERNATIONAL ASCITES CLUB
INR	-	INTERNATIONAL NORMALISED RATIO
LKM	-	LIVER KIDNEY MUSCLE
LVP	-	LARGE VOLUME PARACENTESIS
MAP	-	MEAN ARTERIAL PRESSURE
MARS	-	MOLECULAR ADSORBENT RECIRCULATING SYSTEM
MELD	-	MODEL FOR END STAGE LIVER DISEASE
NO	-	NITROUS OXIDE

NSAID	-	NONSTEROIDAL ANTI INFLAMMATORY DRUGS
PDGF	-	PLATELET DERIVED GROWTH FACTOR
PG	-	PROSTAGLANDINS
PHT	-	PORTAL HYPERTENSION
PSV	-	PEAK SYSTOLIC VELOCITY
RAAS	-	RENIN ANGIOTENSIN ALDOSTERONE SYSTEM
RI	-	RESISTIVE INDEX
RRI	-	RENAL RESISTIVE INDEX
RRT	-	RENAL REPLACEMENT THERAPY
SBP	-	SPONTANEOUS BACTERIAL PERITONITIS
SNS	-	SYMPATHETIC NERVOUS SYSTEM
TGF	-	TRANSFORMING GROWTH FACTOR
TIMP	-	TISSUE INHIBITOR OF METALLOPROTEINASE
TIPS	-	TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT
TNF	-	TUMOUR NECROSIS FACTOR

Introduction

INTRODUCTION

Cirrhosis of liver is the tenth leading cause of death in India and a major cause of disease burden among the population. The expenditure in treatment not only burns out the country's economic resources but also a major cause of sickness absenteeism leading to man days losses.

According to the latest WHO data published in May 2014 "Deaths due Liver Disease" and its complications in India is killing almost 216,865 people and accounts for nearly 2.44% of total deaths and India ranks 61 among the other world nations in mortality due to cirrhosis

The disease course is further altered by the development of numerable complications like varices, hepatic encephalopathy, coagulopathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome that carries a poor prognosis.

Among the various complications the development of hepatorenal syndrome has a devastating course and outcome in cirrhotic patients. HRS is usually an extended spectrum of prerenal azotemia and therefore is potentially reversible.

But after the evolution of the disease, the median survival is only 2 weeks without liver transplantation or management with vasoconstrictors.

HRS is a part of events occurring in the background of cirrhosis with PHT or acute liver injury.

Two important pathogenesis of HRS

- Splanchnic arterial vasodilatation
- Renal arterial vasoconstriction

This leads to progressive renal failure with normal kidneys in histological examination.[3]

Usually HRS can be diagnosed only after the rise in blood urea nitrogen and serum creatinine. By then the disease has progressed so that it is no longer reversible and has a poor outcome. But the disease can be predicted in advance by the estimation of renal resistive index that increases before a considerable period of time by Doppler ultrasound and so measures can be implemented to prevent the disease progression by avoiding the excess use of diuretics and nephrotoxic agents, avoiding large volume paracentesis etc.

Renal dysfunction may be corrected by treating of portal hypertension, liver transplantation, transplantation of the kidneys into a noncirrhotic recipient, and medical management. [4]

Aims & Objectives

AIMS AND OBJECTIVES

- To measure the intrarenal resistive index in patients with liver cirrhosis.
- To estimate the renal vasoconstriction before overt hepatorenal syndrome develops in cirrhotic patients with and without ascites
- To compare the resistive index with MELD and Child Pugh scoring system

Review of literature

REVIEW OF LITERATURE

Hepatorenal syndrome has its original description that dates as far back in late 19th century when Frerichs and Flint reported some cases of renal failure occurring in patients with end stage liver disease.[5]

In 1932, Helvig and Schutz coined the term “liver and kidney syndrome,” to illustrate the type of acute kidney injury that happened after abiliary surgery.[6]

But it was in 1956, Hecker and Sherlock gave the clinical definition of HRS characterised by hyponatremia, oliguria, absence of proteinuria, reduced urinary sodium excretion.[7]All the patients succumbed to the illness and findings in post-mortem revealed normal renal histology. Then they postulated the underlying mechanism as “peripheral vasodilatation”.

Later reports of reversal of renal function when transplantation of kidneys from patients with end stage liver disease to recipients of end stage kidney disease proved the previously postulated theories

CIRRHOSIS

The terminology "cirrhosis" is derived from the Greek word “kirrhos” and “osis” in the year 1830.

- “Kirrhós” means "yellowish or tawny" because of the yellowish colour imparted to the diseased liver
- “Osis” means “condition" in medical term

In 1826, Laennec coined the term "cirrhosis".[8]

In 1930, Roessle explained the pathogenesis of cirrhosis

Cirrhosis is a diffuse process characterised by three processes[9]

- Fibrous septae bridging the portal tracts
- Nodular transformation
- Hepatic architectural disruption.

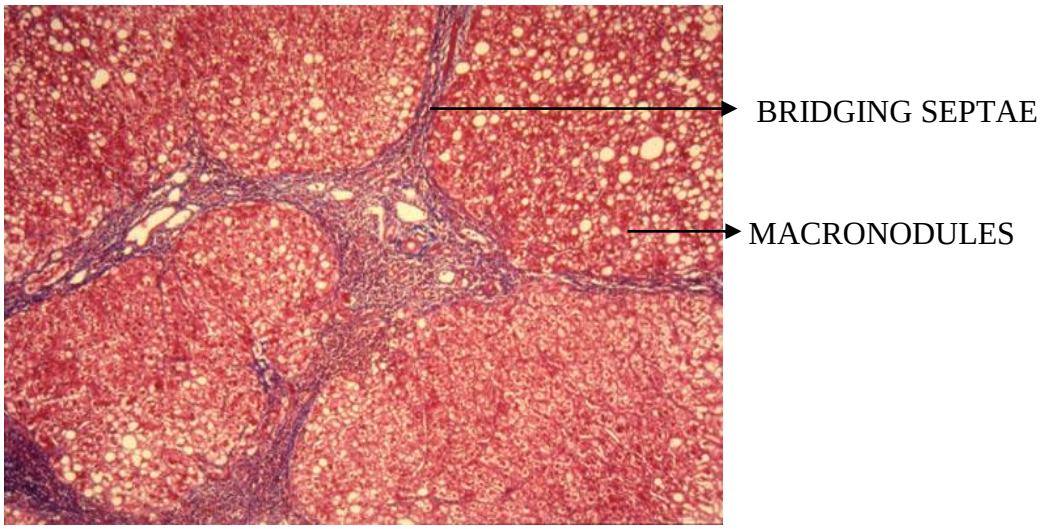


Figure 1: Cirrhosis histology

DISEASE PROGRESSION IN CIRRHOSIS

Chronic liver damage results in a spectrum of hepatocellular injury ranging from fatty infiltration and hepatitis progressing to cirrhosis and hepatocellular carcinoma.[10]

It is characterised by

- Hepatic steatosis
- Necro-inflammation with fibrosis
- Nodular degeneration

FATTY LIVER

- Benign condition caused by accumulation of lipid within the hepatocyte.
- Earliest and predictable response to consumption of alcohol.
- Usually reverses with abstinence.
- 10 % risk of developing cirrhosis in heavy drinkers.[11]

ALCHOHOLIC HEPATITIS

- 10% to 35% of heavy drinkers.
- Formation of necro-inflammation, with or without steatotic changes and fibrosis which is a natural wound-healing response.

- Destruction of the sinusoids, the space of Disse, vascular structures that initiate the occurrence of resistance to blood flow in the liver.

Alcoholic hepatitis is a specific and important clinical condition as patients with severe alcoholic hepatitis have

- Increased short-term mortality rates.
- Alcoholic hepatitis is a clearly defined precursor of cirrhosis.
- Risk is nine times increased than with fatty liver alone.[11]

CIRRHOSIS

- Maladaptive wound healing response & remodelling of scar tissue

MICRONODULAR:

- Also called as Laennec cirrhosis
- 8% to 20% in individuals with heavy consumption of alcohol.
- Fine mesh-like pattern develops with prominent entanglement of the central vein

MACRONODULAR:

- Progressively transforms to form broad bands of fibrosis that split large nodules of liver tissues
- Hepatocellular carcinoma develops in this setting.

MORPHOLOGICAL CHANGES OCCURRING IN DEVELOPMENT OF CIRRHOSIS

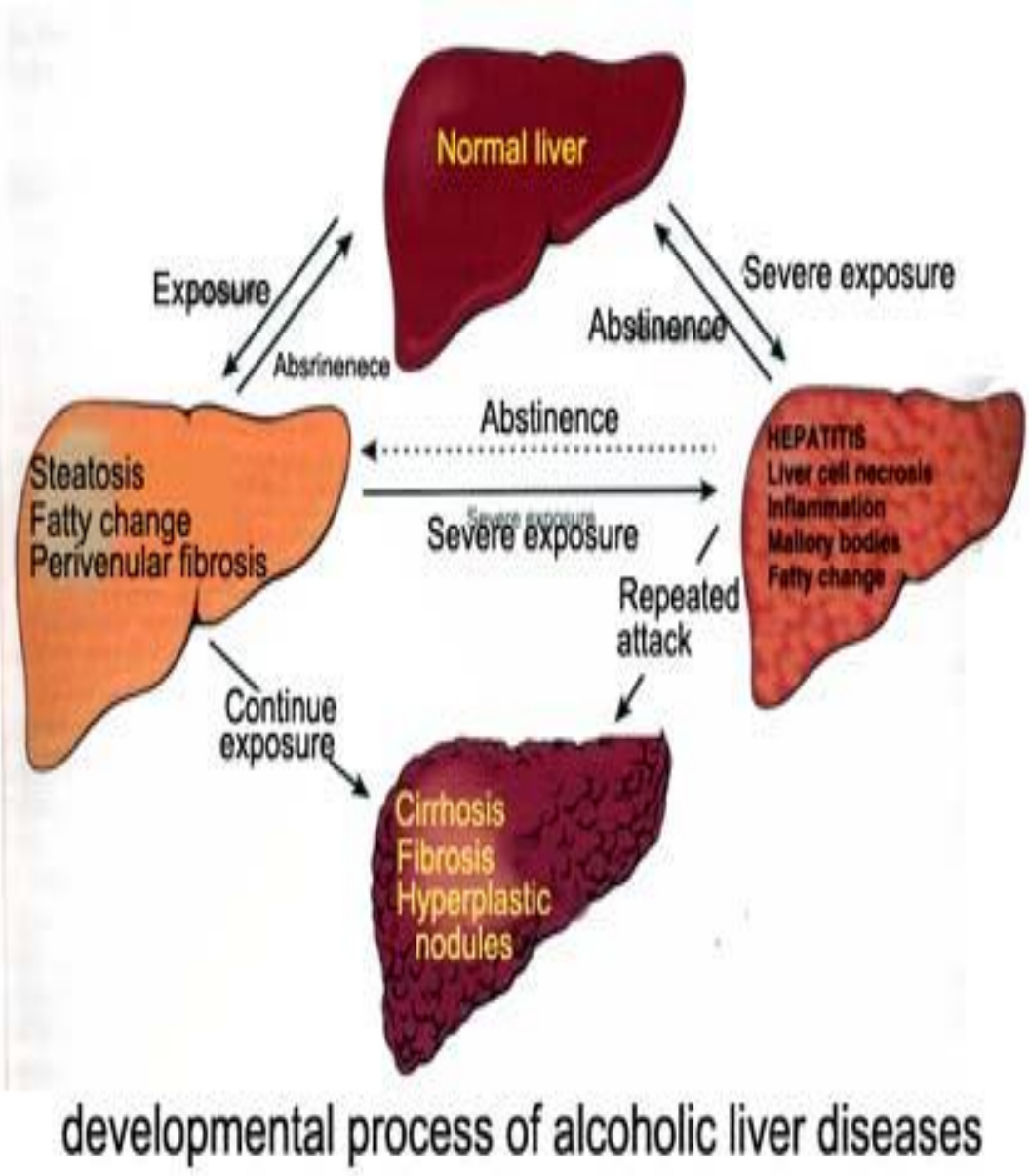


Figure 2: Morphological changes occurring in development of cirrhosis

HISTOPATHOLOGICAL CHANGES IN THE DEVELOPMENT OF CIRRHOSIS

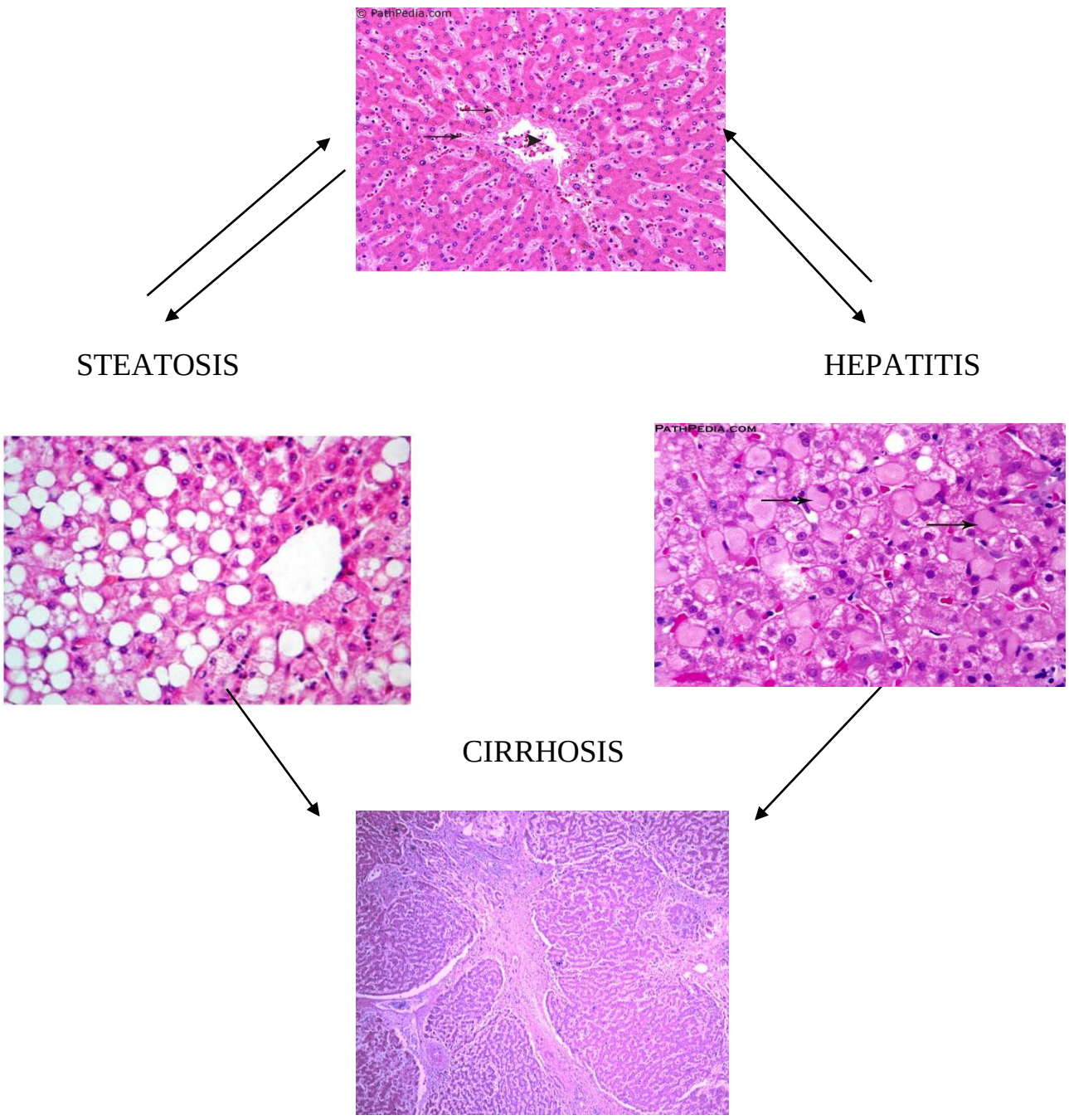
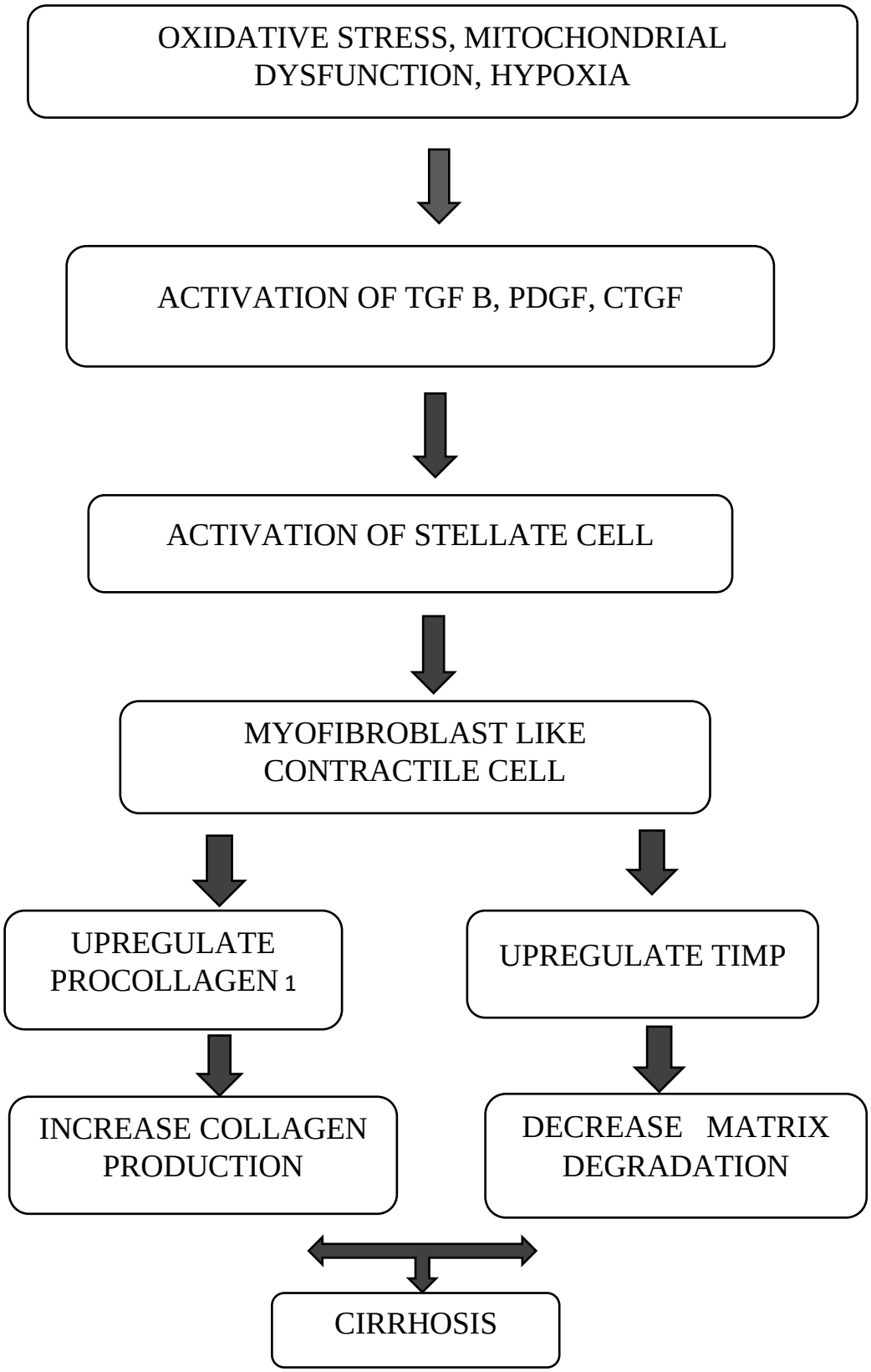


Figure 3: Histopathological changes of cirrhosis

PATHOGENESIS OF CIRRHOSIS[12,13,14,15]



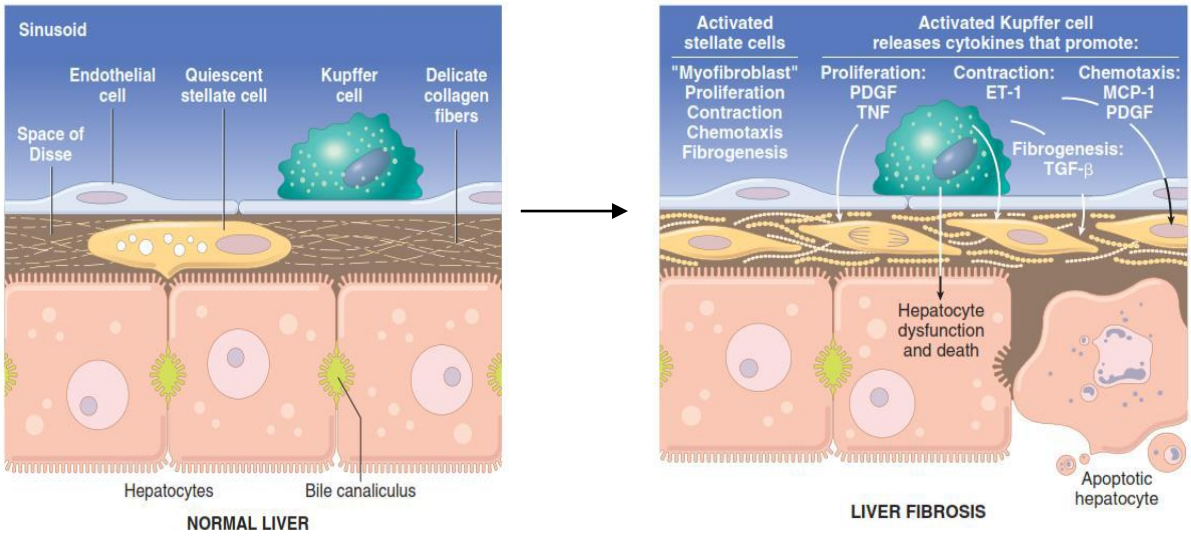


Figure 4: Pathogenesis of cirrhosis

ETIOLOGY OF CIRRHOSIS[16]

Alcoholism	Chronic viral hepatitis
Cardiac cirrhosis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	α_1 Antitrypsin deficiency
Nonalcoholic steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	

Table 1: Etilogy of Cirrhosis

CLINICAL FEATURES

- Fatigue, weakness, anorexia, weight loss.[17]

DIRECT CONSEQUENCE OF LIVER CELL FAILURE

- Jaundice[17]
- Parotid enlargement
- Palmar erythema[18]
- Spider naevi[19]
- Hypogonadism[20]
- Gynecomastia[21]
- Fetor hepaticus [22]
- Enlarged liver or shrunken liver
- Ascites

CONSEQUENCES OF PORTAL HYPERTENSION

- Haemetemesis as a result of esophageal varices
- Splenomegaly [23]
- Caput medusa

MISCELLANEOUS FEATURES

- Hypoalbunemia induced nail changes[24]
- Muehrcke's lines and Terry nails
- Clubbing and Hypertrophic osteoarthropathy.[24]
- Dupuytren's contracture

END STAGE LIVER DISEASE

- Bleeding diathesis
- Hepatic encephalopathy
- Acute kidney injury

LABORATORY FINDINGS IN CIRRHOSIS

LIVER ENZYMES:[25]

- Serum aminotransferases
    - Modest elevation of (ALT) & (AST) even in severe alcoholic hepatitis and cirrhosis.
- Alkaline phosphatase
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
- Gamma-glutamyl transpeptidase (GGT)
    - Alcohol induced chronic liver disease.
    - With alcohol abuse, even in the absence of liver disease due to microsomal enzyme induction.
- Serum Bilirubin : Normal in compensated cirrhosis and increased levels as cirrhosis progresses.
- Coagulation defects : Prolonged Prothrombin time
- Serum albumin : Reduced because albumin is synthesized only in the liver

- Serum globulins: Increased because of shunting of bacterial antigens from liver to lymphoid tissue.
- Reversal of albumin-globulin ratio
- Hyponatremia
    - High levels of ADH and aldosterone.
    - Inability to excrete free water.
    - Correlates with severity of disease.[14]

HAEMATOLOGICAL ABNORMALITIES26

- Anemia
    - Marrow suppression
    - Bleeding from varices
- Leukopenia and neutropenia
    - Due to splenomegalyand splenic sequestration.
- Thrombocytopenia
    - Alcoholic marrow suppression
    - Sepsis
    - Lack of folate
    - Sequesteration in the spleen
    - Decreased thrombopoietin.

OTHERS

- Serology for hepatitis viruses.
- Autoantibodies (ANA, anti-LKM)
- Markers of iron and copper overload, alpha 1 antitrypsin.

IMAGING

ULTRASONAGRAPHY OF ABDOMEN:[27,28]

- Non-invasive test.
- Screening of hepatocellular carcinoma
- Patency of the portal vein
- Presence of ascites, splenomegaly.

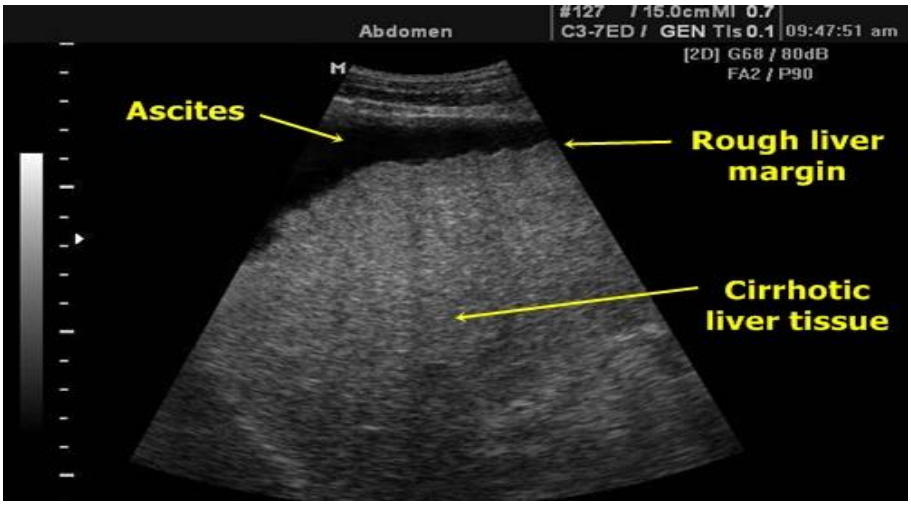


Figure 5: Ultrasound image

FIBROSCAN [29]

- Transient elastography .
- Non – invasive method for evaluation of liver fibrosis and cirrhosis.

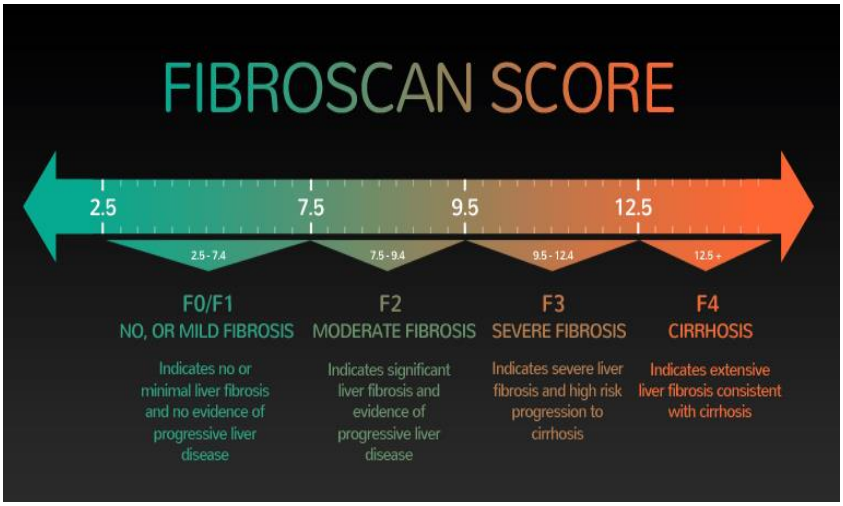


Figure 6: Fibroscan Score

LIVER BIOPSY [30]

- Gold standard for diagnosis
- Diagnosis of the aetiology
- Sensitivity is 80-100%

PROGNOSTIC SCORES FOR CIRRHOSIS

- Child Turcotte Pugh classification (CPC)
- Model for End stage Liver Disease (MELD)

CHILD-TURCOTTE-PUGH CLASSIFICATION

- In assessment of prognosis of liver disease.[31]
- Predicting the survival rates

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criterias	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 International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >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)			

Table 2: Child – Turcotte-Pugh Classification

MELD SCORE

- To prioritize patients for transplantation.[32]
- It is calculated according to the following formula:[33]

$$\begin{aligned}\text{MELD score} = {} & [3.8 \times \log_e(\text{bilirubin in mg/dL})] \\ & + [11.2 \times \log_e(\text{INR})] \\ & + [9.6 \times \log_e(\text{creatinine in mg/dL})] \\ & + [6.4 \times (\text{aetiology: 0 if cholestatic or} \\ & \quad \text{alcoholic, 1 otherwise})]\end{aligned}$$

INTERPRETATION[34]

3 month mortality is:

- 40 or more — 71.3% mortality
- 30–39 — 52.6% mortality
- 20–29 — 19.6% mortality
- 10–19 — 6.0% mortality
- <9 — 1.9% mortality

COMPLICATIONS OF CIRRHOSIS

PORTAL HYPERTENSION

- GastroesophagealVarices
- Portal Hypertensive Gastropathy
- Ascites
- Spontaneous Bacterial Peritonitis
- Hepatic Encephalopathy
- Hepatorenal Syndrome
- Hepato Pulmonary Syndrome
- Cirrhotic Cardiomyopathy
- Portopulmonary Hypertension
- Splenomegaly ,Hypersplenism

HAEMATOLOGICAL ABNORMALITIES

- Anaemia
- Leucopenia
- Thrombocytopenia

CAUSES OF ANEMIA IN LIVER DISEASE

Hemorrhage and/or iron deficiency	Alcoholic gastritis Portal hypertension Peptic ulceration
Hemolysis	Chronic liver disease and/or cirrhosis Zieve syndrome Spur cell anemia of severe liver disease
Reduced erythropoiesis	Anemia of chronic disease Nutritional (e.g. folic acid deficiency) Sideroblastic anemia Alcohol toxicity
Hypersplenism	Portal hypertension
Hemodilution	Fluid retention of chronic liver disease Aggressive intravenous fluid therapy

EFFECTS OF LIVER DISEASE IN HEMOSTATIC MECHANISM

Reduced synthesis of clotting factors
  hepatic dysfunction *per se*
  vitamin K deficiency/ malabsorption
Reduced synthesis of inhibitors of coagulation
Production of abnormal/ dysfunctional proteins
Enhanced fibrolytic activity
  reduced clearance of activators of fibrinolysis
  reduced production of inhibitors of fibrinolysis
Reduced hepatic clearance of activated clotting factors
Disseminated intravascular coagulation
  multifactorial including endotoxaemia
Platelet abnormalities
  number
  function

PORTAL HYPERTENSION

HVPG greater than or equal to 5mm Hg

Significant varices develop at HVPG of 10 mm Hg.[35]

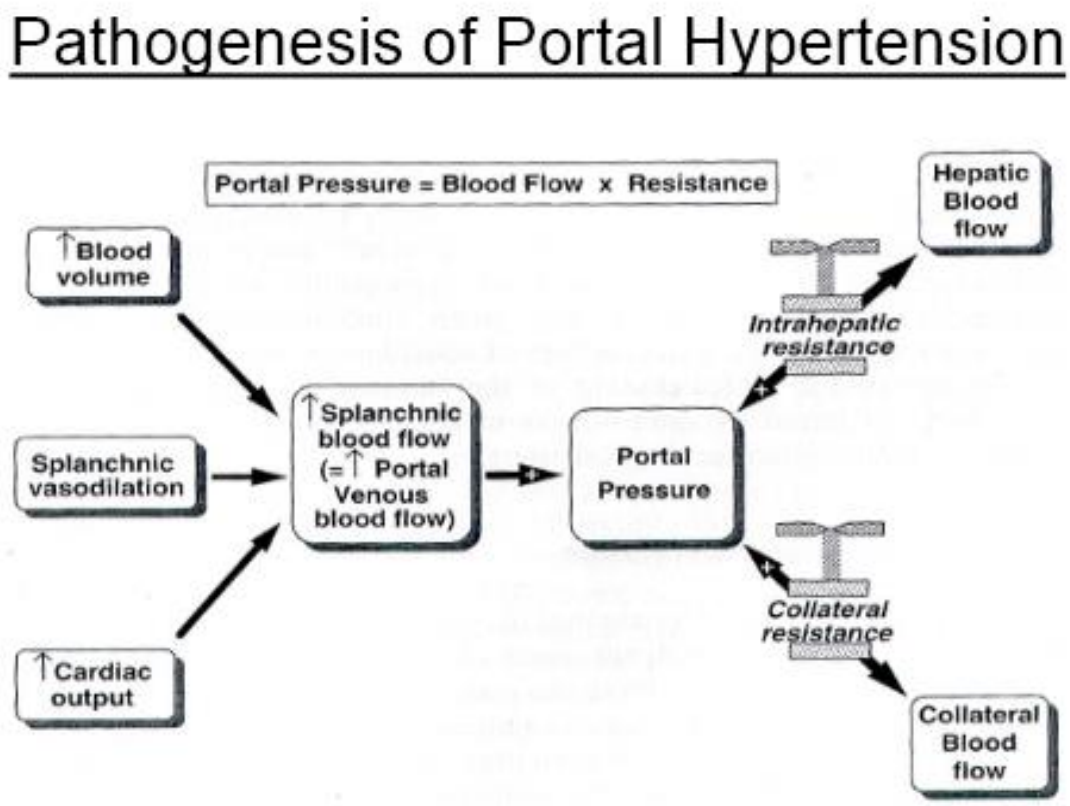


Figure 8: Pathogenesis of Portal Hypertension

Causes of portal hypertension

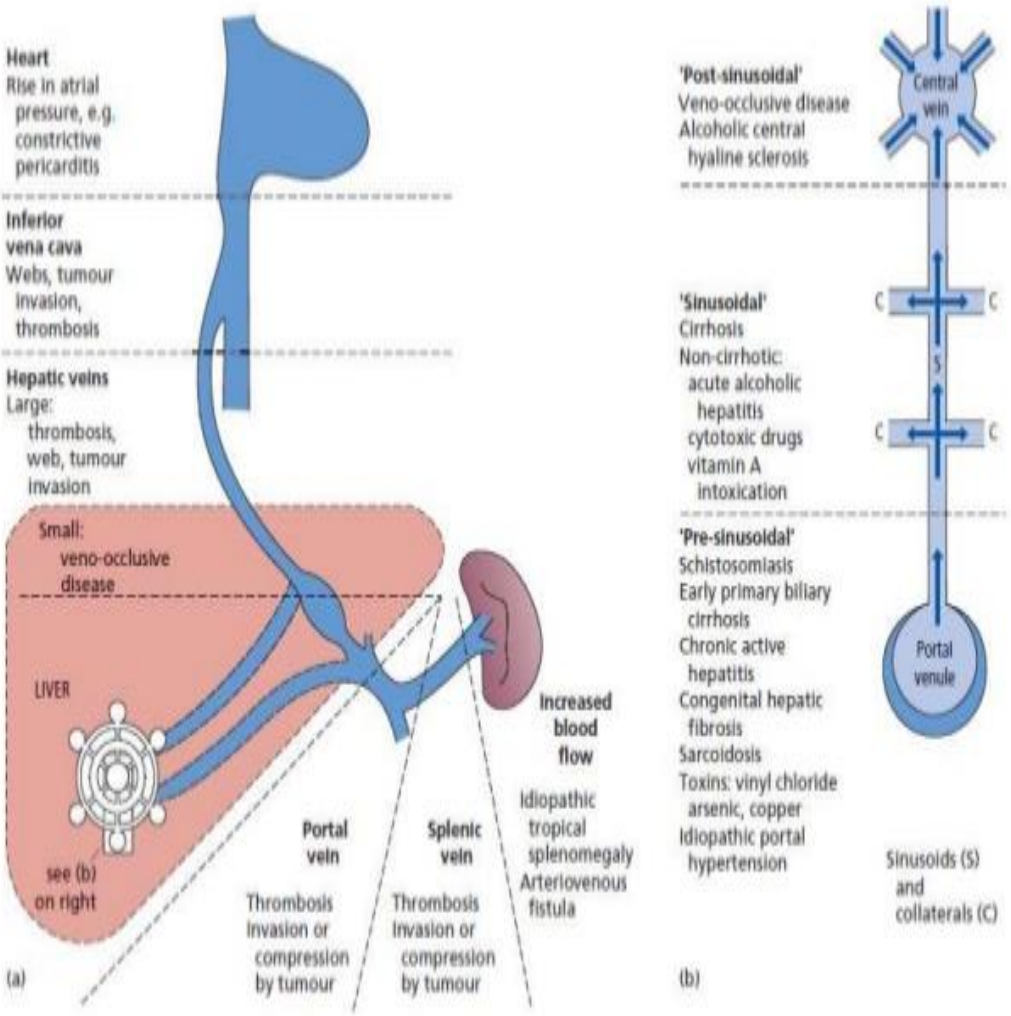


Figure 9: Causes of PHT

VARICEAL HAEMMORHAGE

- Esophageal varices is dreadful complication of PHT.
- Most common cause of UGI bleed in one third of cirrhotics.
- Incidence 5–15% / per year.[36]
- Portal hypertension leads to formation of portosystemic collaterals and varices.

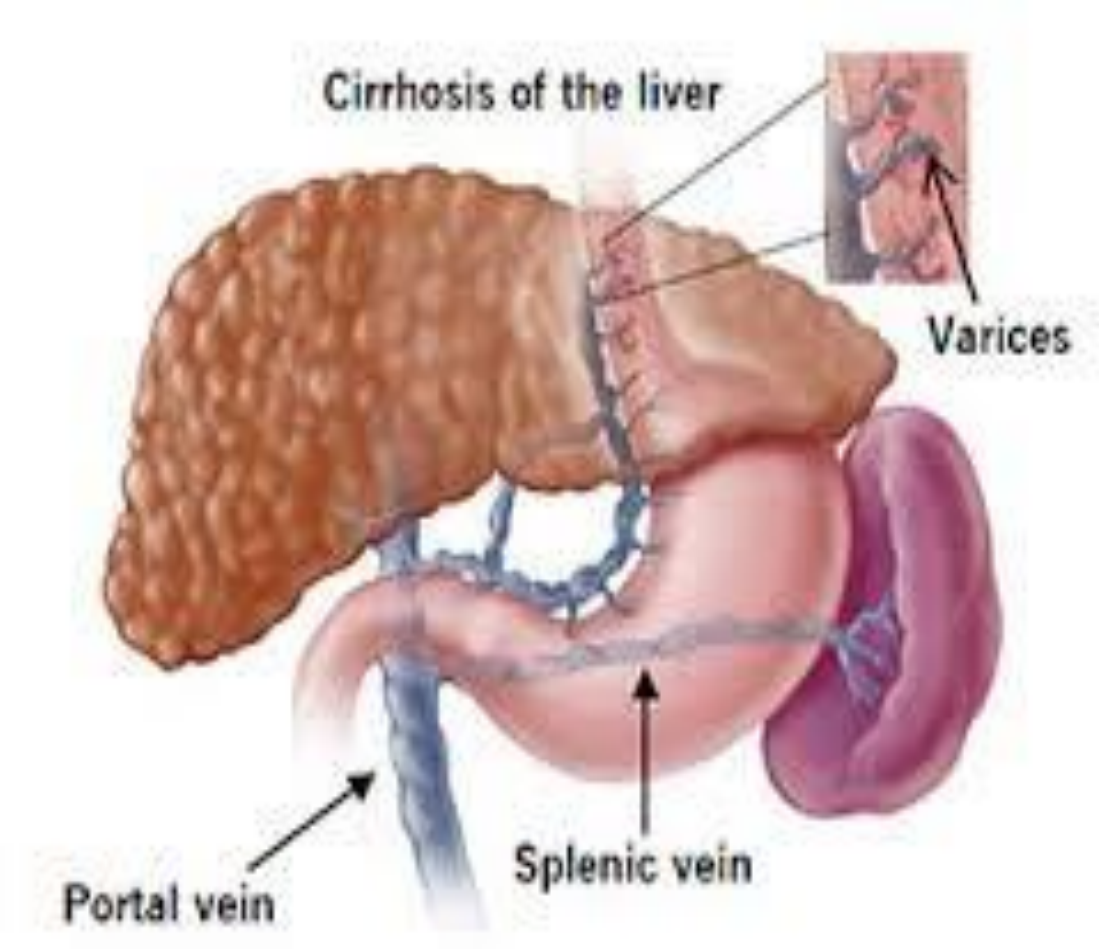


Figure 10: Varices.

ASCITES

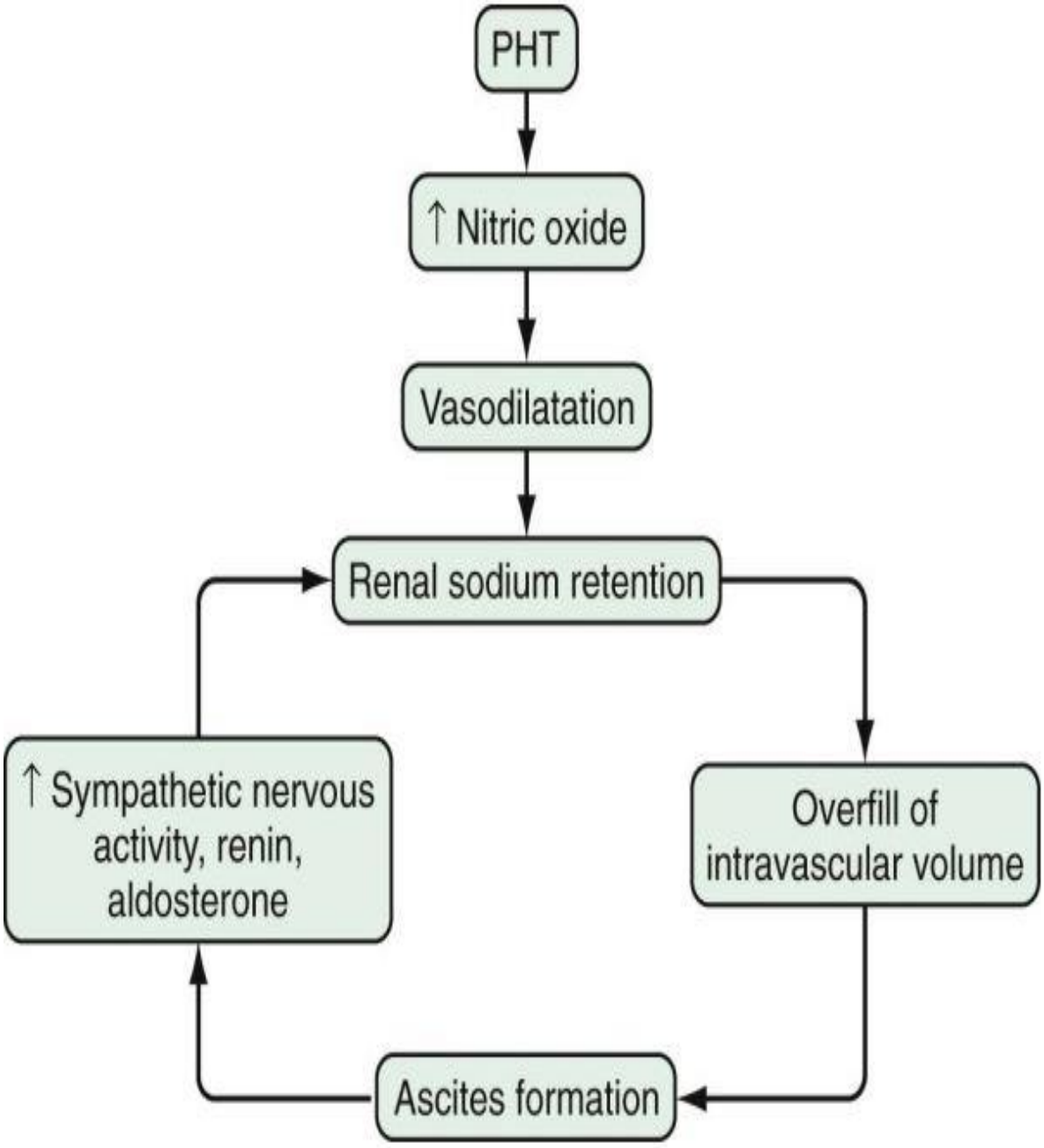


Figure 11: Mechanisam of formation of Ascites

SPONTANEOUS BACTERIAL PERITONITIS

- Spontaneous infection of fluid in abdominal cavity without an intraabdominal source of infection.
- Incidence - 30%
- Most common organism is E.Coli.

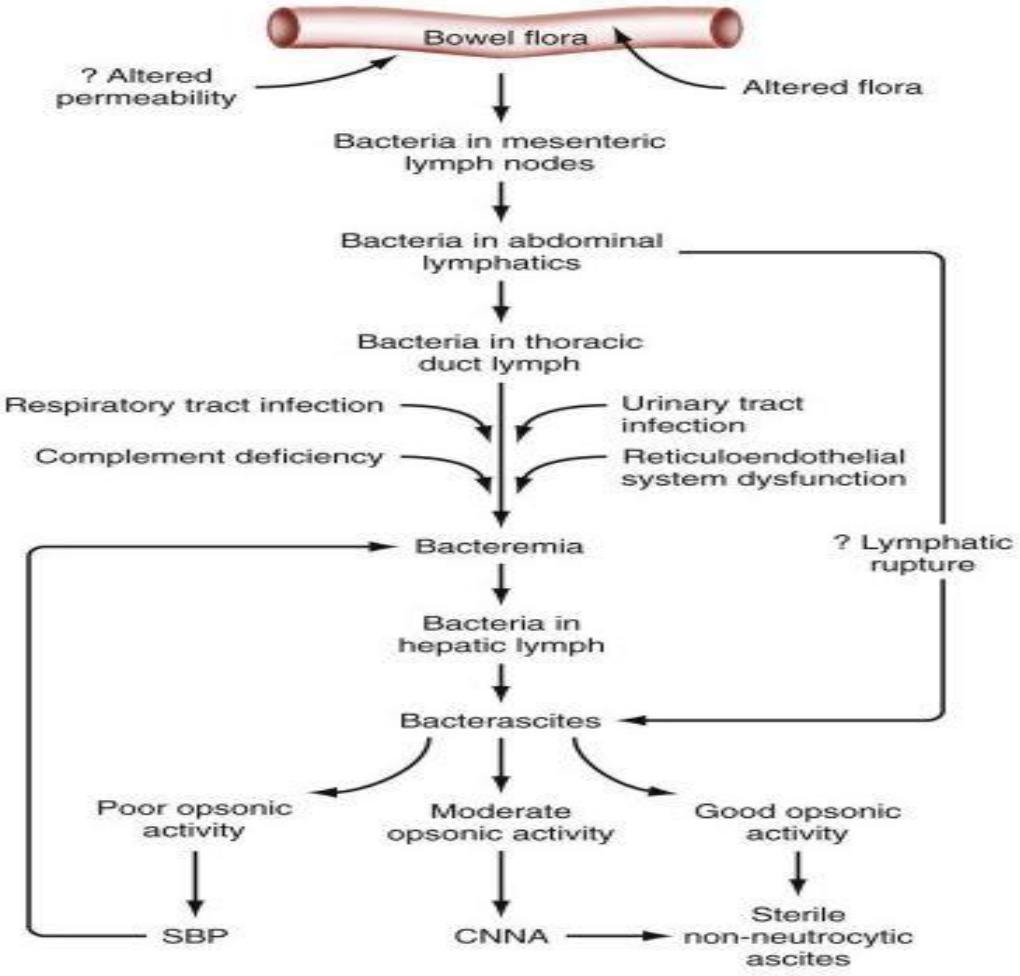


Figure 12: Pathophysiology of Spontaneous Bacterial Peritonitis

HEPATIC ENCEPHALOPATHY

- Wide range that encomposess transient and reversible neurological and psychiatric manifestations.[36]
- Occurs in chronic liver disease with portal hypertension andacute liver failure.
- Incidence 50% to 70% in patients with cirrhosis
- Poor prognostic indicator.
- Three year survival rate 42%,

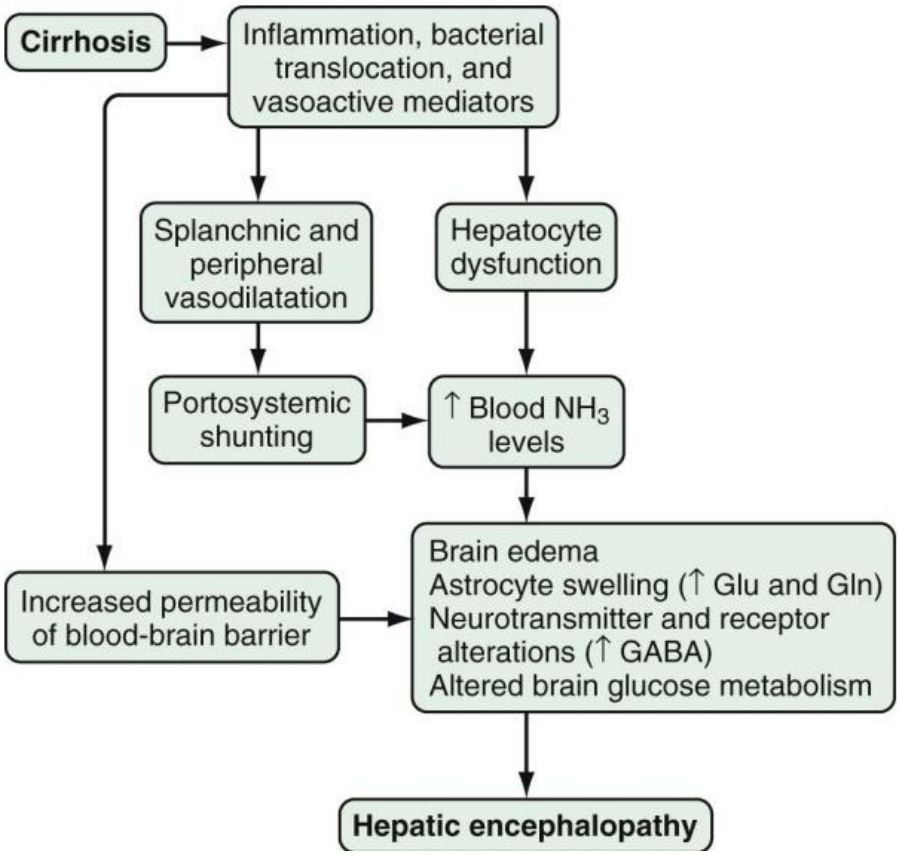


Figure 13: Mechanisam of Hepatic Encephalopathy

PATHOGENESIS OF HRS, HPS, CIRRHOTIC CARDIOMYOPATHY HEPATORENAL SYNDROME

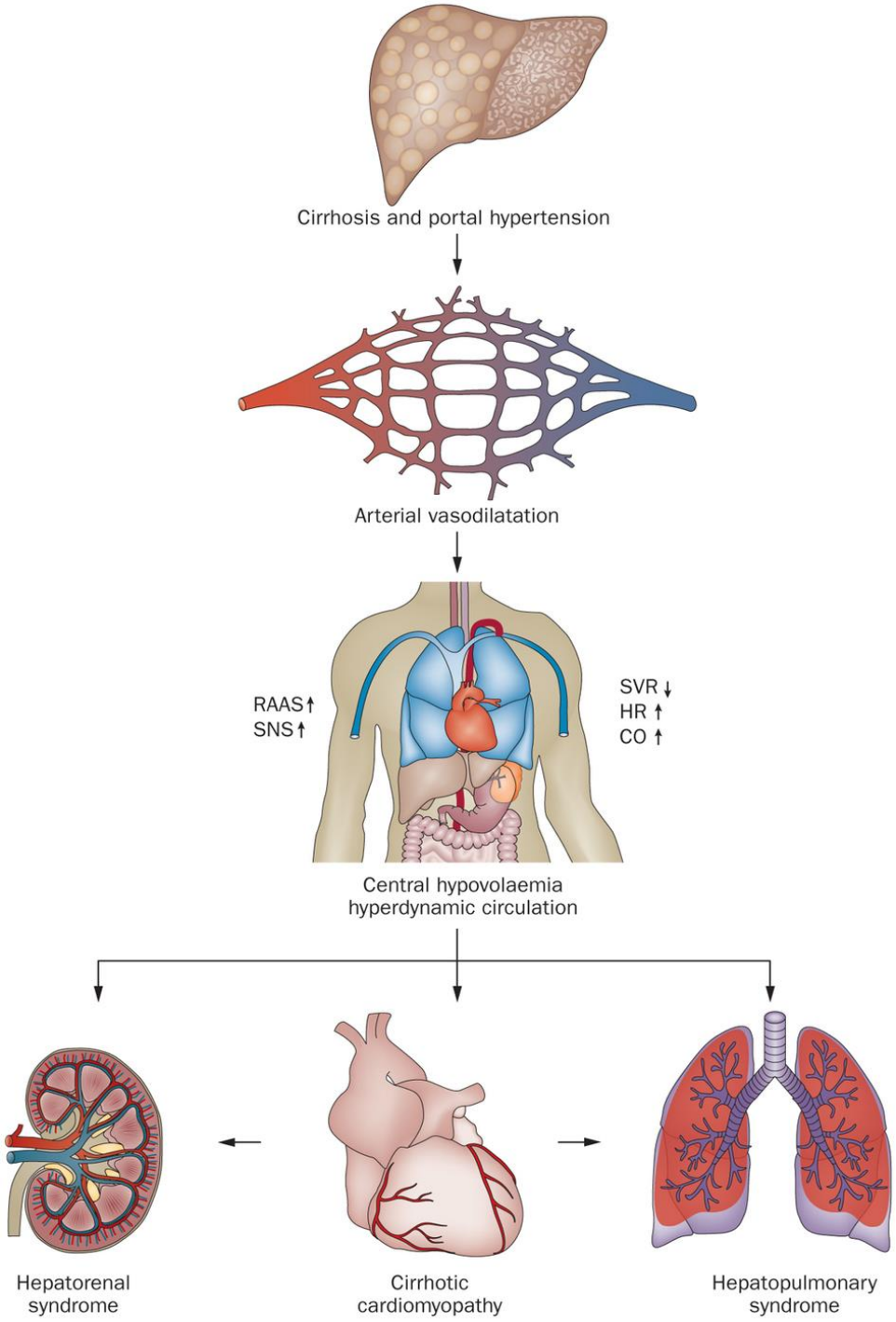


Figure 14: **Pathogenesis of HRS, HPS, Cirrhotic Cardiomyopathy Hepatorenal Syndrome**

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a distinct form of functional renal failurethat occurs as a part of cascade of events related to the intense dilatation of splanchnic bed in the background of cirrhosis with ascites or acute fulminant hepatic failure leading to vasoconstriction of renal arterial bed and progressive renal failure with normal renal histology.[37]

Koppel et al. identified the reversal of the renal failure when kidneys of patients with advanced liver disease and HRS transplanted to the recipients with end-stage renal disease with normal liver function [38]

The outcome is very poor and mean survival is only weeks to months. Due to the absence of diagnostic biomarkers, the diagnosis of HRS lies in the combination of clinical and laboratory informative data.

COURSE OF THE DISEASE

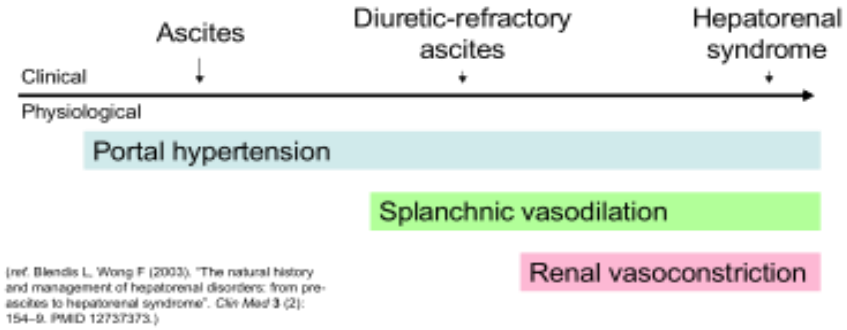


Figure 15: Course of the Disease

CLASSIFICATION OF HEPATORENAL SYNDROME

TYPE 1HRS

- Renal dysfunction which is rapidly progressive with doubling of the serum creatinine to a value > 2.5 mg/dL in less than two weeks.[39]
- Associated with a precipitating factor like spontaneous bacterial peritonitis, GI bleeding, acute liver insult.
- Rapid decline of circulatory , hepatic and renal functions

TYPE 2 HRS

- Renal dysfunction which is steadily progressive with serum creatinine > 1.5 and up to 2.5mg/dL or over weeks to months[39]
- Usually occurs in refractory ascites.
- Gradual decline of circulatory and renal functions

TYPE 3 HRS

- HRS occurring in cirrhotic patients having chronic renal disease[40]

TYPE 4 HRS

- HRS superimposed on fulminant hepatic failure
- More than 50% of acute fulminant liver failure develop HRS

DIAGNOSTIC CRITERIA

In 1996 International Ascites Club (IAC) produced diagnostic criteria for HRS that was accepted internationally.[41]

REVISED DIAGNOSTIC CRITERIA FOR HEPATORENAL SYNDROME DEFINED BY IAC CONSENSUS WORKSHOP IN THE YEAR 2007[42]

- Liver cirrhosis with ascites
- Serum creatinine concentration >1.5 mg/dL (>133 µmol/L), type I: >2.5 mg/dL
- No lowering of the serum creatinine concentration after at least two days without diuretic treatment and after volume expansion with albumin (recommended dose: 1 g per kg body weight per day, up to a maximum of 100 g/d)
- No evidence of shock
- No treatment with nephrotoxic drugs
- No renal parenchymal changes:
  - no proteinuria >500 mg/day,
  - no microhematuria (>50 RBC),
  - normal configuration of kidneys on ultrasonographic examination

EPIDEMIOLOGY

- Annual incidence - 7.6%
- Prevalence - 45.8%
- Age -6 th or 7th decade.
- Gender - Increased male preponderance [43]

HRS predominantly occurs in individuals with cirrhosis and ascites with elevated pressure in the portal vein.

INCREASED INCIDENCE

- Alcoholic cirrhosis
- Coexisting acute severe alcoholic hepatitis increases the risk.[44]
- Fulminant hepatic failure(55%).[45]

RISK FACTORS

- Low mean arterial blood pressure (< 80 mm Hg).
- Dilutional hyponatremia.
- Urinary sodium retention (urine sodium < 5 mEq/L)

PRECIPITATING FACTORS

SPONTANEOUS BACTERIAL PERITONITIS (SBP).

SBP has a definitive correlation with HRS [46]

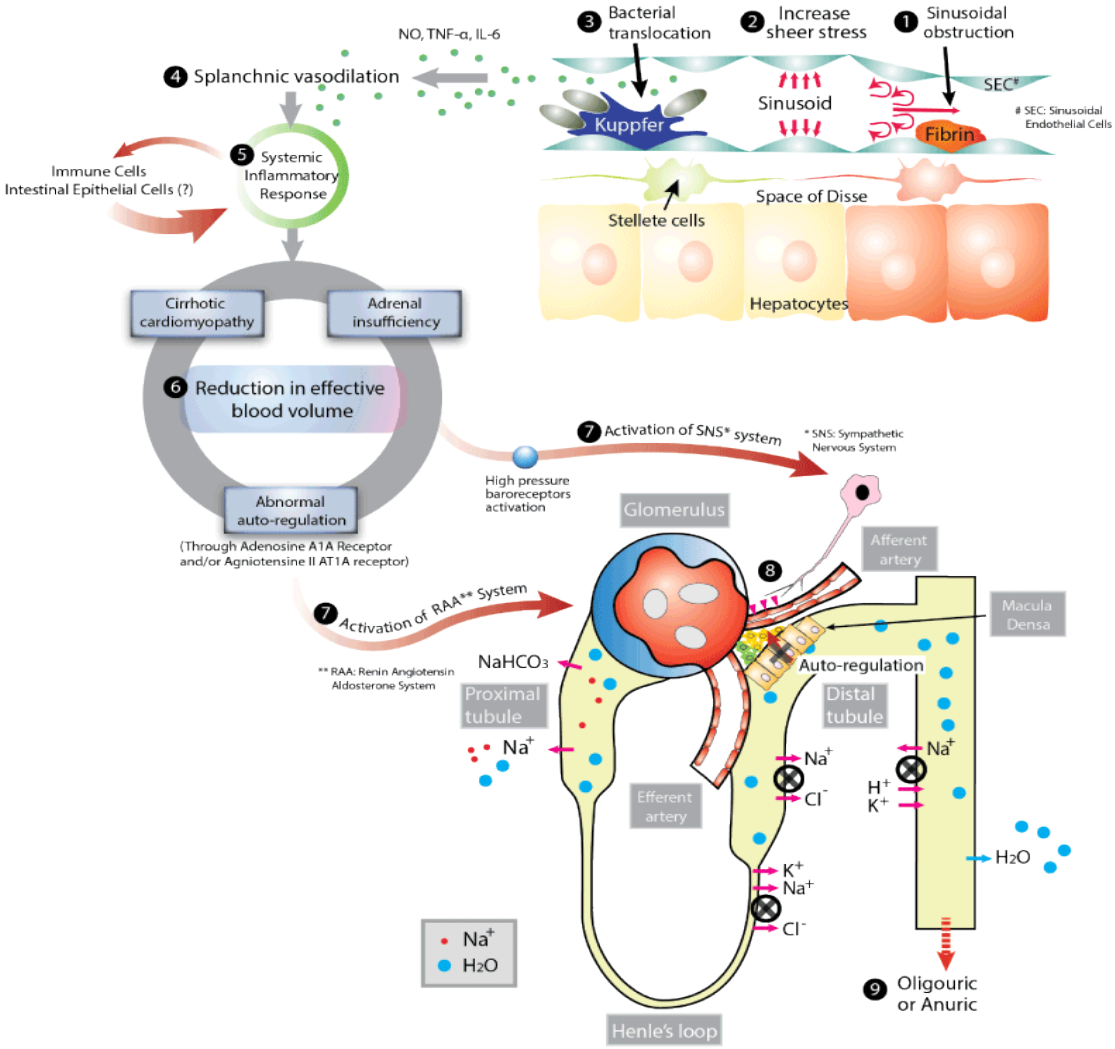


Figure 16: Pathophysiology of Spontaneous Bacterial Peritonitis

SBP trigger HRS by two mechanisms [47,48]

- Release of endotoxins and proinflammatory cytokines (IL-6 and TNF) leading to increased production of NO and other vasodilators.
- Sepsis – related cardiomyopathy leading to reduced cardiac output.

LARGE VOLUME PARACENTESIS WITHOUT PLASMA EXPANSION.

- LVP aggravate hyperdynamic circulation that leads to enhanced systemic vasodilation and arterial underfilling.[49]
- Rapid formation of ascitic fluid after a large volume paracentesis leads to decreased circulating blood volumeand reduced renal perfusionprecipitating acute renal failure.

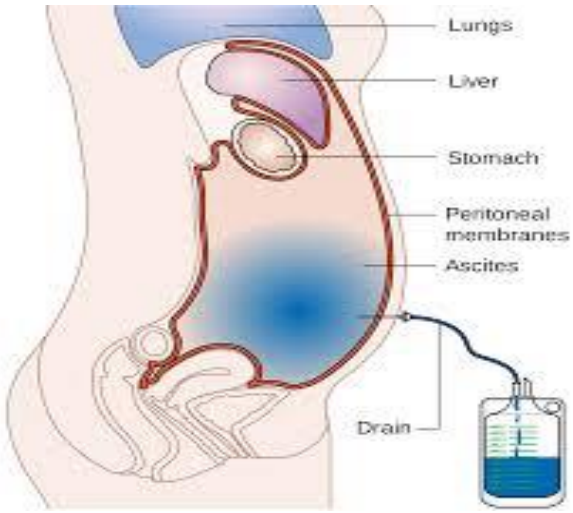
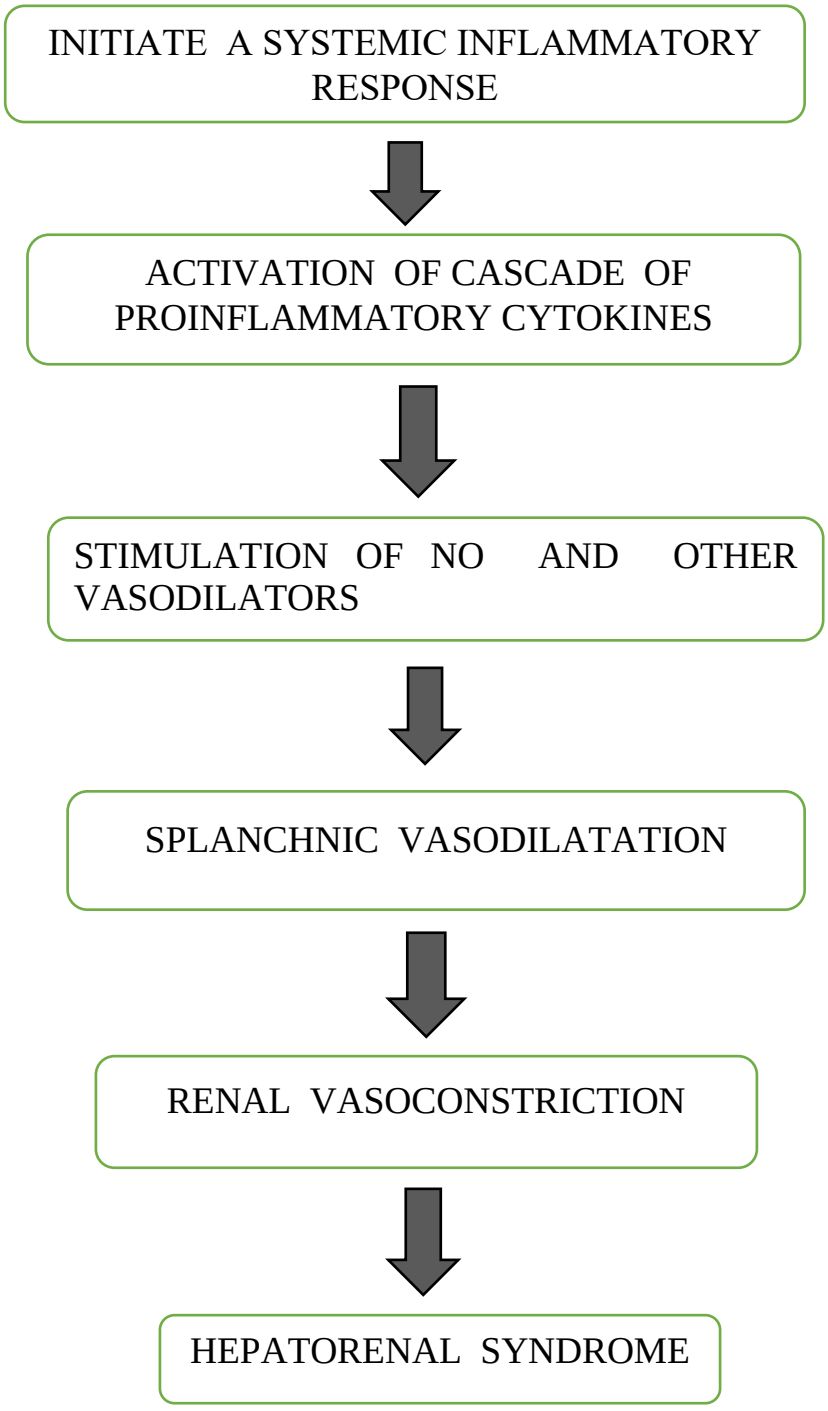


Figure 17: LVP

GASTROINTESTINAL BLEEDING[50]



Susceptibility to infection increases after a GI bleed leading to cytokine storm, further rebleeding and follows a vicious cycle

NSAIDs

NSAIDs worsens HRS in individuals with borderline renal function as initially the renal vasoconstriction is counterbalanced by PGs

DIURETICS

Injudicious use of diuretics leads to intravascular volume depletion and triggers HRS.

BILIARY OBSTRUCTION [51]

Precipitate HRS by two mechanism

1. Increased bile acids

Alter renal handling of water and electrolytes by blocking sodium-hydrogen antiport protein .

2. Oxidative stress

Production of vasoconstrictor substances.

PREDICTORS OF HRS

- No hepatomegaly,
- Increased plasma renin activity,
- Reduced serum sodium[52]

RENAL RESISTIVE INDEX[53]

- Indicator of intrarenal vascular tone
- Intrarenal resisitive index predicts the development of renal vasoconstriction in end stage cirrhotics.

Renal dysfunction occurs in patients when RI is elevated from a baseline (≥0.7).

PATHOPHYSILOGY

The initiation and perpetuation of HRS is complicated and poorly understood.

Three components leading to the evolution of HRS are

- Splanchnic vasodilatation
- Renal vasoconstriction
- Cardiac dysfunction

PATHOPHYSILOGY OF HEPATORENAL SYNDROME

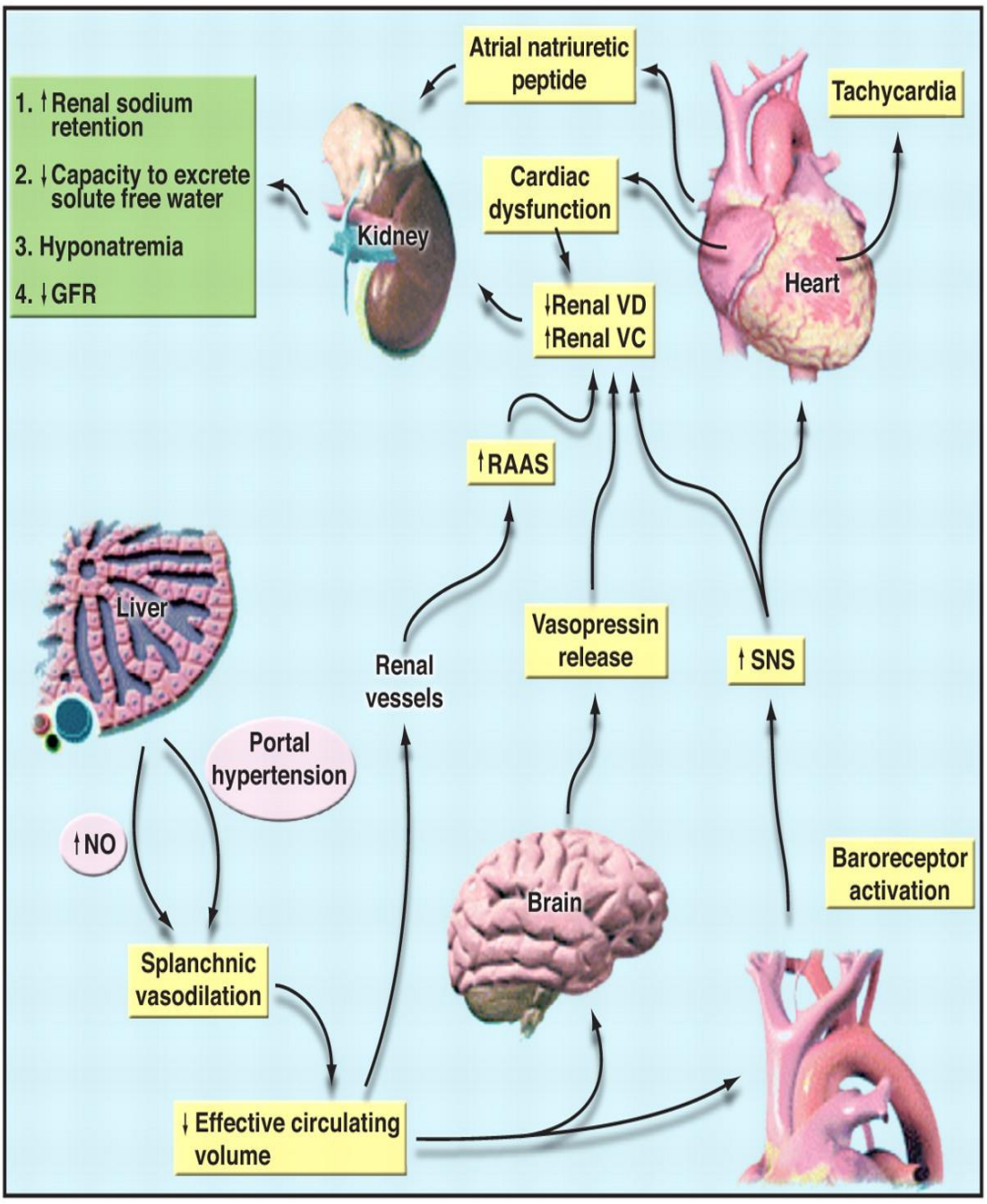


Figure 18: Pathophysilogy of Hepatorenal Syndrome

SPLANCHNIC VASODILATATION

In 1970, Epstein et al. demonstrated the importance of splanchnic vasodilation with renal vasoconstriction as a concept in the pathophysiology of HRS .[54]

- Nitric oxide and other vasodilator substances such as carbonmonoxide, glucagon, vasodilator peptides mediate vasodilatation of splanchnic arterial bed in a cirrhotic liver.[55]

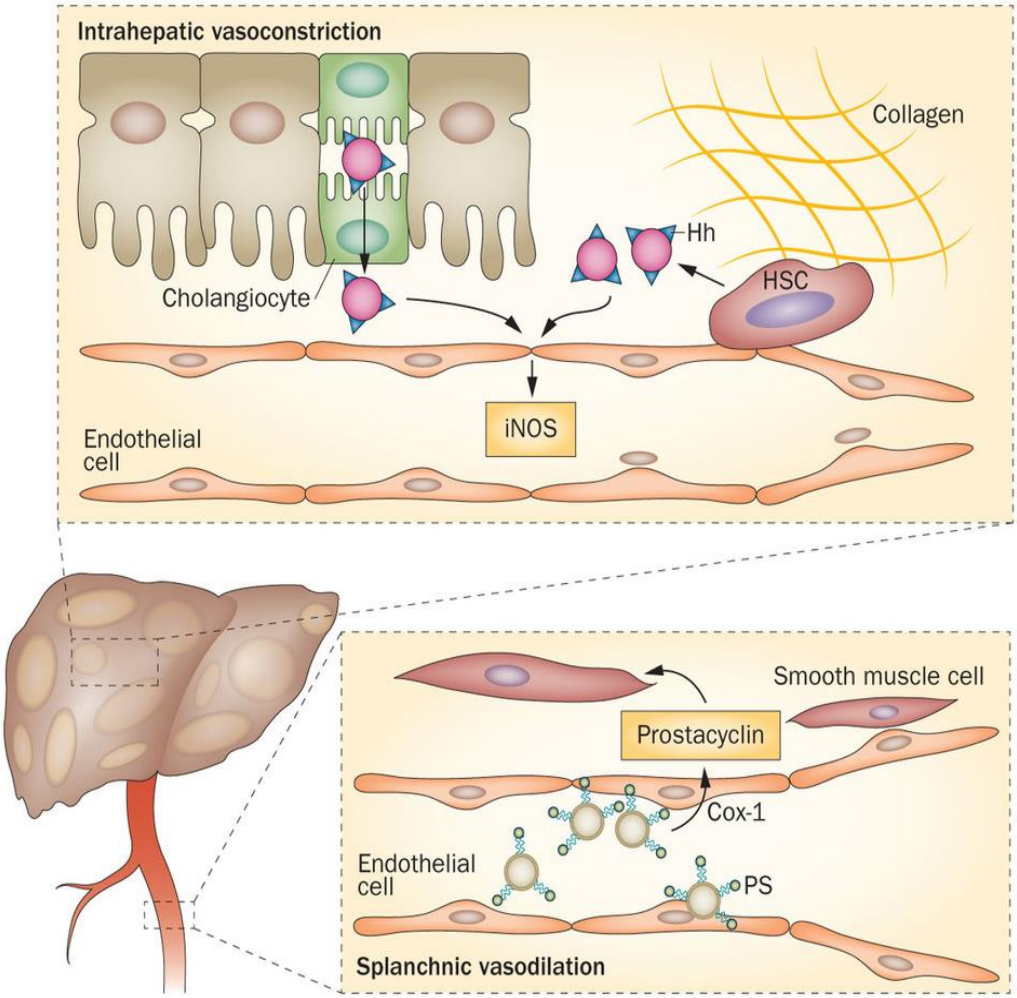


Figure 19: Splanchnic Vasodilatation

- Sequestration of blood in the splanchnic arterial bed leads to decreased effective arterial blood volume ("arterial underfilling") and blood pressure.
- In compensated cirrhosis, heart rate and cardiac output increases and creates a hyperdynamic circulation[56]
- Decompensated cirrhosis ensues as the liver disease progresses and splanchnic vasodilation progresses leading to permanent decrease in effective arterial blood volume.

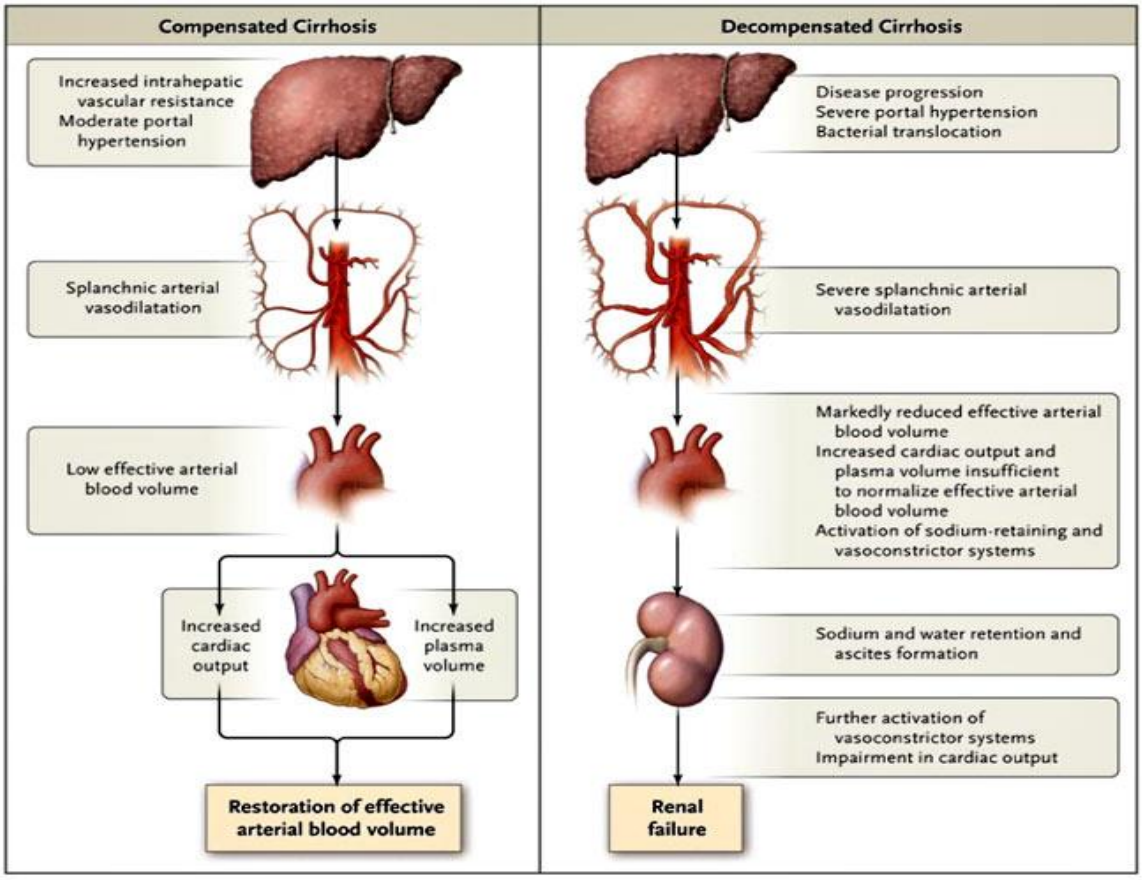


Figure 20: Renal Vasoconstriction

RENAL VASOCONSTRICTION

Schroeder et al., Arroyo et al., and Ring-Larsen et al. contributed to the role of neurohormonal vasoconstrictor pathways (RAAS and SNS) in the development of HRS .[57]

Splanchnic and systemic arterial vasodilatation leads retention of sodium and free water by

- Activation of the RAAS and SNS
- Non osmotic release of AVP that occurs in decompensated cirrhosis
- Altered production endothelins, prostaglandin, kallikreins, and F2 isoprostanes.[58-60]

CARDIAC DYSFUNCTION

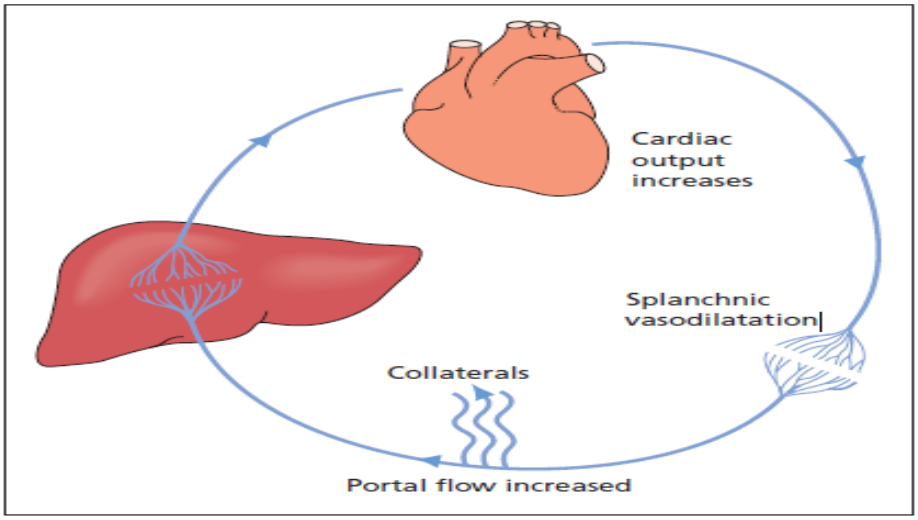


Figure 21: Cardiac Dysfunction

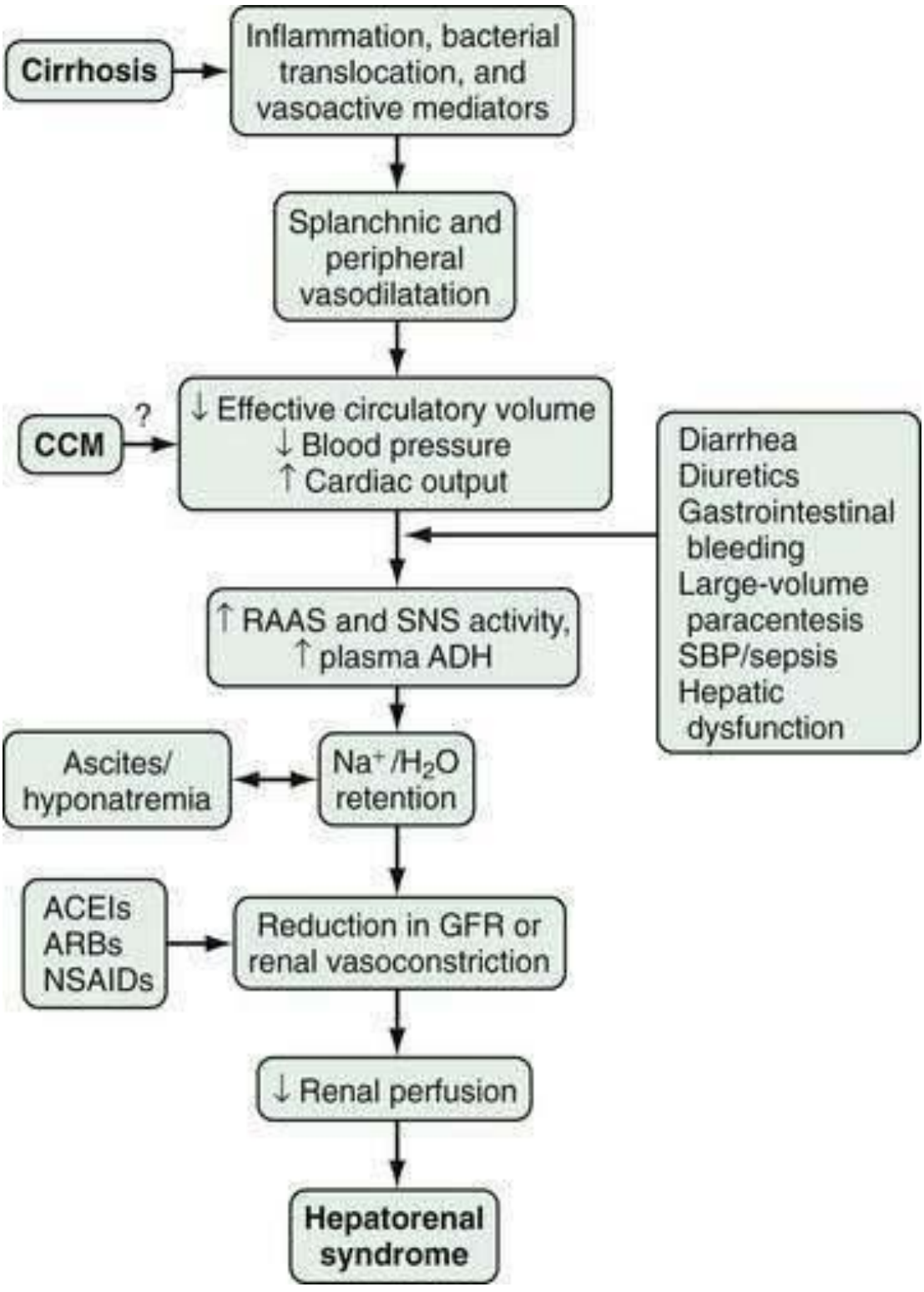


Figure 22: Schematic representation

CLINICAL MANIFESTATION

There are no specific clinical findings for HRS.

Usually it is related to the

1. Severity of liver disease
2. Degree of renal dysfunction
3. Hemodynamic abnormalities.

1. CLINICAL MANIFESTATIONS RELATED TO LIVER DISEASE

- Constitutional disturbances.
- Jaundice
- Ascites
- Features of portal hypertension (e.g., GI varices,splenomegaly hepatic encephalopathy).
- Coagulopathy
- Finger clubbing
- Palmar erythema
- Spider naevi
- Gynaecomastia

2.RENAL DYSFUNCTION

- Acute reduction in urine output in type 1 HRS
- Gradual decline of urine output in type 2 HRS.

3.HEMODYNAMIC ABNORMALITIES

Features of hyperdynamic circulation and reduced systemic vascular resistance.

- Tachycardia
- Low JVP
- Wide pulse pressure
- Low MAP

LABORATORY FINDINGS [61]

- Elevated blood urea nitrogen and serum creatinine
- Hyponatremia and hyperkalemia
- Elevated plasma renin and noradrenaline activity
- Low plasma osmolality
- Increased urine osmolality
- Reduced urine sodium excretion

MANAGEMENT OF HEPATORENAL SYNDROME

- Measures to prevent variceal bleeding
- Administration of pentoxiphylline for alchoholic hepatitis

PREVENTION[62]

- Cautious use of nephrotoxins.
- Early detection and management of spontaneous bacterial peritonitis and other infections
- Avoiding conditions producing intravascular volume depletion.
- Lactulose administration,
- Avoid large volume paracentesis without replacing adequate intravenous albumin
- Diuretics

MEDICAL MANAGEMENT

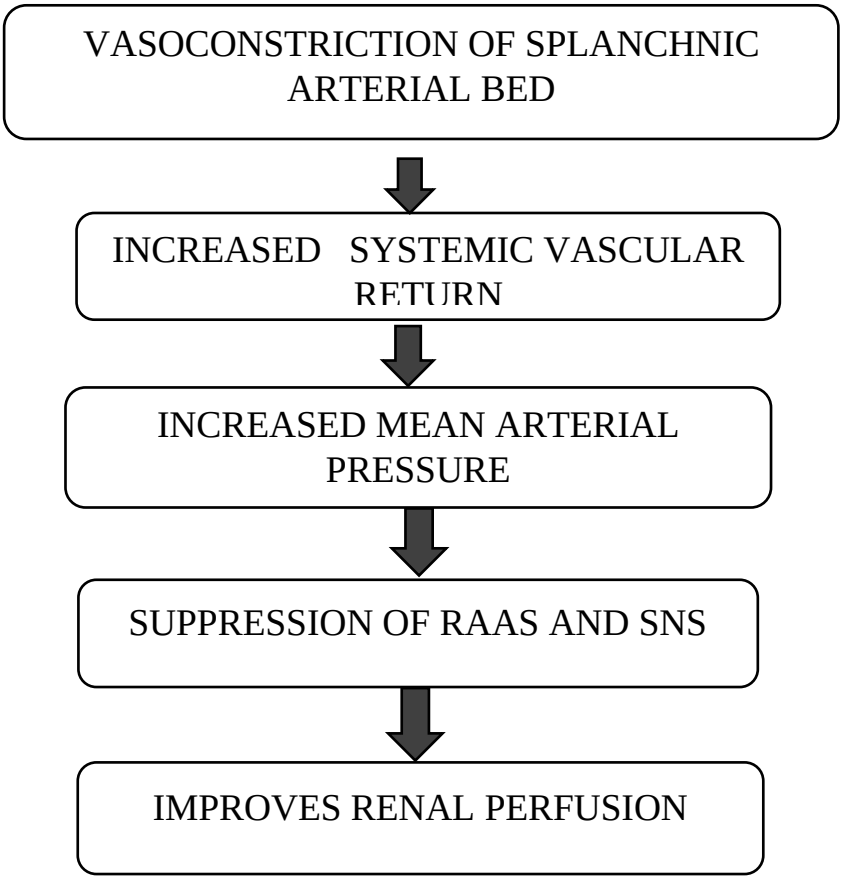
INTRAVENOUS ALBUMIN

Expansion of the volume of the plasma with albumin given intravenously.[63]Start with a dose 1g/kg/day to a maximum of 100g/day followed by 20-60g/day

VASOPRESSORS

- Vasopressin
- Noradrenaline
- Midodrine
- Octreotide

MECHANISM OF ACTION



Addition of intravenous Albumin enhances the potency of vasoconstrictor drugs by increasing the effective arterial blood volume and cardiac function.[64]

VASOPRESSIN ANALOGUES – TERLIPRESSIN,[65,66,67]

- Terlipressin is the drug of choice.
- It is a vasopressin analogue with affinity to V1 receptors in vascular smooth muscles

The Acute Dialysis Quality Initiative (ADQI) work group recommends the combined use of vasoconstrictor drugs with intravenous albumin as first line of management for treatment for type 1 HRS.[68]

BETTER PREDICTORS OF RESPONSE[69,70]

- Pretreatment bilirubin less than 10 mg/dl
- Increase in MAP more than 5mmHg at third day of therapy

CONTRINDICATIONS OF TERLIPRESSIN

- Cardiovascularproblems
- Peripheral vascular disease. [71]
- Cerebrovascular incidents.

A multicentre randomised controlled trial compared the advantage of terlipressin and albumin to only albumin in 46 patients with HRS.[72.] This showed improvement in renal function in the former group (43.5% versus 8.7%)

No advantage of survival in either group at three months.

MIDODRINE[73]

- Midodrine is a potent orally administered α1-adrenergic agonist.
- Increases the circulating blood volume by splanchnic vasoconstriction and increasing the renal perfusion
- Titrated to a MAP increase of 15 mm Hg

OCTREOTIDE[74,75]

- Somatostatin analog that inhibits endogenous vasodilator peptides.

NOREPINEPHRINE[76]

- Alpha 1 adrenergic agonist
- Titrate to a MAP increase of at least 10 mm Hg

Drug	Dose range	Observed adverse events
Terlipressin	0.5–2.0 mg i.v. every 4–6 h	Cardiac: arrhythmia, angina, myocardial infarction GI: abdominal cramps, diarrhoea, nausea, vomiting, intestinal ischaemia Peripheral: livedo reticularis, finger ischaemia, cutaneous necrosis at the infusion site, scrotal necrosis Others: arterial hypertension, dyspnoea, bronchospasm, respiratory acidosis
Vasopressin	0.01–0.8 U/min (continuous intravenous infusion)	None reported although expectedly same as for terlipressin
Noradrenaline	0.5–3.0 mg/h (continuous i.v. infusion)	Chest pain with or without ventricular hypokinesia
Octreotide + midodrine	100–200 µg subcutaneously three times a day 7.5–12.5 mg orally three times a day	Diarrhoea Tingling Goosebumps
	25 µg → 25 µg/h (continuous intravenous infusion) 2.5 mg/day orally	

i.v., intravenous; GI, gastrointestinal.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

TIPS involves the insertion of an transjugular intrahepatic stent connecting portal vein to the hepatic vein that shunts the blood from portal to systemic circulation.

This lowers portal venous pressure and decreases venous pooling in splanchnic circulation thus increasing the systemic venous return and supresses the arterial under filling and the over activity of the RAAS and SNS and renal function

CONTRAINDICATIONS

- INR > 2
- Bilirubin > 5mg/dl
- CP score > 11
- Cardiac and pulmonary disease.

INDICATIONS

- Diuretic-resistant ascites, a precursor to type 2 HRS.[77]
- TIPS may be used as a bridge to transplantation for the patients planned for surgery to improve the outcome.

Overall survival following TIPS

- 81% at three months,

- 71% at six months,
- 48% at 12 months,
- 35% at 18 months.

Recommendations from ADQI group

TIPS should not be used as the first line treatment modality for type 1 HRS

EXTRACORPOREAL SUPPORT SYSTEM

Lack of a definitive survival benefit and it is more expensive

- Renal replacement therapy
- Continuous veno veno hemofiltration
- Molecular adsorbent recirculating system
- Prometheus

RENAL REPLACEMENT THERAPY

Often used as a bridge to liver transplantation when life threatening complications of renal failure like volume overload status metabolic acidosis, hyperkalaemia, and uraemic symptoms present.

INDICATIONS

Not responding to vasoconstrictor drugs

ADVERSE EFFECTS

- Hypotension
- Infection
- Coagulopathy

Renal replacement therapy is not advisable in patients with type 1 HRS unless the condition is reversible or there is plan for transplantation.[78]

VENOVENOUS HAEMOFILTRATION

- Unstable patients
- Raised intracranial pressure.

MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS)

The dialysis technique is modified in such a way that the albumin bound and water soluble particles such as NO, TNF, cytokines are removed .

RELIEF TRIAL

Compared MARS with standard therapy on patients with chronic liver failure[79]

No improvement of overall survival and providing only temporary benefits.

PROMETHEUS[80]

Fractional plasma separation and removal of albumin bound substances with hemodialysis.

LIVER TRANSPLANTATION

Liver transplantation is the best treatment modality for the management of HRS.

Iwatsuki et al. reported that liver transplantation in three cirrhotic patients with HRS led to improved liver and renal function within two weeks of operation..

TRANSPLANTATION WITH HRS

- Three year survival rate 60%
- Poor postoperative outcome with increased mortality
- Long term RRT in postoperative period.[81]

TRANSPLANTATION WITHOUT HRS

- 3 year survival rate 70% to 80% [82]
- Better outcome.

The 3-year survival rate for living donor liver transplantation was 85.3% compared with 60.9% for orthotopic liver transplantation.

OUTCOME

Recovery of renal function after transplantation is 58% - 94%[83]

Recovery of renal function fails to occur when [84]

- The time duration between the onset of HRS and liver transplantation≥ 4–6 weeks.
- Dialysis for ≥ 8 weeks in preoperative period
- Serum creatinine of ≥ 2mg/dL

Combined liver and kidney transplantation is advantageous in such groups.85

PROPHYLAXIS

- Reduces the risk of developing HRS
- Combination of cefotoxime and albumin has a reduced incidence to develop HRS than using only cefotoxime
- Pentoxifylline, a phosphodiesterase inhibitor has advantageous effectsin reduction in development of HRS

RENAL RESISTIVE INDEX

RRI is a Doppler derived parameter often used as an indicator for assessing the renal vascular resistance. Importance of RRI is that even in presence of normal glomerular filtration rate the RRI is elevated thus indicating a poorer prognostic outcome

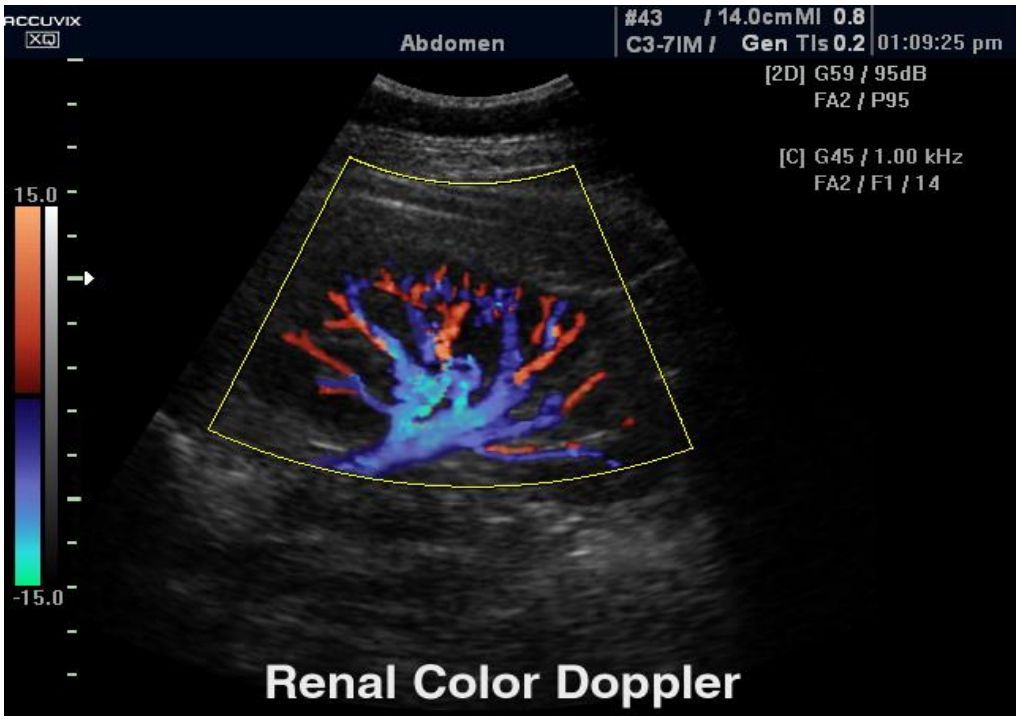


Figure 23: Renal Color Doppler

Localisation of the vessel is done by a high frequency probe combined together with a colour Doppler.

The RRI is usually sampled from the interlobar and arcuate arteries near the medullary pyramids as the resistance gradually increases from the hilar branches to the peripheral branches.

Measurements should be repeated in various parts of both kidneys (superior, median, and lower). Minimum of three reproducible waveforms has to be determined.

FORMULA FOR RI CALCULATION

RI - (PSV– EDV/PSV)

The mean of three values in each kidney is preferentially taken in the end of the procedure.

CUT OFF VALUES[86]

- normal - 0.60 ± 0.01 (mean_SD)
- upper limit -0.7

EXCEPTION

- Children less than 1 year[87]
- Healthy elderly adults

PITFALLS IN RRI

Difficulty in obtaining the value in the presence of arrhythmic disorders like AF.

Affected by stiffening of vasculature and fibrosis of interstitium and other related pathological changes.

ADVANTAGES

RRI is useful in the evaluation of

- Renal artery stenosis [89,90]
- Chronic rejection of renal allograft [91]
- Progression in course of CKD
- Obstructive renal disease[92]

RRI also has an important role in predicting survival outcome in critically ill patient as it not only correlates with alteration in intrarenal perfusion but reflects the hemodynamics in systemic circulation thus leading to prognostic clues and treatment modalities.[93,94]

This application of RI is deployed in the determination of the degree of renal vasoconstriction in advanced cirrhosis patients and for its prognosis and treatment.

According to the study, increased RIs may even predict in earlier the progression of the liver disease before overt changes develops.

RRI AND CREATININE

Renal resistive index is better parameter than creatinine to predict the development of HRS because

- Decreased endogenous creatinine formation because of reduced synthesis by liver.
- Low muscle mass from malnutrition
- Drug related tubular secretion of creatinine
- Fluctuations in serum creatinine in cirrhotic patients because of diuretic therapy and large volume paracentesis with volume expansion.
- Underestimation of creatinine values due to its interactions with the bilirubin.[95,96]

Hence new renal biomarkers like cystatin and N GAL are advocated but they are very expensive and not available widely.

Materials & Methods

MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 diagnosed to have cirrhosis of liver, fulfilling the inclusion and exclusion criteria were included in the study group. 100 such patients were taken up for this study.

STUDY DESIGN:

A hospital based observational study

STUDY DURATION:

6 months: March 2015-August 2015

INCLUSION CRITERIA:

- Proven cases of cirrhosis liver by clinical, laboratory and sonographic evidence with normal renal functions

EXCLUSION CRITERIA:

- Diabetic kidney disease
- GI Bleeding
- Spontaneous bacterial peritonitis
- Overt hepatorenal syndrome

DATA COLLECTION AND METHODS:

Data was collected in a pretested proforma from eligible patients. 100 patients were selected on the basis of simple random sampling. They were subjected to detailed history taking and clinical examination. The following investigations were done.

- Complete blood count
- LFT
- RFT with electrolytes
- Coagulation profile
- Chest X-ray
- Electrocardiogram
- Viral markers
- USG of abdomen
- Portal Doppler
- Renal Doppler

RENAL DOPPLER

Patients who were enrolled in the study were subjected to sonographic evaluation of the liver and the kidneys and the Doppler ultrasound was done on each kidneys. All patients were made to fast for at least 6 hours prior to the examination. All examinations were done

using 5-12 MHz transducer. Patients were made to lie in supine position, right lateral and left lateral position.

Abdominal aorta was identified and the ostium of right and left main renal arteries were identified and the corresponding PSV and EDV were taken. Then the PSV and EDV were taken from the renal arteries at the hilum, lobar, lobular and arcuate arteries. Then mean RI was calculated for each right and left kidney and finally mean of the two values was calculated as the RI by the formula

RI - (PSV– EDV/PSV)

RRI value of more than 0.7 was taken as the cut off

STASTICAL METHODS APPLIED:

Data were analysed by SPSS software. Statistical significance was shown by the Chisquare test. Variables were considered to be significant if $p<0.05$.

Observation & Results

OBSERVATION AND RESULTS

Table 1: AGE DISTRIBUTION

Age Group (Years)	Frequency	Percentage
10-20	2	2.0
21-30	10	10.0
31-40	20	20.0
41-50	33	33.0
51-60	23	23.0
Above 60	12	12.0
Total	100	100.0

Among 100 patients included in our study, most cases of cirrhosis (33 patients) occur in the age group of 41-50 (33.0%) years.

Chart 1: AGE DISTRIBUTION

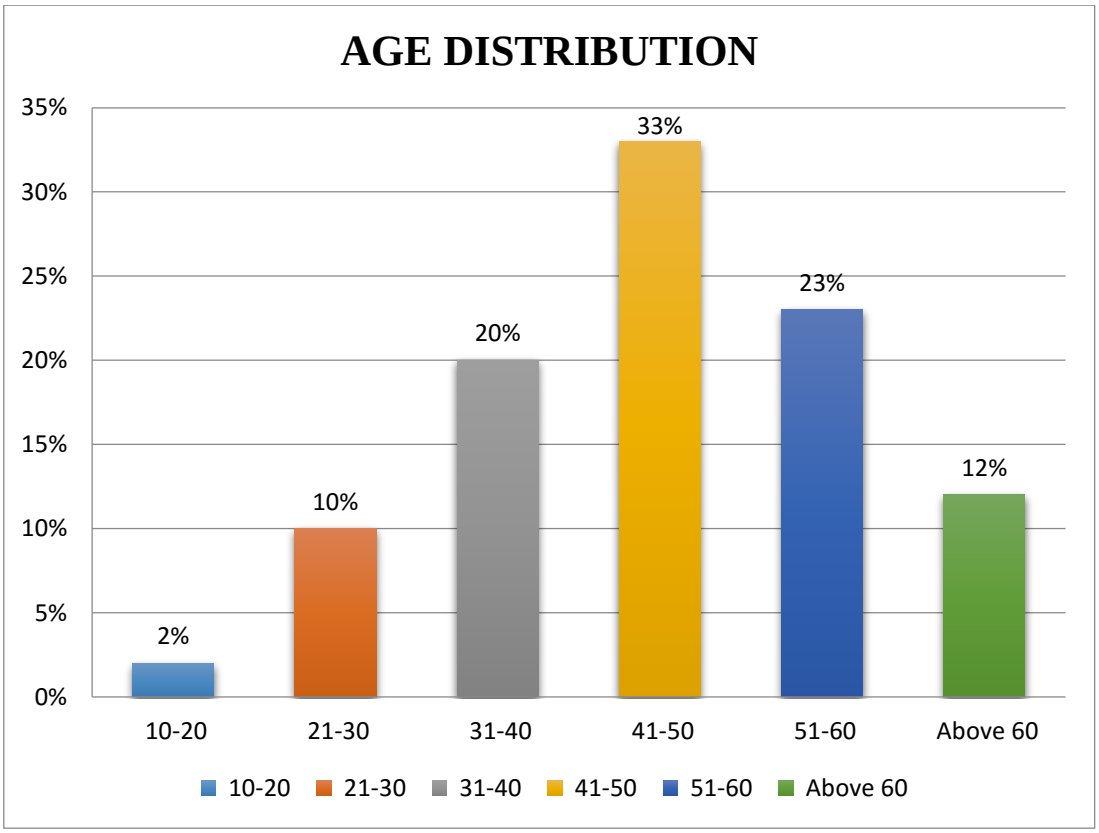


Table 2: SEX DISTRIBUTION

Sex	Frequency	Percentage
MALE	88	88.0
FEMALE	12	12.0
TOTAL	100	100.0

Among 100 patients included in our study, 88 patients (88.0%) were males and 12 patients (12.0%) were females.

Chart 2: SEX DISTRIBUTION

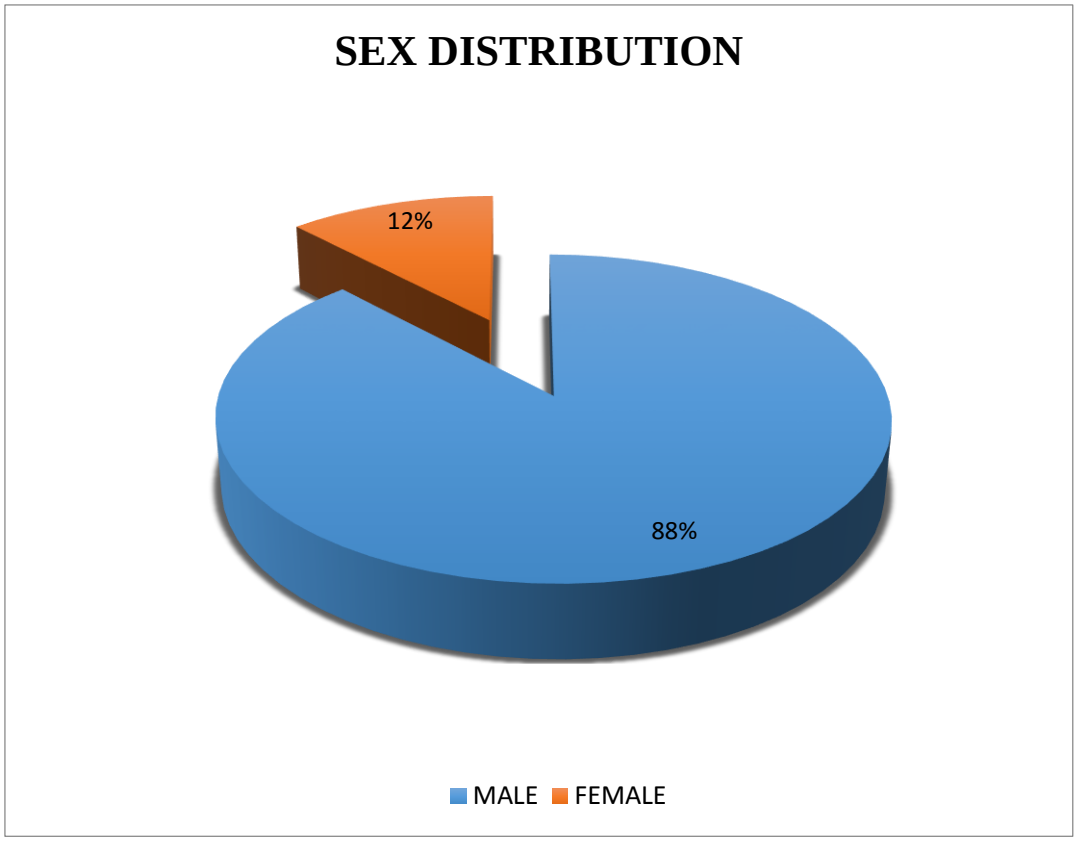


Table 3: ETIOLOGY

	Frequency	Percentage
ALCHOHOL	75	75
VIRAL	13	13
OTHERS	12	12
TOTAL	100	100

In our study, etiology of cirrhosis was alcohol related in 75 patients (75%), viral for 13 patients (13%), and other miscellaneous causes were present for 12 patients. (12%)

Chart 3: ETIOLOGY

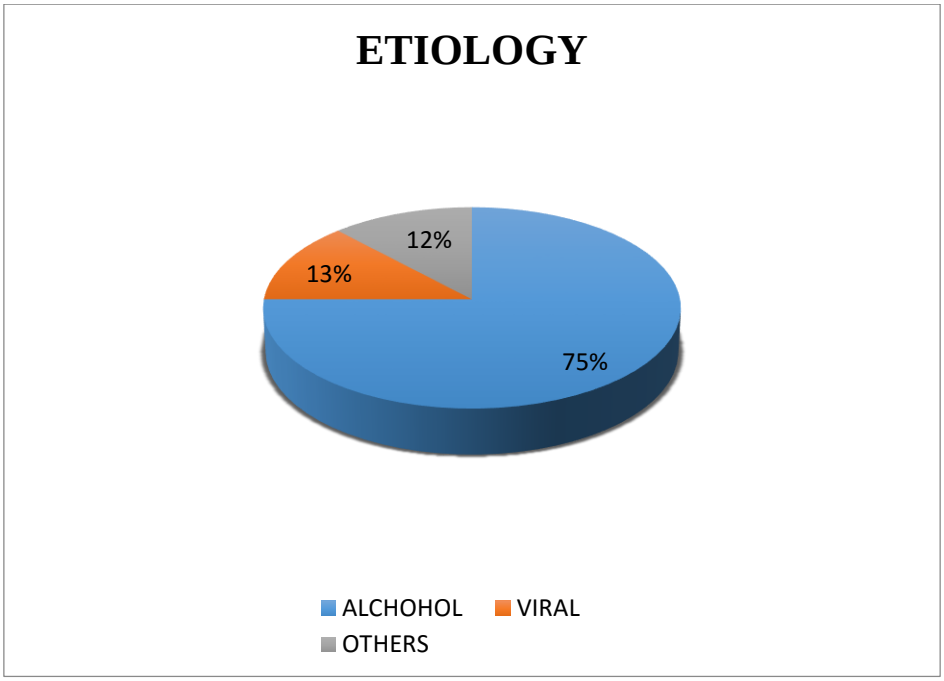


Table 4: DISTRIBUTION OF ICTERUS

	Frequency	Percentage
Yes	83	83.0
No	17	17.0
Total	100	100.0

Out of 100 patients studied, 83 patients (83%) had icterus and 17 patients (17%) were anicteric.

Chart 4: DISTRIBUTION OF ICTERUS

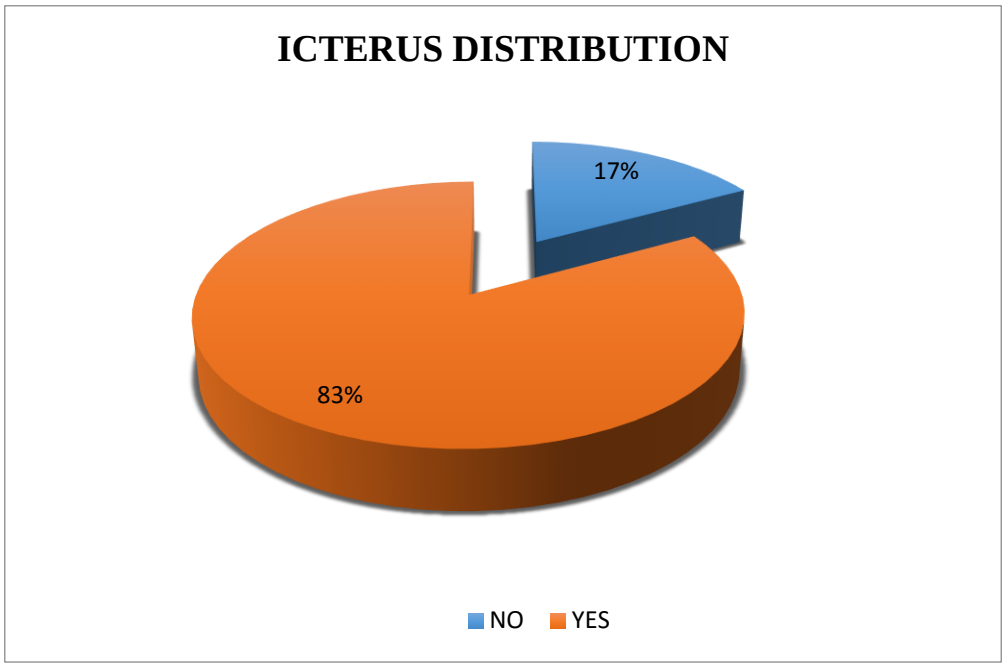


Table 5: DISTRIBUTION OF PEDAL EDEMA

	Frequency	Percentage
Yes	63	63.0
No	37	37.0
Total	100	100.0

Among 100 patients included in our study, 63 patients (63%) had pedal edema.

Chart 5: DISTRIBUTION OF PEDAL EDEMA

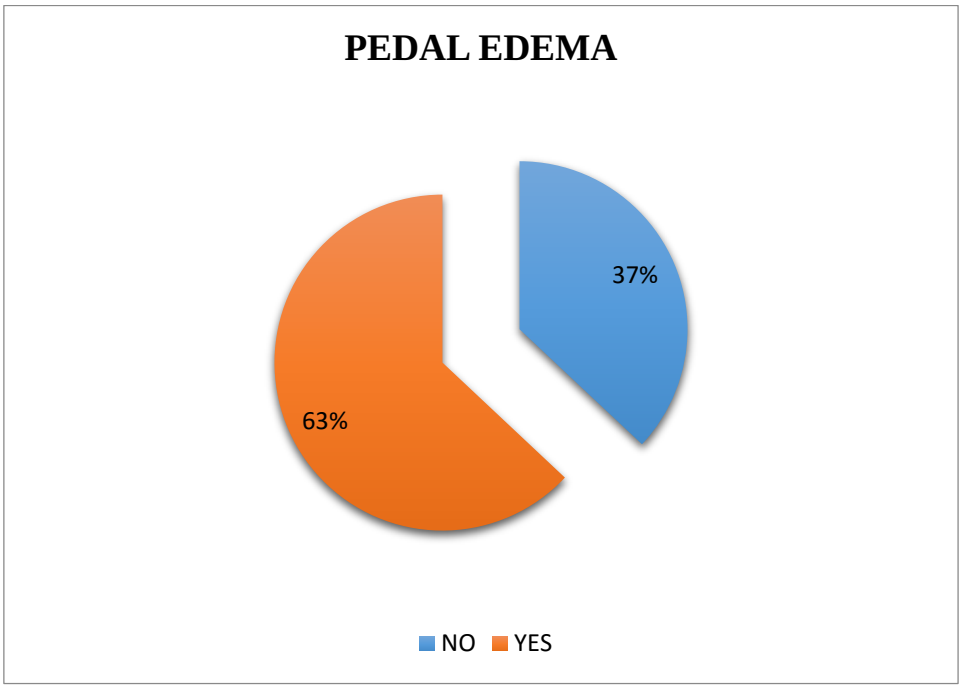


Table 6: DISTRIBUTION OF ASCITES

	Frequency	Percentage
Yes	80	80.0
No	20	20.0
Total	100	100.0

Among 100 patients included in our study, 80patients (80%) had ascites.

Chart 6: DISTRIBUTION OF ASCITES

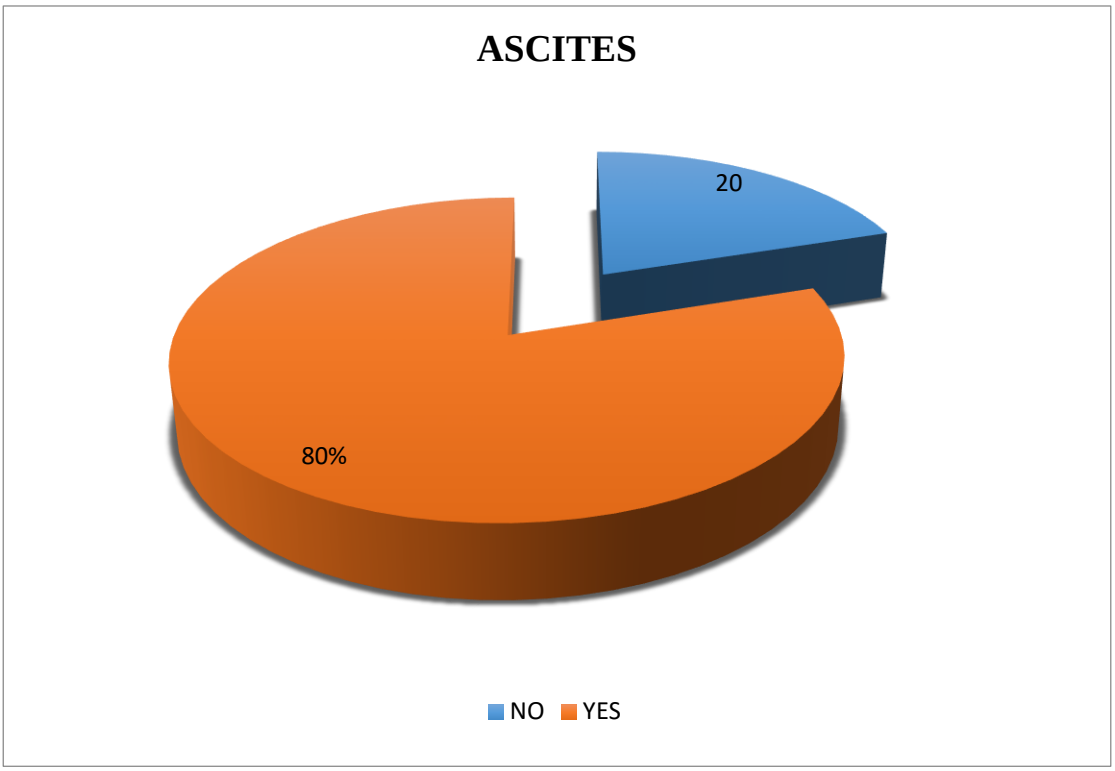


Table 7: DISTRIBUTION OF HEPATIC ENCEPHALOPATHY

Grades	Frequency	Percentage
Gr 1	21	21.0
Gr 2	3	3.0
None	76	76.0
Total	100	100.0

In our study 21 patients (21%) had grade 1 hepatic encephalopathy, 3 patients (3%) had grade 2 encephalopathy.

Chart 7: DISTRIBUTION OF HEPATIC ENCEPHALOPATHY

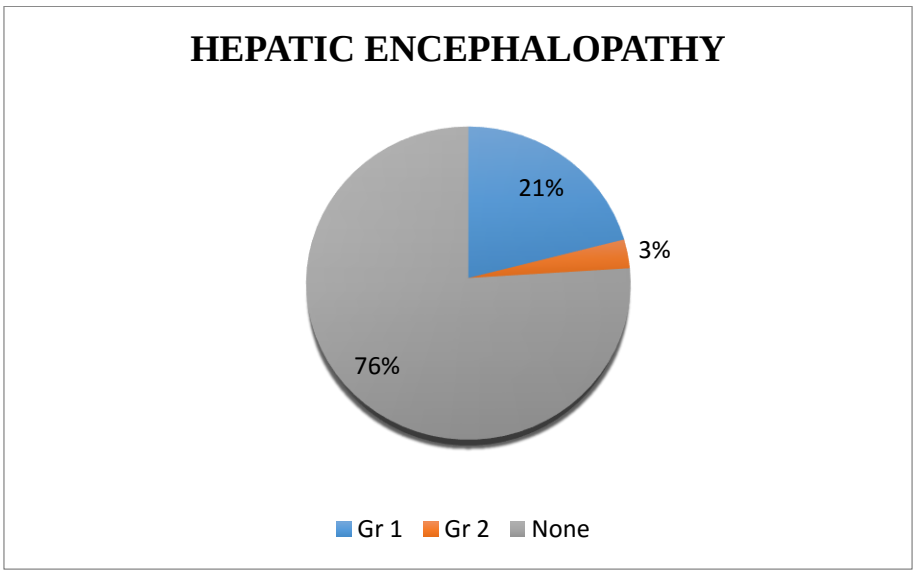


Table 8: GRADING OF ASCITES

	Frequency	Percentage
ABSENT	20	20.0
MILD-MODERATE	42	42.0
SEVERE	38	38.0
TOTAL	100	100.0

Out of 100 patients, ascites was absent in 20 patients (20%), mild to moderate ascites in 42 patients (42%), severe ascites in 38patients (38%).

Chart 8: GRADING OF ASCITES

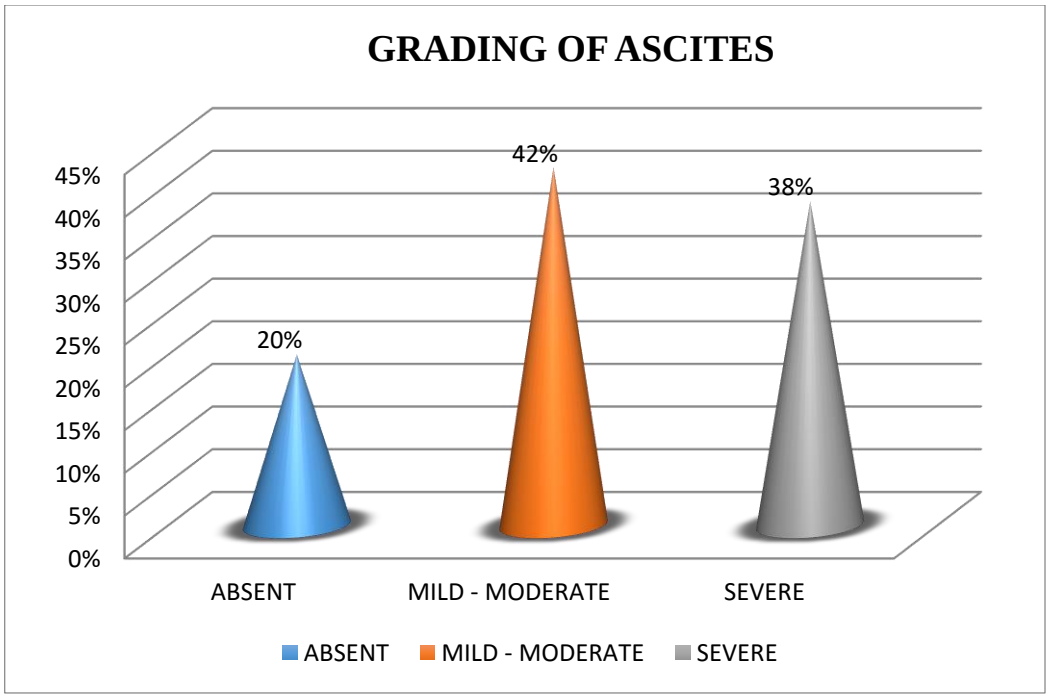


Table 9: PORTAL HYPERTENSION

	Frequency	Percentage
Yes	27	27.0
No	73	73.0
Total	100	100.0

In our study portal hypertension was seen in 73 patients (73%).

Chart 10: PORTAL HYPERTENSION

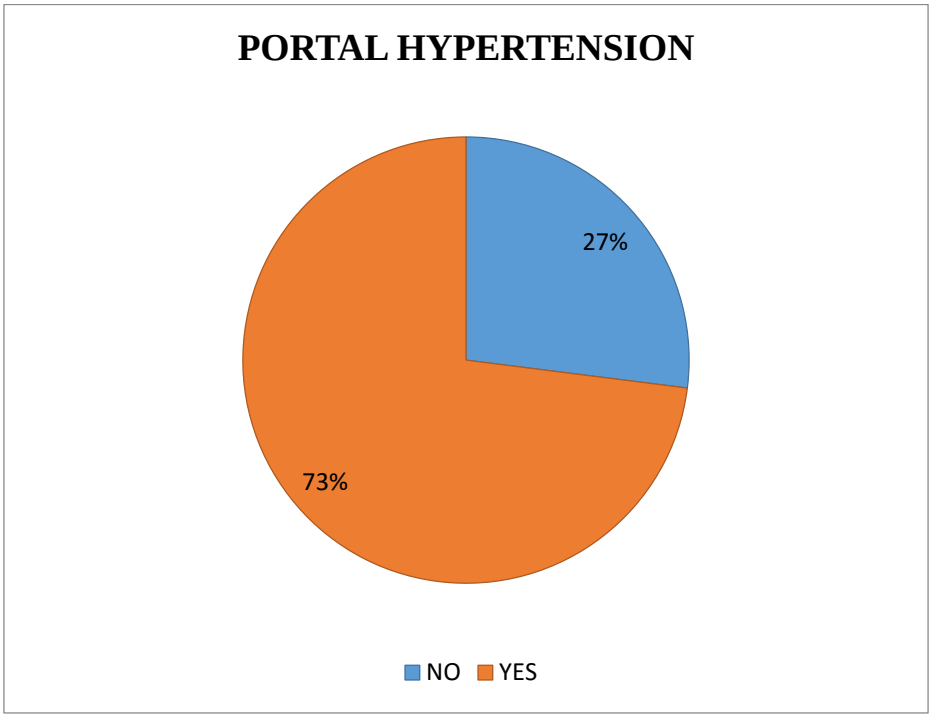


TABLE 10: CTP SCORE

	Frequency	Percentage
A	12	12.0
B	34	34.0
C	54	54.0
TOTAL	100	100.0

In our study, out of 100 patients, 12 patients (12%) were in class A, 34 patients (34%) were in class B and 54 patients (54%) were in class C.Majority of patients were in class C. Child-Pugh class is an indicator of severity of liver disease.

Chart 10: CTP SCORE

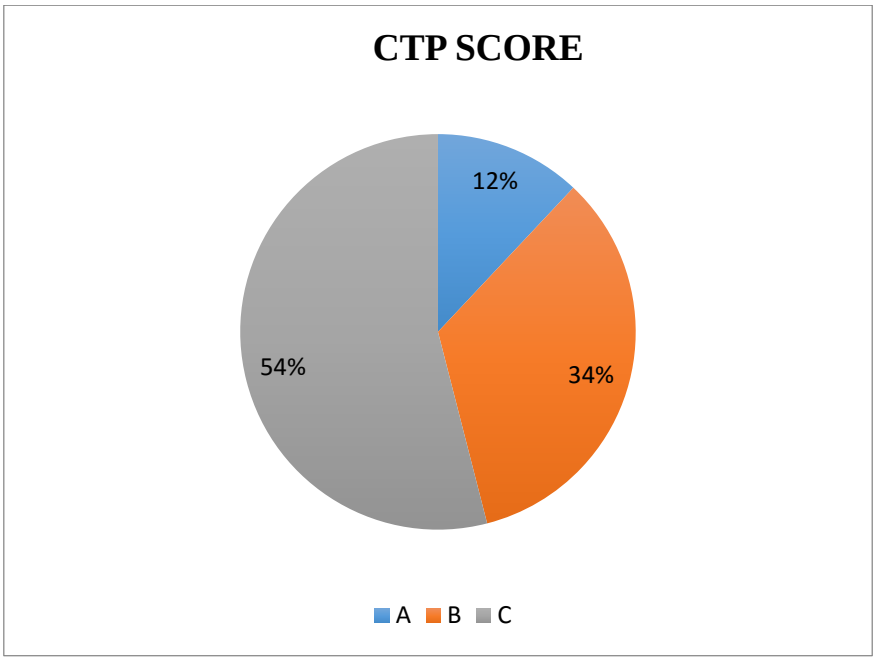


Table 11: MELD SCORE

Age Category	Frequency	Percentage
< 9	2	2.0
10 - 19	63	63.0
20 - 29	35	35.0
TOTAL	100	100.0

Among 100 patients included in our study, below are the findings:

- <9 - 2 patients (2%)
- 10 - 19 - 63 patients (63%)
- 20 - 29 - 35 patients (35%)

Chart 11: MELD SCORE

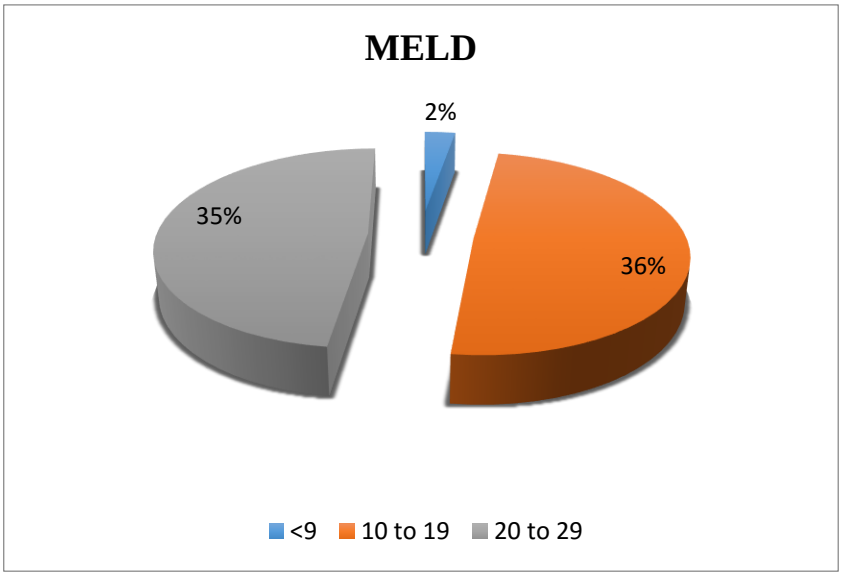


Table 12.RESISTIVE INDEX

	Frequency	Percentage
<=0.7	29	29.0
>0.7	71	71.0
TOTAL	100	100.0

In our study resistive index was more than 0.7 for 71 patients (71%) and less than 0.7 for 29 patients (29%).

Chart 12: RESISTIVE INDEX

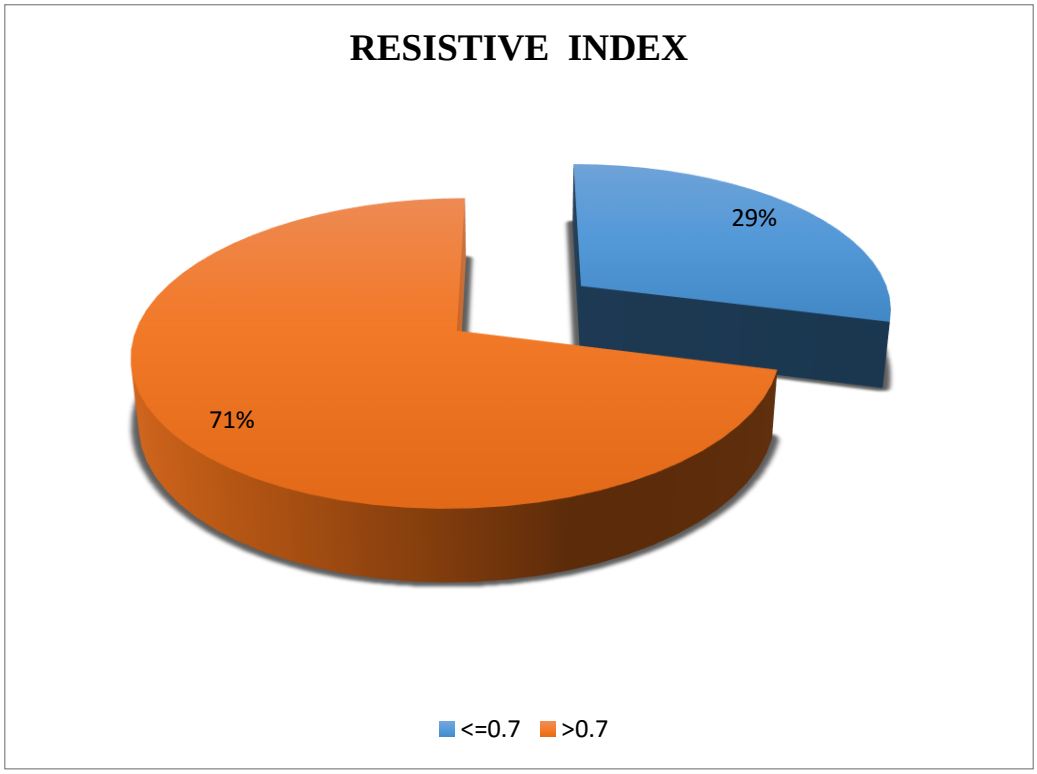
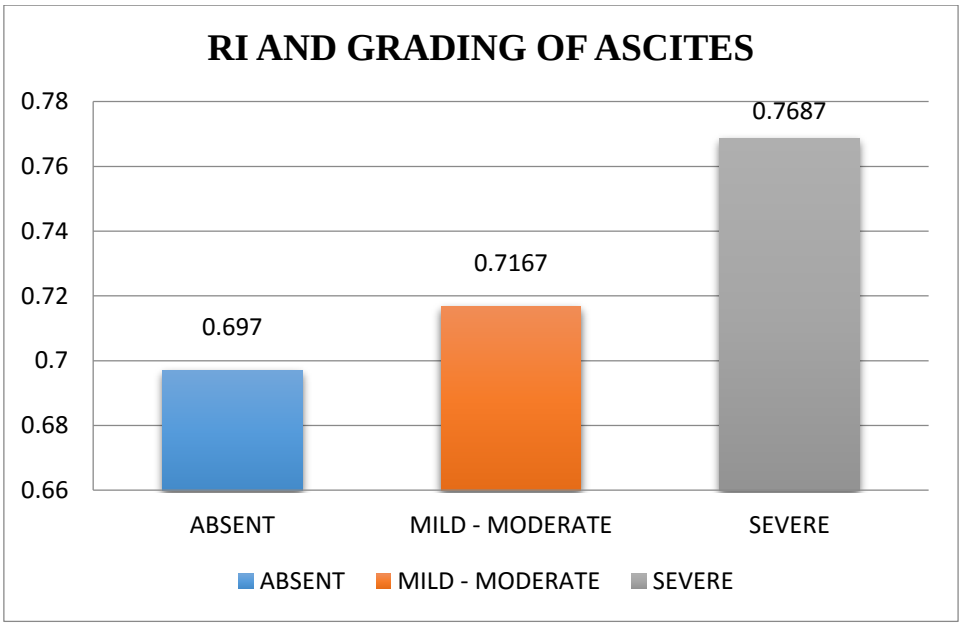


Table 13: RESISTIVE INDEX AND GRADING OF ASCITES

Category	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ABSENT	20	0.697	0.0213	0.00476	0.687	0.707	0.67	0.76
MILD - MODERATE	42	0.717	0.01762	0.00272	0.7112	0.7222	0.69	0.76
SEVERE	38	0.769	0.02133	0.00346	0.7617	0.7757	0.71	0.8
Total	100	0.733	0.03534	0.00353	0.7255	0.7395	0.67	0.8

When the grading of ascites was compared with the resistive index the resistive index was more with the patients having severe ascites and the p value (<0.0001) is significant.

Chart 13: RESISTIVE INDEX AND GRADING OF ASCITES



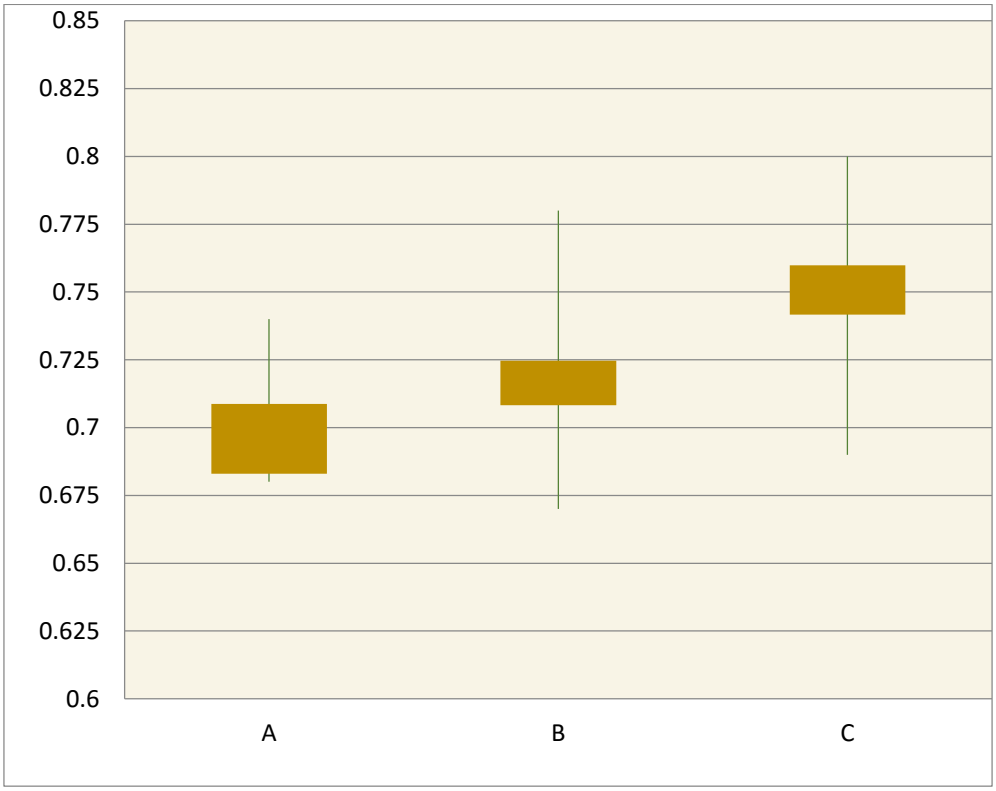
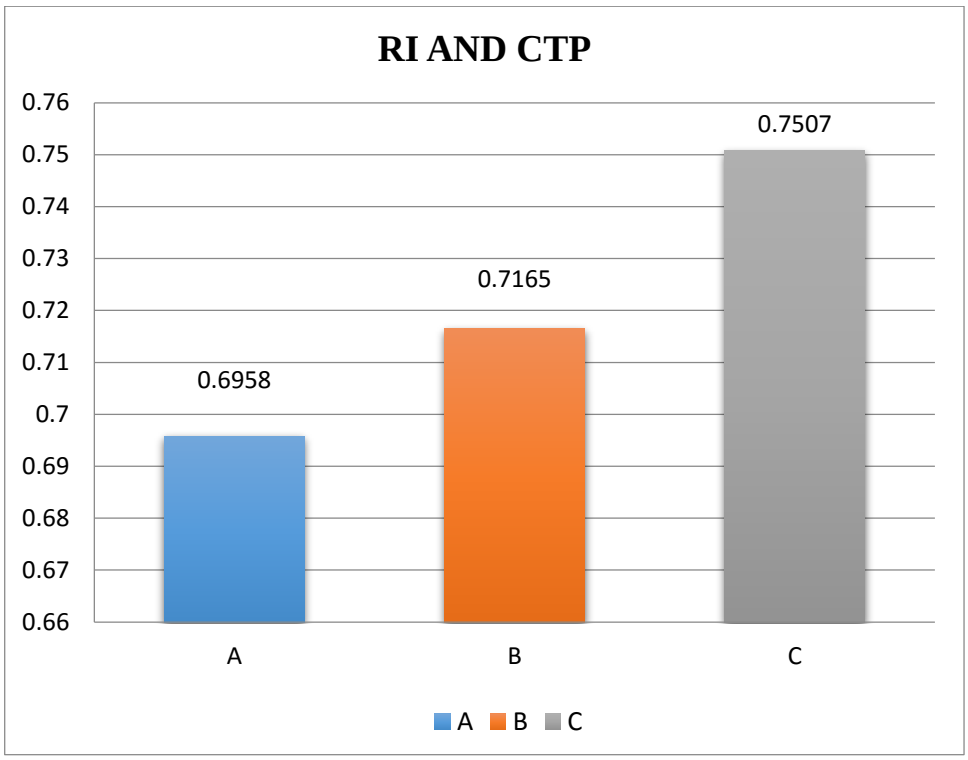


Table 14: RESISTIVE INDEX AND CTP SCORE

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
A	12	0.6958	0.02021	0.00583	0.683	0.7087	0.68	0.74
B	34	0.7165	0.02347	0.00402	0.7083	0.7247	0.67	0.78
C	54	0.7507	0.03313	0.00451	0.7417	0.7598	0.69	0.8
Total	100	0.7325	0.03534	0.00353	0.7255	0.7395	0.67	0.8

On comparing the three groups A, B, C resistive index is higher in C group ($p<0.001$) than the other signifying that severity of liver disease is related to increased RI values.

Chart 14: RESISTIVE INDEX AND CTP SCORE



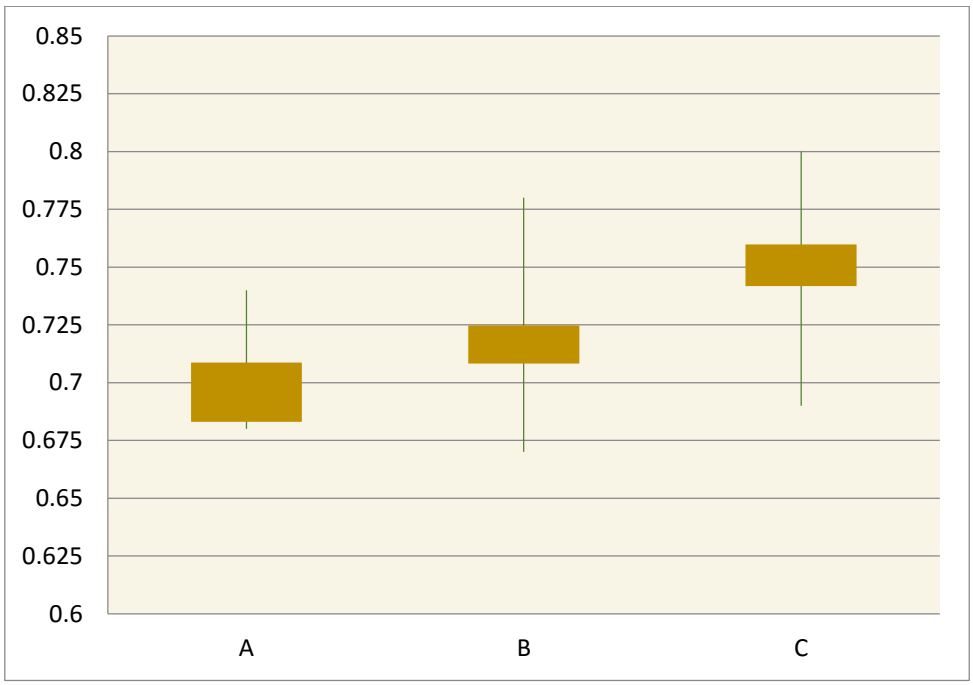


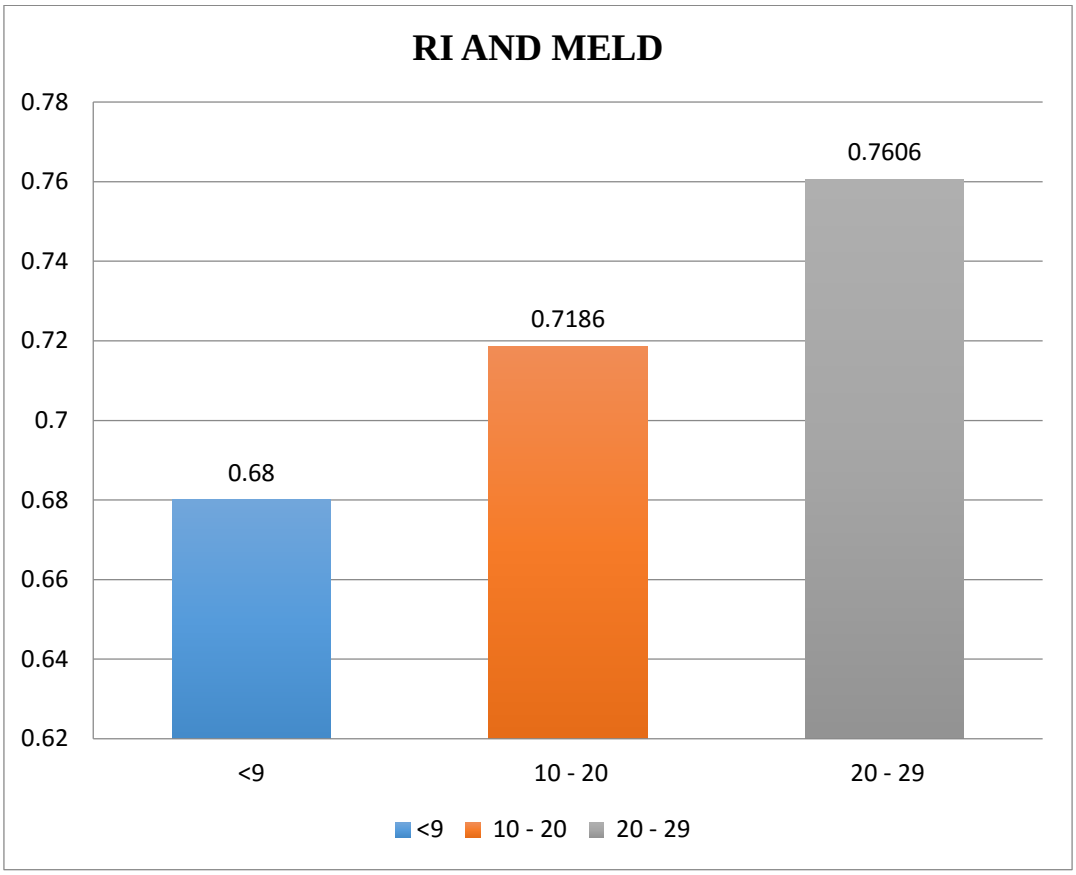
Table 15: RESISTIVE INDEX AND MELD SCORE

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
<9	2	0.68	0	0	0.68	0.68	0.68	0.68
10 - 20	63	0.7186	0.02873	0.00362	0.7113	0.7258	0.67	0.79
20 - 29	35	0.7606	0.02828	0.00478	0.7509	0.7703	0.7	0.8
Total	100	0.7325	0.03534	0.00353	0.7255	0.7395	0.67	0.8

Among 100 patients included in our study, below are the patients' findings about MELD:

- 0-9 have RI ranging from 0.68 to 0.68
- 10-29 have RI ranging from 0.67 to 0.79
- 20-29 have RI values from 0.70 to 0.80

Chart 15: RESISTIVE INDEX AND MELD SCORE



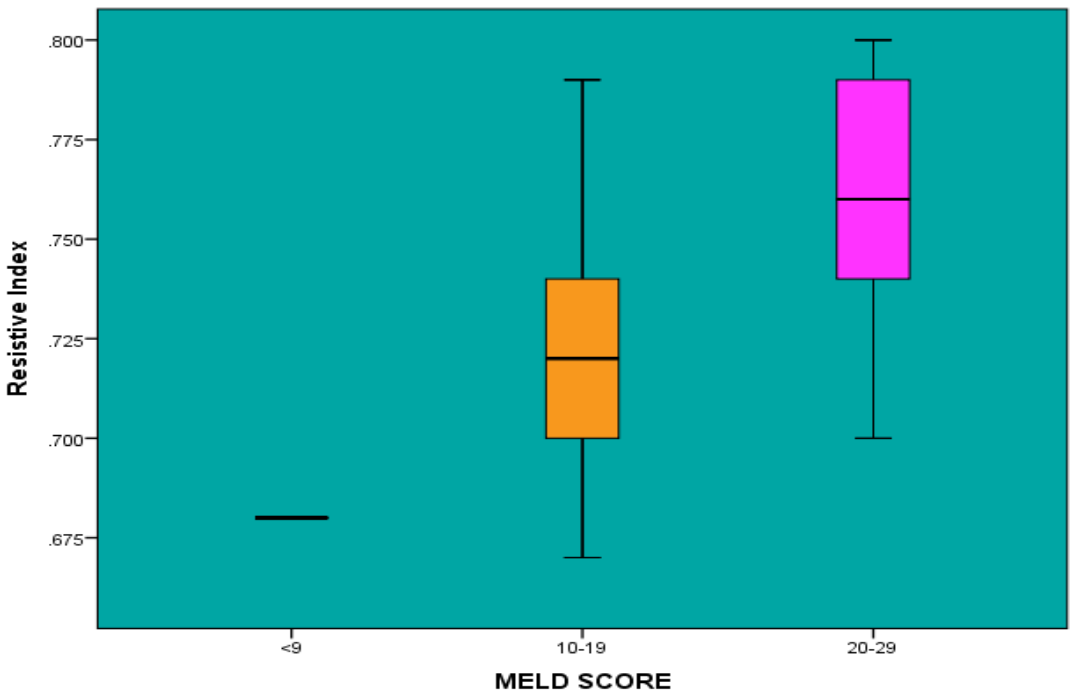


Table 16: CORRELATION BETWEEN PHT AND RI

			RELATIVE INDEX SCORE		Total	Chi square	P value
			<=0.7	**>0.7**			
Portal hypertension	No	Count	22	5	27	49.476	P<0.0001
		% within RELATIVE INDEX SCORE	75.90%	7.00%	27.00%		
	Yes	Count	7	66	73		
		% within RELATIVE INDEX SCORE	24.10%	93.00%	73.00%		
Total		Count	29	71	100		
		% within RELATIVE INDEX SCORE	100.00%	100.00%	100.00%		

In patients with PHT 93% had RI more than 0.7 and 24.1% had <0.7 .In patients without PHT 7 % had had RI more than 0.7 and 75.9 patients had more 0.7.This signifies that presence of portal hypertension increases the intrarenal resistance and hence leading to HRS.

Chart 16: CORRELATION BETWEEN PHT AND RI

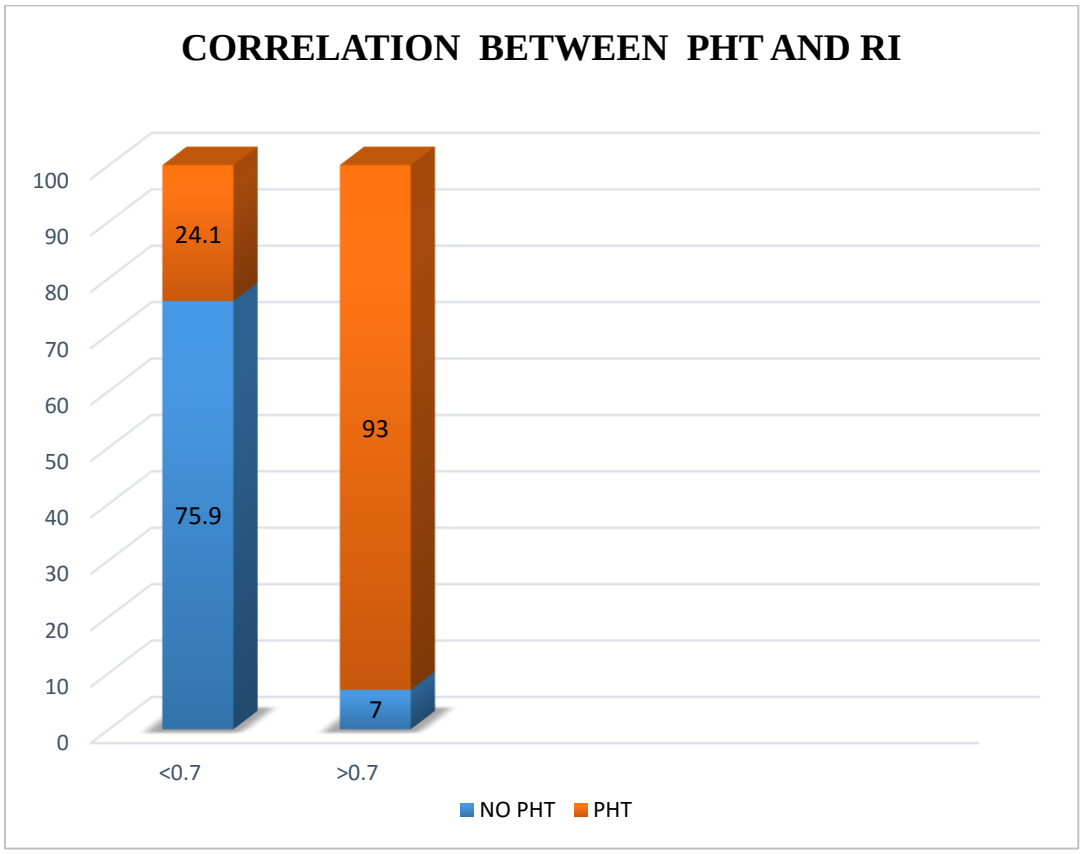


Table 17: CORRELATION BETWEEN CTP AND RI

			RELATIVE INDEX SCORE		Total	Chi square	P value
			<=0.7	>0.7			
CTP Score	A	Count	9	3	12	16.507	P<0.001
		% within RELATIVE INDEX SCORE	31.00%	4.20%	12.00%		
	B	Count	11	23	34		
		% within RELATIVE INDEX SCORE	37.90%	32.40%	34.00%		
	C	Count	9	45	54		
		% within RELATIVE INDEX SCORE	31.00%	63.40%	54.00%		
Total		Count	29	71	100		
		% within RELATIVE INDEX SCORE	100.00%	100.00%	100.00%		

Patients under CTP A class had RI ranging from o.68 to 0.74, CTP B class had the range from 0.67 to 0.78 and CTP C had RI from 0.69 to 0.80.So the value was higher among patients under group C indicating as the severity disease increases RI also increases. RI less than 0.7 was seen in 31% in CTP A , 37.9% CTP B, 31% CTP and more than 0.7 seen in 4.2 % in CTP A , 32.4% CTP B, 63.4% CTP C.

Chart 17: CORRELATION BETWEEN CTP AND RI

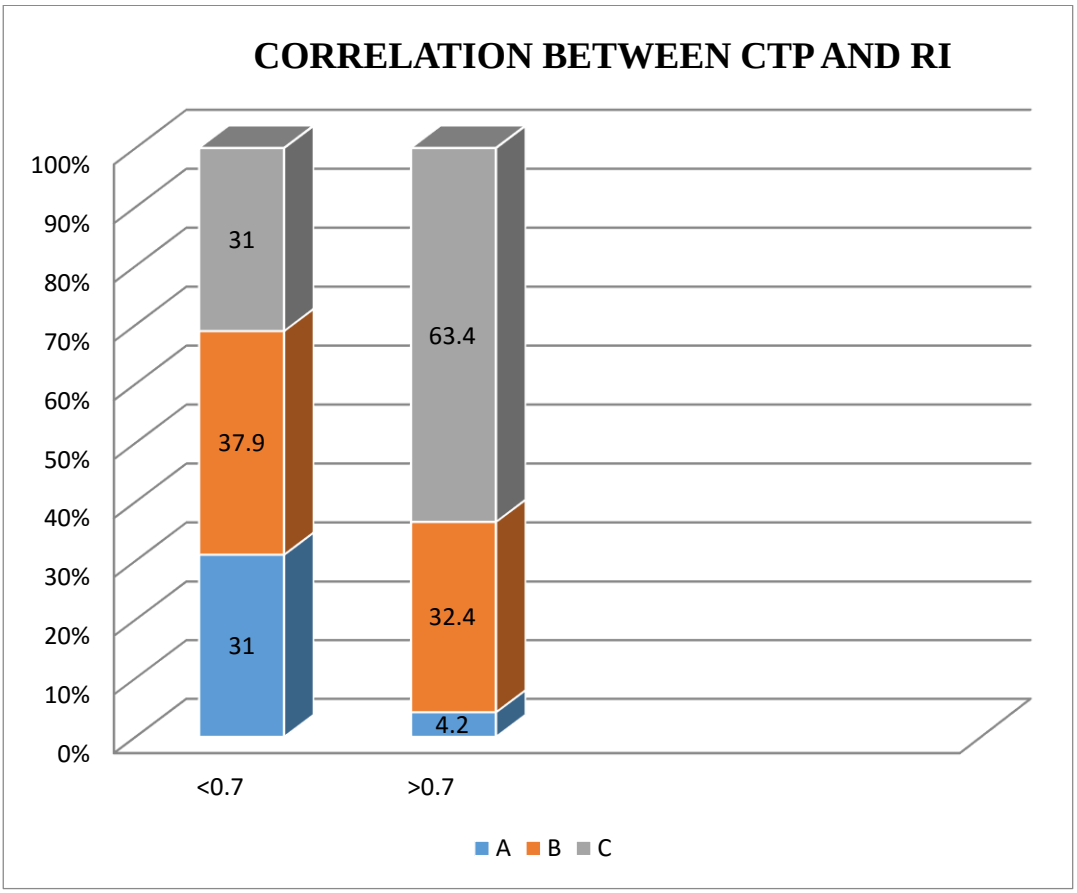


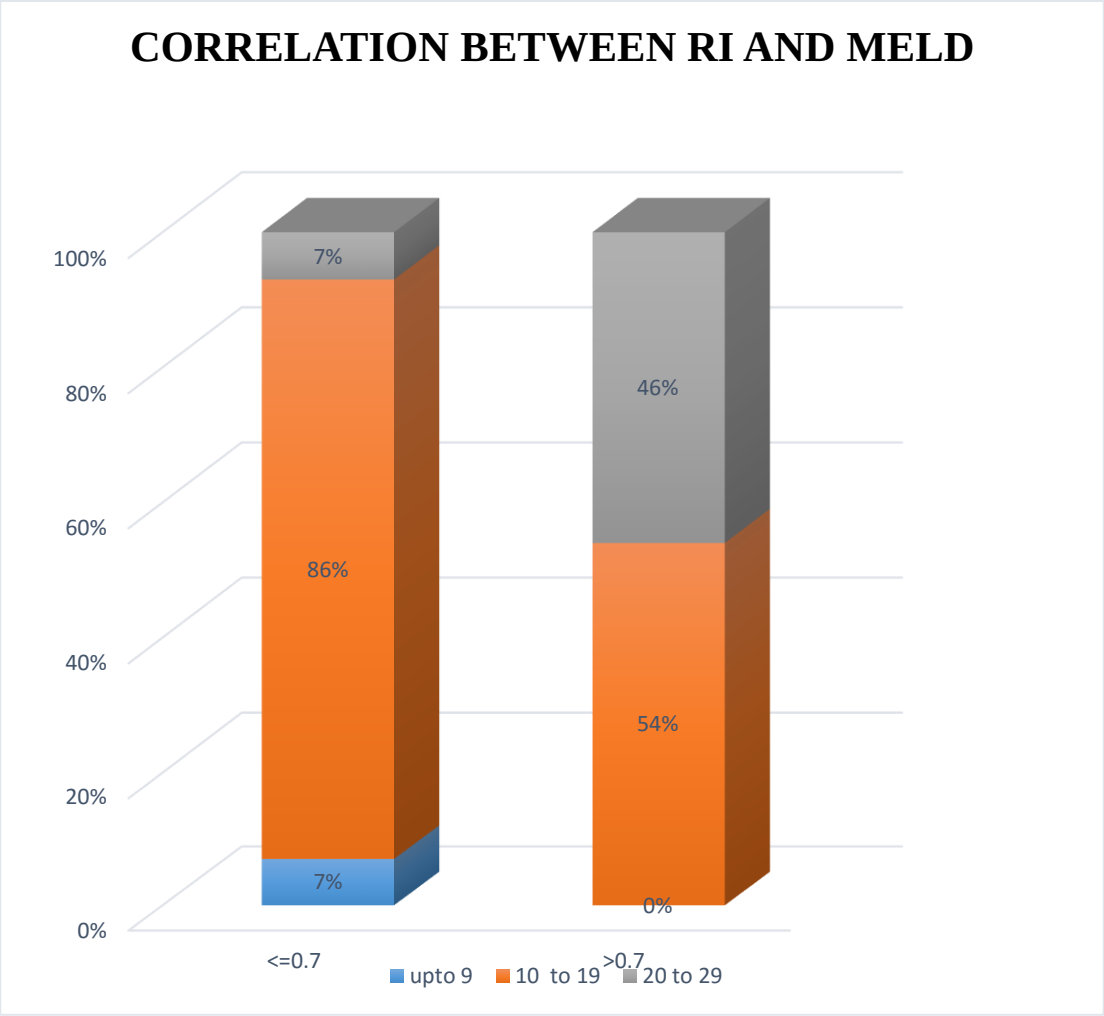
Table 18: CORRELATION BETWEEN RI AND MELD

MELD		RELATIVE INDEX SCORE		Total	CHI SQUARE	P VALUE
		<=0.7	>0.7			
<9	Count	2	0	2	17.605	P<0.001
	% within RELATIVE INDEX SCORE	6.90%	0.00%	2.00%		
10 - 19	Count	25	38	63		
	% within RELATIVE INDEX SCORE	86.20%	53.50%	63.00%		
20 - 29	Count	2	33	35		
	% within RELATIVE INDEX SCORE	6.90%	46.50%	35.00%		
Total	Count	29	71	100		
	% within RELATIVE INDEX SCORE	100.00%	100.00%	100.00%		

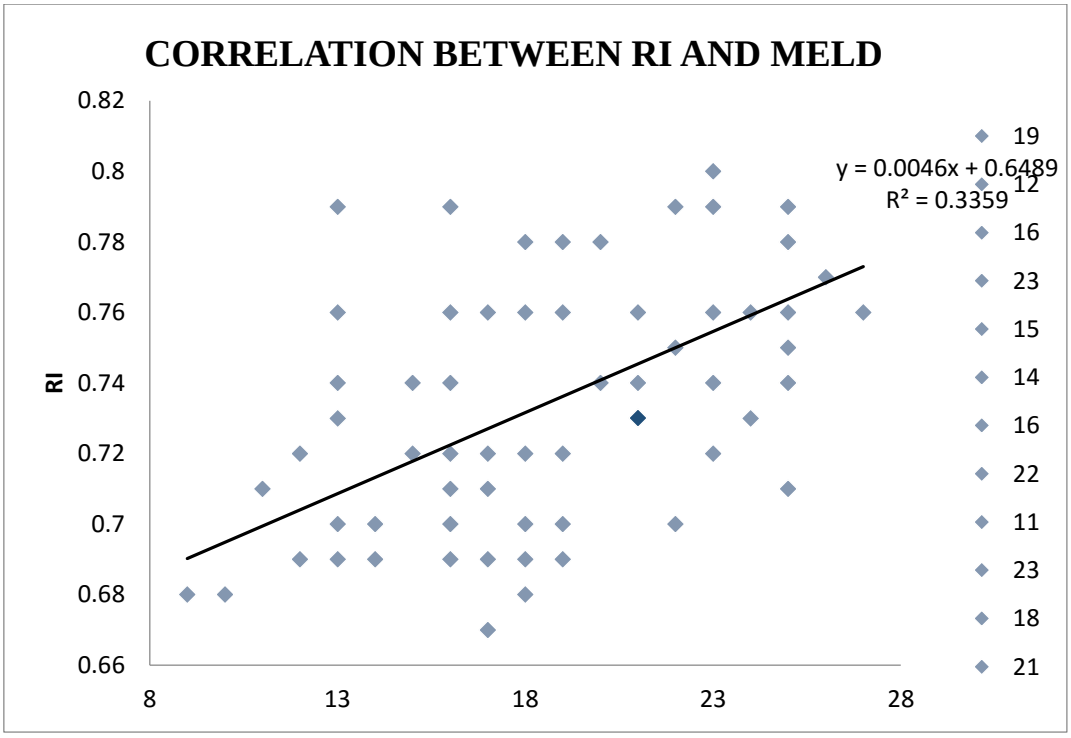
In our study RI values less than 0.7 was seen in 6.9%having score of 0-9, 86.2% having score of 10-19, 6.9% having 20-29.

RI values more than 0.7 was seen in 0%having score of 0-9, 53.5% having score of 10-19, 46.5% having 20-29.

Chart 18: CORRELATION BETWEEN RI AND MELD

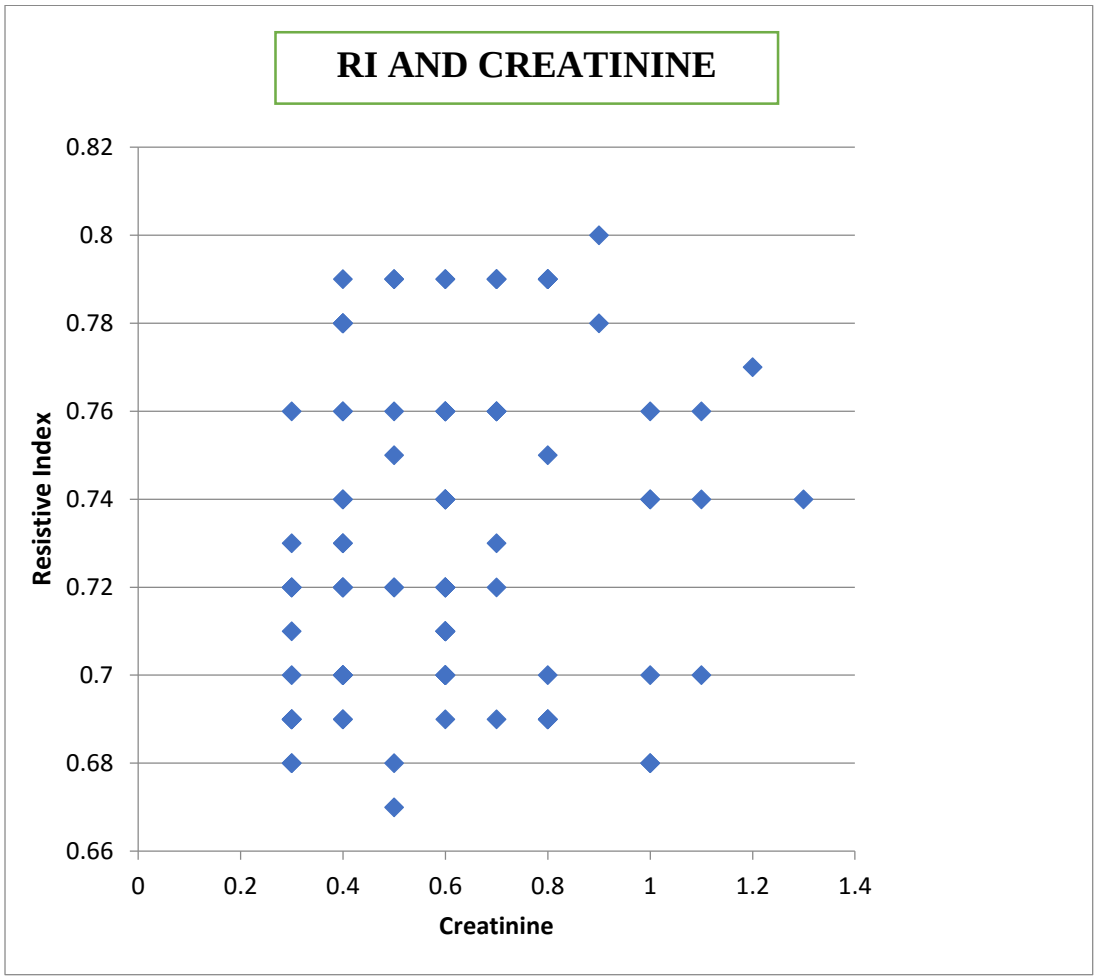


There was a significant linear correlation between renal resistive index and MELD scoring as shown by the plot



Pearson Correlation	0.578
P value	<0.001
N	100

There was no significant correlation between the RRI and serum creatinine values



Discussion

DISCUSSION

Our study was conducted in patients with cirrhosis liver to estimate the value of renal resistive index by Doppler ultrasound Our study population included 100 patients who were diagnosed to have cirrhosis of liver either by clinical examinations and investigations, or sonographic evidence.

Portal Doppler was done to assess portal hypertension. All 100 patients were subjected to Doppler ultrasound and the value of renal resistive index was calculated. Analysis was made to correlate the value of RI in patients with absent, mild- moderate and severe ascites. Comparison with CTP scores and MELD scores were also done.

Following were the observations made from our study in cirrhotic patients

AGE DISTRIBUTION:

Out of 100 patients, majority of cases were in the age group of 41 – 50 years (33%)). This showed that cirrhosis is most commonly seen in middle age adults.

SEX DISTRIBUTION

Out of 100 patients in this study, 88 patients (88%) were males and 12 patients (12%) were females. Male to female ratio is 7:1.

ETIOLOGY

Among 100 patients, Alcohol was the most common etiology in 75 patients (75%), viral etiology in14 patients (14%) followed by other causes of cirrhosis in 11 patients (11%).

CLINICAL SIGNS:

Out of 100 patients studied, 83 patients (83%) had icterus, 62 patients (62%) had pedal edema,80 patients (80%) had ascites, grade I hepatic encephalopathy in 21 patients(21%), and grade 2 encephalopathy in 3(3%) patients

GRADING OF ASCITES

Out of 100 patients, ascites was absent in 20 patients (20%), mild to moderate ascites seen in 42(42%) patients, severe ascites seen in 38(38%) patients.

PORTAL HYPERTENSION

Out of 100 patients PHT was there in patients in 73(73%) patients and absent in 27(27%) patients.

CHILD-PUGH CLASS:

In our study, out of 100 patients, 12 patients (12%) were in class A, 34 patients (34%) were in class B and 54 patients (54%) were in class C. Majority of patients were in class C. Child-Pugh class is an indicator of the severity of liver disease.

MELD

In our study according to MELD score<9 - 2 patients (2%) 10-19 - 63 patients(63%) 20-29 - 35 patients(35%).

RESISTIVE INDEX

In our study the resistive index was more than 0.7 for 71 patients (71%) and less than 0.7 for 29 patients (29%)

ASCITES AND RI

The value of RI in patients for whom there was no ascites was ranging from 0.67 to 0.76, mild to moderate ascites was 0.69 to 0.76 and for severe ascites was from 0.71 to 0.80. so the RI was significantly

higher in patients with severe ascites. This was comparable to the study done by M.Gotzberger et al.

PHT AND RI:

In patients with PHT 93% had RI more than 0.7 and 24.1% had < 0.7. In patients without PHT 7 % had had RI more than 0.7 and 75.9% patients had more 0.7.This Signifies that presence of portal hypertension increases the intrarenal resistance and hence leading to HRS.

CPC AND RI

Patients under CPC A class had RI ranging from o.68 to 0.74, CPC B class had the range from 0.67 to 0.78 and CPC C had RI from 0.69 to 0.80.so the value was higher among patients under group C indicating as the severity disease increases RI also increases.

RI less than 0.7 was seen in 31% in CPC A , 37.9% in CPC B, 31% in CPC C and more than 0.7 seen in 4.2% in CPC A , 32.4% CPC B, 63.4% in CP C C.

MELD AND RI

Patients having a MELD scoring of 0-9 have RI ranging from 0.68 to 0.68,10-29 have RI ranging from 0.67 to 0.79 and 20-29 have RI values from 0.70 to 0.80

In our study RI values less than 0.7 was seen in 6.9%having score of 0-9 86.2% having score of 10-19, 6.9% having 20-29 and RI values more than 0.7 was seen in 0% having score of 0-9, 53.5% having score of 10-19, 46.5% having 20-29.

There is a significant direct linear relationship between RI and MELD scores.

RRI AND SERUM CREATININE

Patients having higher resitive index had normal creatinine suggesting that normal value of creatinine underestimates the actual scenario in cirrhotic patients.

RENAL RESISTIVE INDEX AND CIRRHOSIS

Renal resistive index is higher in cirrhotic patients and among them it is significantly higher in patients with severe ascites.

1.This is similar to the study conducted by M.Gotzberger et al, Kaiser et al, N.Landeur et al.

"INTRARENAL RESISTANCE INDEX FOR ASSESSMENT OF EARLY RENAL DYSFUNCTION IN PATIENTS WITH CIRRHOSIS" which concluded that significant higher RI found in patients with cirrhosis with ascites

2. There is a correlation between MELD and RI as similar to the study conducted by Sameh Ahmed Abdel-bary et al

"VALUE OF RENAL RESISTIVE INDEX IN HEPATITIS C VIRUS RELATED LIVER CIRRHOSIS." which concluded that RI is strongly associated with liver cirrhosis severity as showed by Child Pugh, MELD scores. RI also had a prognostic value correlating with MELD score.

Conclusion

CONCLUSION

- Cirrhosis liver is commonly seen patients in their 4th decade (41-50) and more common in males than in females.
- Alcohol consumption is the major risk factor in the development of disease with viral hepatitis as the second risk factor.
- Icterus, pedal edema ascites were the predominant findings in the patients
- Mild to moderate ascites was seen more commonly among the patients with ascites
- PHT was seen in most of the patients
- Majority of the patients were in CPC class C and having MELD score between 10-19
- Intra renal resistive index more than 0.7 in was seen in majority of patients with cirrhosis
- The RI values were more higher in patients with severe ascites than patients with mild to moderate ascites and still lower inpatients with no ascites
- There was no significant correlation between serum creatinine and the value of RI
- Patients with PHT had increased RI than without PHT
- The RI values were significantly higher in CPC class C

- Patients with MELD score between 20-29 had higher RI compared to patient with score of less than 9 and between 10-19.
- Significant correlation was seen between the severity of liver disease and the renal resistive index as compared with CPC and MELD scoring system.
- Serum creatinine was normal in patients having significant high RRI thus indicating that serum creatinine is a poor predictor of development of HRS and underestimates the renal dysfunction.

Summary

SUMMARY

Development of hepatorenal syndrome in cirrhosis has so many clinical implications in the course of their disease as they carry a poor prognosis. Diagnosis of HRS needs a very high index of suspicion in cirrhotic patients.

As the prognosis of HRS is so devastating after the disease manifests with rise in serum creatinine and BUN all patients with cirrhosis liver should be screened for the presence of elevated renal resistive index by Doppler ultrasound of kidneys so that the onset of HRS can be prevented.

RI values are higher in cirrhotic patients and among them it was more in patients with ascites than patients without ascites. There is a significant correlation between the RI values and the severity of liver disease as compared with MELD and CPC scoring.

Screening of all cirrhotic patients especially with ascites and PHT to estimate the value of RRI by Doppler ultrasound is essentially important as the degree of intrarenal vasoconstriction can be predicted early before overt HRS develops and so preventive measures should be undertaken.

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Annexures

PROFORMA

PATIENT DETAILS:

Name: Age: Sex:

IP No. :

ON ADMISSION:

Main Complaints :

- Jaundice
- Abdominal Distension
- Pedal Oedema
- Reduced Urine Output
- Breathlessness
- Orthopnoea/Pnd
- Haemetemesis
- Melena
- Seizures
- Altered Sensorium
- Altered Sleep Pattern
- Chest Pain
- Abdominal Pain
- Fever
- Constipation
- Intake Of Any Drugs

SIGNIFICANT PAST HISTORY:

- Ischemic heart disease
- Hypertension
- Diabetes
- Pulmonary TB
- Bronchial asthma
- Blood transfusion
- Jaundice

PERSONAL HISTORY:

- Smoking
- Alcohol

GENERAL EXAMINATION:

- Built
- Nourishment
- Height
- Weight
- Pallor
- Icterus
- Clubbing
- Cyanosis
- Pedal edema
- Lymphadenopathy
- Jugular venous pulse
- Signs of Liver cell failure

VITAL SIGNS:

- PR-
- BP-
- RR

SYSTEMIC EXAMINATION:

- PER ABDOMEN:
- CARDIOVASCULAR SYSTEM:
- RESPIRATORY SYSTEM:
- CENTRAL NERVOUS SYSTEM

INVESTIGATIONS :

- Hemogram
- Renal Function Test
- Liver Function Test
- BT/CT/PT/INR
- Blood Grouping
- ECG
- CXR
- USG Abdomen and pelvis
- Portal Doppler
- Renal Doppler

INFORMATION SHEET

We are conducting a study on **"THE ROLE OF RENAL RESISTIVE INDEX IN ASSESSING THE EARLY RENAL DYSFUNCTION OF CIRRHOSIS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your cooperation may be valuable to us.

The purpose of this study is to measure the intrarenal resistive index in patients with liver cirrhosis, to estimate the renal vasoconstriction before overt hepatorenal syndrome develops in cirrhotic patients with and without ascites .and to compare the resistive index with MELD and Child Pugh scoring system with the following factors Age, Sex, Presenting Complaints, Etiology of cirrhosis, Clinical findings, USG abdomen, Portal Doppler and Renal Doppler. We are selecting certain cases and if you are found eligible, we may be doing Renal Doppler Ultrasound your blood samples to do certain 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 Investigator Signature of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail : **"THE ROLE OF RENAL RESISTIVE INDEX IN ASSESSING THE EARLY RENAL DYSFUNCTION OF CIRRHOSIS"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

Patient may check (☑) these boxes

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. ☐

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. ☐

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. ☐

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. ☐

I hereby consent to participate in this study ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression

Patient’s Name and Address:

Signature of Investigator

Study Investigator’s Name:

Dr. NIVETHITHA KARTHIKA

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின்தலைப்பு கல்லீரல் இழைநார் வளர்ச்சியில் ஏற்படும் சிறுநீரக பாதிப்பினை ஆரம்ப நிலையில்க ண்டறிய சிறுநீரகத்தில் உள்ள சிறுதமணிகளின் குருதி பாய்வு எதிர்ப்பின் மூலம் கண்டறிதல்.

ஆராய்ச்சிசெய்பவரின்பெயர் : நிவேதிதா கார்த்திகா ல.

ஆராய்ச்சிமையம்: ராஜீவ்காந்தி அரசுபொது மருத்துவமனை
சென்னை – 600003

_____எனும் நான் எனக்கு கொடுத்துள்ள தகவல் தாளை படித்து புரிந்து கொண்டேன். நான் பதினெட்டு வயதை கடந்துள்ளதால் என்னுடைய சுயநினைவுடனும் முழ சுகந்திரதுடனும் இந்த ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

1. நான் எனக்கு அளிக்கப்பட்ட ஒப்புதல் படிவத்தையும் தகவல்களையும் படித்து புரிந்து கொண்டேன்.
2. ஒப்புதல் படிவத்தில் உள்ள தகவல்கள் எனக்கு விளக்கிக் கூறப்பட்டன
3. ஆய்வின் தன்மை பற்றி எனக்கு விளக்கப்பட்டது
4. என்னுடைய உரிமைகளையும் பொறுப்புகளையும் ஆராய்ச்சியாளர் விளக்கிக்கூறினார்.
5. நான் இதுவரை எடுத்துள்ள / எடுத்து கொண்டிருக்கும் அணைத்து விதமான சிகிச்சை முறைகளையும் ஆராய்ச்சியாளரிடம் கூறியுள்ளேன்.
6. இந்த ஆராய்ச்சியினால் ஏற்படும் தீமைகள் பற்றிவிளக்கப்பட்டன.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளரின் கையொப்பம்

தேதி
இடம்

ஆராய்ச்சியில் பங்கேற்பவர்கான தகவல்அறிக்கை

ஆராய்ச்சியின் தலைப்பு கல்லீரல் இழை நார் வளர்ச்சியில் ஏற்படும் சிறுநீரக பாதிப்பினை ஆரம்பநிலையில் கண்டறிய சிறுநீரகத்தில் உள்ள சிறுதமணிகளின் குருதி பாய்வு எதிர்ப்பின் மூலம்கண்டறிதல்.

பங்கு கொள்வரின் பெயர் :

ஆராய்ச்சி செய்பவரின் பெயர் : நிவேதிதா கார்த்திகா ல.

இடம் : ராஜீவ்காந்தி அரசு பொதுமருத்துவமனை, சென்னை – 600003

இந்த ஆராய்ச்சி / ஆய்வு / செய்முறை / சோதனையில் தாங்கள் பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கேலமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

இந்த ஆய்வின் நோக்கம்என்ன?

கல்லீரல் இழைநார் வளர்ச்சியில் ஏற்படும் சிறுநீரக பாதிப்பினை ஆரம்பநிலையில் கண்டறிய சிறுநீரகத்தில் உள்ள சிறுதமணிகளின் குருதிபாய்வு எதிர்ப்பின் மூலம் கண்டறிதல்..

ஆய்வுமுறைகள் :

விரிவான நோய்க்குறிப்புகளும் மருத்துவ பரிசோதனைகளும் செய்யப்படும்.நோயாளிகள், அவர்கள் சம்மதத்திற்கு பின் குருதிச் சீரத்தில் கோலினெஸ்டெரேஸ் எனும் என்சைம்மின் அளவு கணக்கிடப்படும்.

ஆய்வினால் மக்களுக்கு ஏற்படும் நன்மைகள் :

இந்த ஆய்வின் முடிவில் கிடைக்கும் தகவல்கள் சமுதாயதிற்கு பயனுள்ளதாகவும், எதிர்காலத்தில் நோயாளிகளுக்கு மருத்துவ தீர்வாகவும் அமையும்.

தங்களிடமிருந்து பெறப்படும் தகவல்களின் நம்பிகத்தன்மை :

தங்களிடமிருந்து பெறப்படும் தகவல்கள் பாதுகாக்கப்படுவதற்கான முழு உரிமையும் தங்களுக்கு உண்டு.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளரின் கையொப்பம்

தேதி

இடம்

THE ROLE OF RENAL RESISTIVE INDEX IN ASSESSING THE EARLY RENAL DYSFUNCTION OF CIRRHOSIS

MASTER CHART

S.no	Age	Sex	IP no	Alchohol intake	Icterus	Pedal edema	Ascites	Hepatic encephalopathy	Blood urea	creatinine	Serum bilurubin	PT/ INR	Serum albumin	Viral markers	Free fluid in USG	Portal hypertension	CTP score	MELD	Resistive Index
1	45	M	83609	+	+	+	+	none	32	0.6	6.5	1.6	2.4	Neg	Severe	+	C	19	0.76
2	56	M	88766	+	-	+	+	none	21	0.3	2.3	1.2	3.1	Neg	Absent	_	B	12	0.69
3	34	M	72600	+	+	-	-	none	17	1.1	4.6	1.3	3.5	Neg	Absent	-	A	16	0.7
4	54	M	67869	+	+	+	+	Gr 1	37	0.7	8.5	2.1	1.9	Neg	Severe	+	C	23	0.79
5	48	F	76788	-	+	+	+	none	21	0.4	3.2	1.4	2.4	HbsAg	Moderate	+	C	15	0.74
6	39	M	69350	+	-	-	-	none	27	0.8	2.9	1.4	2.9	Neg	Absent	-	A	14	0.69
7	65	M	86662	+	+	-	-	none	30	0.6	3.7	1.5	3.4	Neg	Mild	-	B	16	0.71
8	40	M	75738	+	+	+	+	Gr 2	36	0.8	7.8	2.0	2.1	Neg	Severe	+	C	22	0.75
9	64	M	78205	-	-	-	-	none	32	0.6	3.2	1.0	2.9	HCV	Mild	-	B	11	0.71
10	41	M	92335	+	+	+	+	Gr 1	28	0.7	14.2	1.8	2.2	Neg	Severe	+	C	23	0.79
11	48	M	91741	+	+	+	+	Gr 1	27	0.8	6.4	1.5	1.6	Neg	Moderate	+	C	18	0.7
12	28	F	69898	-	-	+	+	none	34	0.6	2.3	2.6	2.6	Neg	Severe	+	B	21	0.74
13	53	M	73855	+	-	-	+	none	40	0.3	2.8	1.3	2.8	Neg	Mild	-	B	13	0.69
14	56	M	72852	+	+	-	+	none	29	0.5	4.3	1.3	3.4	Neg	Moderate	+	B	15	0.72
15	44	M	84184	-	+	+	+	Gr 2	37	1.2	9.3	2.3	2.4	HbsAg	Severe	+	C	26	0.77
16	32	M	63656	+	+	-	+	none	34	0.7	8.4	1.4	3.5	Neg	Mild	-	B	19	0.69
17	46	M	70981	+	+	+	+	Gr 1	29	0.6	6.4	1	3	Neg	Moderate	+	C	14	0.7
18	49	M	83723	+	+	-	+	none	20	0.4	4.5	2.1	3.4	Neg	Moderate	+	B	21	0.73
19	34	M	67428	-	-	-	-	none	18	0.5	1.8	0.9	3.5	Neg	Absent	-	A	9	0.68
20	57	M	90660	+	+	+	+	Gr 1	23	0.7	10.3	1.2	2.1	Neg	Severe	+	C	17	0.76
21	70	M	88579	-	+	+	+	none	34	0.4	7.8	1.4	2.6	Neg	Moderate	+	B	18	0.72
22	69	M	74582	+	+	+	+	Gr 1	38	0.4	15.4	2	3	neg	Severe	+	C	25	0.78
23	24	F	72137	-	+	+	+	none	40	0.7	4.6	1.4	3.6	Neg	Severe	+	B	16	0.76

24	30	M	70300	+	+	+	+	none	34	0.8	6.5	2.3	2.3	neg	Severe	+	C	23	0.79
25	35	M	64728	-	+	-	+	none	32	0.6	5.4	1.4	2.6	neg	Moderate	-	C	17	0.69
26	43	M	62329	+	+	+	+	none	19	0.3	6.2	1.6	3.6	Neg	Moderate	+	B	19	0.72
27	55	M	78748	+	-	-	+	none	32	0.6	4.3	1.4	2.8	neg	Absent	-	B	16	0.7
28	57	M	75447	+	+	+	+	none	26	0.4	7.5	1.4	2.4	neg	Mild	+	B	18	0.72
29	19	M	90475	+	+	+	+	Gr 1	18	1	10.6	1.9	3	neg	Severe	+	C	23	0.76
30	39	M	92818	+	+	-	-	none	26	0.6	4.3	1.1	2.8	neg	Absent	+	B	13	0.7
31	37	M	76862	+	+	-	+	none	32	0.6	6.4	1.4	2.8	neg	Moderate	+	C	17	0.72
32	40	M	65552	+	+	+	+	none	40	0.6	10.8	2.1	2.1	HbsAg	Severe	+	C	24	0.76
33	59	F	79158	-	+	+	+	none	27	0.6	9.6	1.8	2.4	neg	Severe	+	C	22	0.79
34	62	F	86485	+	-	-	-	none	14	0.3	2.5	0.9	3.5	neg	Absent	-	A	10	0.68
35	29	M	80591	+	+	+	+	none	35	0.4	13	1.6	2.4	neg	Severe	+	C	21	0.76
36	50	M	69630	+	+	-	+	none	27	0.6	6.4	1.2	3	neg	Moderate	+	B	16	0.74
37	49	M	77811	+	+	+	+	Gr 1	34	0.4	5.4	2.1	2.3	neg	Moderate	-	C	22	0.7
38	69	M	61086	+	+	-	-	none	14	0.8	7.4	1.2	2.6	neg	Absent	-	B	16	0.69
39	54	M	83721	+	+	+	+	none	27	0.5	12	1.7	2.4	neg	Severe	+	C	23	0.79
40	32	M	92863	+	+	+	+	none	33	0.4	8.8	1.6	3	neg	Severe	+	B	20	0.78
41	45	M	67987	+	+	+	+	Gr 2	31	1	9.6	2	2.9	neg	Moderate	+	C	23	0.74
42	25	M	63328	+	+	+	+	Gr 1	41	1.3	14.3	1.3	2.5	neg	Severe	+	C	25	0.74
43	35	F	66173	-	-	-	-	none	36	1	1.8	1	3	HCV	Absent	-	A	9	0.68
44	46	M	76258	+	+	+	+	none	26	0.4	9.3	1.9	1.8	neg	Severe	+	C	22	0.79
45	41	M	86470	+	+	+	+	none	14	0.6	4.6	1.4	2.6	neg	Moderate	+	B	16	0.71
46	42	M	72655	+	+	+	+	none	19	0.4	12.6	2.1	2.4	neg	Severe	+	C	25	0.78
47	47	M	75694	+	+	+	+	none	49	0.6	5.5	1.4	3	neg	Absent	+	A	17	0.72
48	52	M	79169	+	+	+	+	none	27	0.4	6.8	1.6	2.6	HbsAg	Moderate	+	C	19	0.7
49	41	M	74020	+	+	+	+	none	21	0.9	8.6	1.7	2.8	neg	Severe	+	C	23	0.8
50	36	M	77739	+	+	+	+	none	30	0.5	4.5	1.5	2.6	neg	Absent	-	B	17	0.67
51	45	M	89847	-	-	-	-	none	25	0.3	2.6	1.2	3.6	Neg	Absent	-	A	12	0.69
52	45	M	86248	+	+	+	+	Gr1	32	0.7	3.6	1.2	2.5	Neg	Moderate	+	C	13	0.73
53	53	M	71289	-	+	-	-	none	26	0.6	3.4	1.6	2.7	HbsAg	Mild	+	C	16	
54	37	M	64995	+	+	+	+	none	33	0.5	9.1	2.2	2.5	Neg	Severe	+	C	24	0.76
55	41	M	77301	+	-	+	+	none	21	0.3	2.3	1.2	3.1	Neg	Absent	_	A	12	0.72

56	30	M	86726	+	+	-	-	none	16	1	4.5	1.2	3.4	Neg	Mild	-	B	14	0.7
57	36	M	85154	+	+	+	+	Gr 1	36	0.8	8.4	2.1	1.9	Neg	Severe	+	C	23	0.79
58	45	M	65349	-	+	+	+	none	21	0.4	3.2	1.4	2.4	HbsAg	Moderate	+	A	15	0.74
59	54	M	69396	-	-	-	-	none	32	0.6	3.2	1	2.9	HCV	Mild	-	B	11	0.71
60	26	M	76222	+	+	+	+	Gr 1	31	0.7	13.8	1.8	2	Neg	Severe	+	C	13	0.79
61	51	F	69477	-	+	+	+	none	27	0.3	5.3	1.5	2	Neg	Moderate	+	C	18	0.7
62	46	M	83888	-	+	+	+	none	34	0.6	13	1.4	2.6	Neg	Severe	+	C	20	0.74
63	54	M	69838	+	-	-	-	none	40	0.3	2.8	1.3	2.8	Neg	Absent	-	A	13	0.69
64	57	M	92236	-	+	-	+	none	29	0.5	3.4	1.4	3	Neg	Moderate	+	B	15	0.72
65	45	M	74493	-	+	+	+	Gr 1	37	1.1	12.9	2.3	2.5	HbsAg	Severe	+	C	27	0.76
66	36	M	65697	+	+	-	+	none	32	0.4	7.2	1.4	3.5	Neg	Mild	-	B	18	0.69
67	34	M	77838	+	+	+	+	Gr 1	29	0.6	6.4	2.3	2.4	Neg	Moderate	-	C	23	0.72
68	48	M	78233	+	+	-	+	none	32	0.3	4.8	2.1	3	Neg	Absent	-	B	13	0.73
69	31	M	85172	+	+	+	+	Gr 1	21	0.6	6.4	1.5	1.9	neg	Severe	+	C	18	0.76
70	43	M	88566	+	+	-	+	none	40	0.6	4.4	1.1	2.6	neg	Moderate	+	C	13	0.74
71	47	M	85592	+	+	-	+	none	26	0.4	5	1.4	2.8	neg	Moderate	+	B	17	0.72
72	54	M	81710	+	+	+	+	Gr 1	40	0.6	10.8	2.1	2.1	HbsAg	Severe	+	C	24	0.76
73	68	F	78844	-	+	+	+	none	20	0.6	9.7	2.1	2.2	neg	Severe	+	C	23	0.79
74	29	F	69129	-	-	-	-	none	14	0.3	2.5	0.8	3.5	neg	Absent	-	A	10	0.68
75	56	M	63025	+	+	+	+	GR1	35	0.4	13.4	1.9	2.4	neg	Severe	+	C	24	0.73
76	46	M	71251	+	+	-	+	none	27	0.6	6.4	1.2	3	neg	Moderate	+	B	16	0.74
77	67	M	62712	+	+	+	+	none	34	0.4	5.4	2.1	2.3	neg	Moderate	-	C	22	0.7
78	48	M	93215	+	+	-	-	none	14	0.8	4.4	1.2	2.6	neg	Absent	-	B	14	0.69
79	50	M	79159	+	+	+	+	none	27	0.5	6.4	1.3	2.4	neg	Severe	+	C	16	0.79
80	43	M	64224	+	+	+	+	none	29	0.9	4.8	1.6	3	neg	Severe	+	C	18	0.78
81	46	M	82072	+	+	+	+	none	31	1.1	13.5	2	2.9	neg	Severe	+	C	25	0.74
82	33	M	66749	+	+	+	+	Gr 1	41	1	2.3	1.3	3	neg	Mild	+	B	13	0.74
83	55	F	77020	-	-	-	-	none	36	1	2.8	1.9	3	HCV	Absent	-	A	18	0.68
84	22	M	91778	+	+	+	+	none	32	0.8	11.8	1.9	1.8	neg	Severe	+	C	23	0.79
85	65	M	87538	+	+	-	+	none	14	0.6	5.7	1.4	2.6	neg	Moderate	+	B	17	0.71
86	54	M	93223	+	-	+	+	none	19	0.4	2.6	2.1	2.4	neg	Severe	+	C	19	0.78
87	43	M	69378	+	+	+	+	none	31	0.6	7.7	1.4	3	neg	Mild	+	B	18	0.72

88	60	M	79407	+	+	+	+	none	27	0.4	6.8	1.6	2.6	HbsAg	Moderate	+	C	19	0.7
89	56	M	67106	+	+	-	-	Gr 1	24	0.7	4.2	1.1	2.6	Neg	Absent	+	C	13	0.76
90	32	F	61616	-	+	-	+	none	32	0.7	7.8	1.4	2.6	Neg	Moderate	+	B	18	0.72
91	66	M	91736	+	+	+	+	Gr 1	32	0.8	16.3	2.1	3	neg	Severe	+	C	25	0.79
92	75	M	80087	-	+	+	+	none	40	0.3	4.6	1.4	3.5	Neg	Moderate	+	B	16	0.76
93	17	M	64695	+	+	+	+	none	42	0.5	12.4	2.3	2.3	neg	Severe	+	C	25	0.75
94	64	M	87865	-	+	-	+	none	34	0.4	7.1	1.4	2.3	neg	Moderate	-	C	18	0.69
95	59	M	75742	+	+	+	+	none	23	0.3	6.2	1.6	3.6	Neg	Moderate	+	B	19	0.72
96	41	M	65486	+	-	-	+	none	28	0.6	2.4	1.4	2.8	neg	Absent	-	B	14	0.7
97	38	M	87474	+	+	+	+	none	35	0.4	4.8	1.4	2.4	neg	Moderate	+	C	16	0.72
98	49	M	80797	+	+	+	+	Gr 1	18	0.4	17.4	1.9	2.6	neg	Severe	+	C	25	0.76
99	53	F	78631	-	+	-	+	none	23	0.6	8.5	1.1	2.8	neg	Moderate	+	C	16	0.72
100	28	M	87906	+	+	+	+	none	12	0.3	9.7	2.5	2.6	Neg	Severe	+	C	25	0.71

PHT – portal hypertension

PT INR – prothrombin time/ internationally normalised ratio

CTP – child turcot pugh

MELD – model for end stage liver disease

Gr 1 – grade 1

Gr 2 – grade 2

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.L.Nivethitha Karthika
Postgradaute M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.L.Nivethitha Karthika,

The Institutional Ethics Committee has considered your request and approved your study titled **"The role of renal resistive index in assessing the early renal dysfunction of cirrhosis" No.12052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.S.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.S.Vasanth, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., 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.

23/6/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
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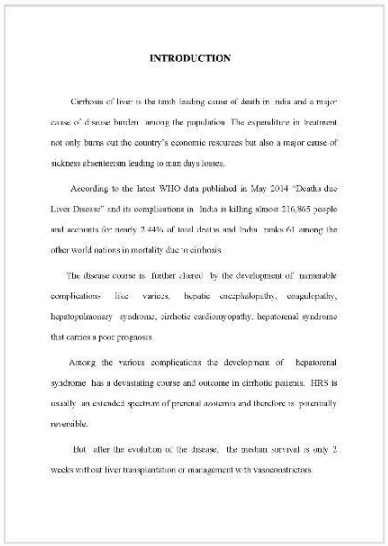


INTRODUCTION

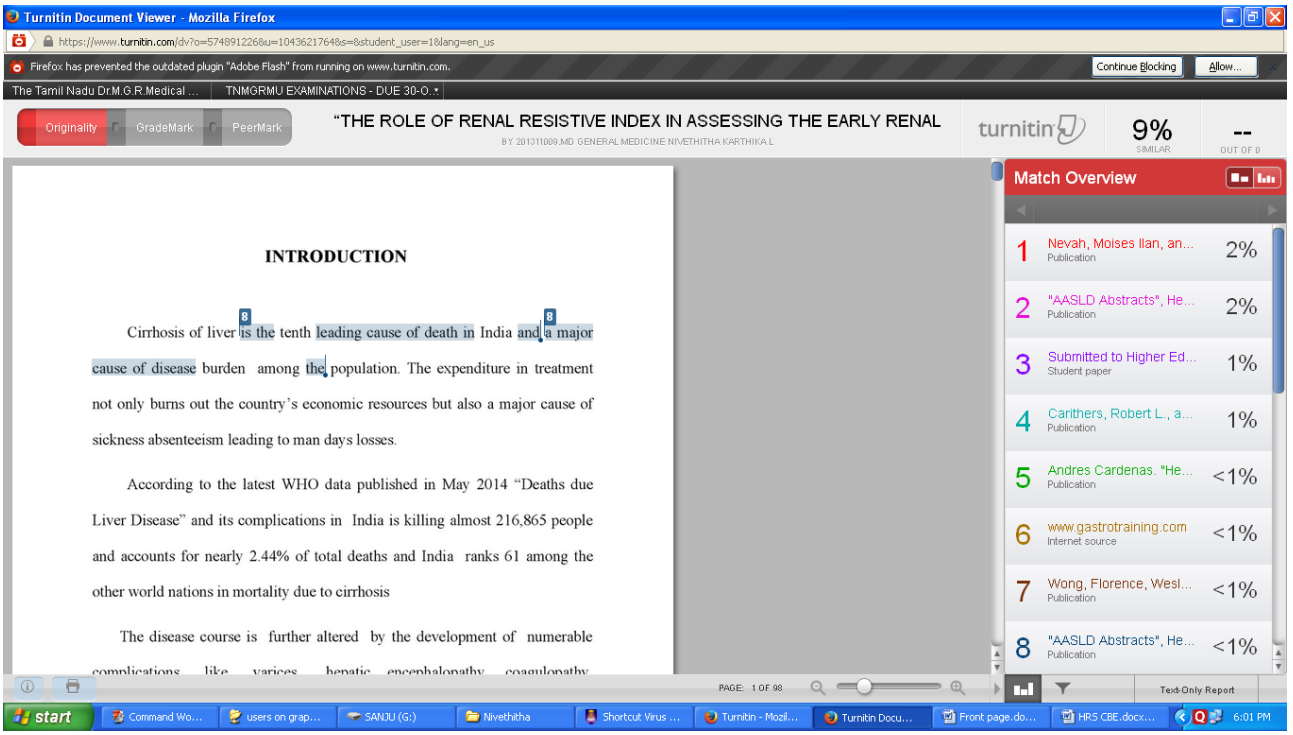
Cirrhosis of liver is the tenth leading cause of death in India and a major cause of disease burden among the population. The expenditure in treatment not only burns out the country's economic resources but also a major cause of sickness absenteeism leading to man days losses.

According to the latest WHO data published in May 2014 "Deaths due Liver Disease" and its complications in India is killing almost 216,865 people and accounts for nearly 2.44% of total deaths and India ranks 61 among the other world nations in mortality due to cirrhosis.

The disease course is further altered by the development of numerable complications like varices, hepatic encephalopathy, coagulopathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome that carries a poor prognosis.

Among the various complications the development of hepatorenal syndrome has a devastating course and outcome in cirrhotic patients. HRS is usually an extended spectrum of prerenal azotemia and therefore is potentially reversible.

But after the evolution of the disease, the median survival is only 2 weeks without liver transplantation or management with vasoconstrictors.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Cirrhosis of liver is the tenth leading cause of death in India and a major cause of disease burden among the population. The expenditure in treatment not only burns out the country's economic resources but also a major cause of sickness absenteeism leading to man days losses.
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The disease course is further altered by the development of numerable
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