"AUTONOMIC DYSFUNCTION IN CIRRHOSIS OF LIVER-A ONE YEAR CROSS SECTIONAL STUDY"

By

REG NO. BG0114010

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELAGAVI, KARNATAKA

APRIL - 2017

KLE UNIVERSITY, BELAGAVI,

KARNATAKA

Endorsement by the Head of Department, Principal/ Head of the Institution

This is to certify that the dissertation entitled **AUTONOMIC DYSFUNCTION IN CIRRHOSIS OF LIVER -A ONE YEAR CROSS SECTIONAL STUDY** is a bonafide research work done **REG NO. BG0114010**

Dr. Rekha Patil MD
Professor and Head,
Department of Medicine,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi.

Dr. N. S. Mahantshetti MD
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi.

LIST OF ABBREVATIONS USED

ALD	-	ALCHOLIC LIVER DISEASE
CLD	-	CHRONIC LIVER DISEASE
HBV	-	HEPATITIS B VIRUS
HCV	-	HEPATITIS C VIRUS
CVD	-	CARDIOVASCULAR DISEASE
CO	-	CARDIAC OUTPUT
TIPPS	-	TRANSJUJULAR INTRAHEPATIC PORTO-SYSTEMIC SHUNT
RCT	-	RANDOMISED CONTROL TRAIL
HVPG	-	HEPATIC VEIN PRESSURE GRADIENT
DNA	-	DEOXYRIBONUCLIC ACID
NO	-	NITRIC OXIDE
SCD	-	SUDDEN CARDIAC DEATH

ABSTRACT

BACKGROUND AND OBJECTIVES

Cirrhosis is a chronic disease of the liver of various aetiology that leads to a number of complications,some of which may eventually prove fatal. Over the years, some studies have reported that patients with chronic liver disease who have associated autonomic neuropathy respond inappropriately or defectively to major events such as septicemia and variceal haemorrhage. The quality of life in these patients is impaired and the risk of sudden cardiac death in these patients is high. Studies on the above given topic are few and hence study is undertaken and to know the prevalence of autonomic dysfunction which helps in effective treatment of the disease.

METHODOLOGY

The present one year cross-sectional study was done in the Department of General Medicine at KLES Dr Prabhakar kore Hospital and Medical Research Centre Belagavi. A total of 100 patients were included in the study. Patients were subjected to clinical examination, laboratory workup like complete blood count, liver function test, electrocardiogram, ultrasound abdomen and autonomic functions were assessed with help of electrocardiogram, and presence of dysautonomia in these patients was assessed based on the test results.

RESULTS

Majority of the patients had evidence of dysautonomia ie 83 patients.There were more cases of dysautonomia in age group of 41-60 years.In our study there were 95% males and 5% females. Clinical presentation of dysautonomia was dizziness and impotence. Majority of patients had early dysautonomia rather than definite dysautonomia.Evidence of dysautonomia was more common with cirrhosis secondary to HBV,HCV as compared to alcoholics.

CONCLUSION AND INTERPRETATION

Autonomic dysfunction was seen in majority of our patients.In patients with aetiology like HBV, HVC, autoimmune, had more autonomic dysfunction as compared to alcohol related cirrhosis of liver. There is strong evidence of dysautonomia in majority of patients with various aetiology.The evidence of dysautonomia was more observed with patient with increasing age.

KEYWORDS

Cirrhosis of liver, autonomic dysfunction, autoimmune, hepatitis-B hepatitis-C, alcoholics, dizziness, impotence .

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Cirrhosis is a chronic disease of the liver that leads to a number of complications, some of which may eventually prove fatal. Over the years, some studies have reported that patients with chronic liver disease who have associated autonomic neuropathy respond inappropriately or defectively to major events such as septicaemia and variceal haemorrhage.[4]

Cirrhosis and chronic liver failure are leading causes of morbidity and mortality in the United States, with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or nonalcoholic fatty liver disease.

Cirrhosis often is an indolent disease; most patients remain asymptomatic until the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding from portal hypertension. Physical examination of patients with cirrhosis may reveal a variety of findings that necessitate a hepatic- or gastrointestinal-based work-up to determine the etiology.[16,23,35]

Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices andhepatocellular carcinoma. Lately, this perception has been challenged, because1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events.[3]Chronic liver disease is accompanied by several circulatory changes.

Hyperdynamic circulatory syndrome is a common feature of advanced cirrhosis.1 It is characterized by splanchnic blood pooling, opening of portal-systemic collaterals, arterial vasodilatation and compensatory increase in blood volume.[1,2]

The resultant autonomic regulatory system events results in an increase in heart rate and cardiac output and reduced peripheral vascular resistance. [1,3]

It is becoming increasingly clear that quality of life in cirrhosis of liver ,patients is impaired and autonomic dysfunction in these patients is significantly more[1]

The prevalence of autonomic dysfunction in cirrhosis of liver is as high as 67% in some populations and 57% in alcoholic liver disease and cannot be ignored[1]

The pathogenesis of autonomic dysfunction in these patients is not fully understood.

There is increased risk of sudden cardiac death in these patients[2]

The autonomic regulatory system of the splanchnic circulation is complex. In healthy individuals, the splanchnic vascular bed contains a large, highly compliant, venous circulation to an extent of 25% of the blood volume at rest.[7]It has been considered as the primary blood volume reservoir for reflex control of cardiovascular homeostasis during exercise.[8] This richly innervated vascular bed's vasoconstriction activity is mediated by α-1 receptor. An impaired autonomic function is expected to lead to impairment of cardiovascular autonomic reflexes and hemodynamic instability.

The prevalence autonomic dysfunction (AD) in cirrhosis has varied from 8% - 80% in different series. Its occurrence is irrespective of the etiology of chronic liver disease: ethanol or non ethanol related.[9]and increases in parallel with the severity of liver disease.

Other factors contributing to AD in cirrhosis include that affecting nerve integrity such as alterations in lipid metabolism, vitamin E deficiency, alcohol consumption, immunologic mechanisms and retention of toxic metabolites.[15,16] Vagal dysfunction due to elevated angiotensin II production and sympathetic dysfunction due to blunted responsiveness owing to either a production of weak neurotransmitters or a receptorial&postreceptorial defect has been documented.[4] Presence of AD irrespective of the cause is often associated with an adverse prognosis.[16]

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide,[8] 170 000 per year in Europe,[9] and 33 539 per year in the USA.10 Cirrhosis is the main indication for 5500 liver transplants each year in Europe.9

We undertook this study to find the prevalence of autonomic dysfunction in patients with cirrhosis of liver which would help on better management of these patients.

OBJECTIVE OF THE STUDY

- To evaluate autonomic dysfunction in patients with cirrhosis of liver

REVIEW OF LITERATURE

Cirrhosis is a slowly progressing disease in which the liver tissue is replaced with scar tissue, eventually preventing the liver to function. The scar tissue formed blocks the flow of blood through the liver and slows the processing of nutrients, hormones, drugs, and naturally produced toxins.[5]

ANATOMY

Anatomy: The basic histologic unit is the lobule; the lobules are surrounded by portal spaces, containing branches of the bile ducts, hepatic artery and portal vein (hence the term portal triad). The lobules contain hepatocytes arranged in one cell-thick plates which radiate from the central vein to the adjacent lobules,[1] the hepatocytic plates are separated by sinusoids, which are lined by stellate and Kupffer cells.

The distribution of blood is from the portal branches of the hepatic artery and portal vein towards the central vein; from the central veins the blood flows into the hepatic veins. Bile flow is in the opposite direction to the blood circulation. Bile is secreted by hepatocytes into canaliculi, formed by apposed surfaces of contiguous liver cells and from there goes to the bile ducts in the portal tracts and through larger ducts into the right and left hepatic ducts, common bile duct ending in the duodenum[2].

The functional unit of the liver is the acinus, with a center in the portal tract, as opposed to the histologic unit. The acinus is classically divided in three zones; zone one is the most oxygenated, around the portal tracts and contains the highest concentration of nutrients and hormones. Zone three, around the central veins, is poor

in oxygen; Zone two is intermediate. Each liver cell has two sinusoidal surfaces, lined by microvilli. The sinusoidal surface is separated from] the liver surface by the space of Disse[1 2 3].

As already mentioned the bile canaliculi are formed by apposed liver cells and are also lined by microvilli. There are tight functional complexes between liver cells, preventing bile leakage. The hepatocyte has rough and smooth endoplasmic reticulum, Golgi complexes, mitochondria, lysosomes, peroxisomes, glycogen and fat.

There are three types of sinusoidal cells:

a) Endothelial cells, which line the sinusoids in a discontinuous fashion. There are openings within endothelial cells called fenestrae, allowing free communication between the sinusoidal lumen and the space of Disse
b) Kupffer cells, located between endothelial cells on or on their surface. They have a macrophage function and contain cytokines e.g. tumor necrosis factor, interleukins, interferon[3]
c) Stellate cells, which store vitamin A and secrete extracellular collagens. There are type I collagen fibers in the space of Di]sse.

CIRRHOSIS OF LIVER

Cirrhosis and chronic liver failure together were the 12th most common cause of death in the United States in 2002, accounting for 27,257 deaths (9.5 per] 100,000 persons), with a slight male predominance.[4] Approximately 40 percent of patients with cirrhosis of liver are asymptomatic, and the condition is discovered during a routine examination with laboratory or radiographic studies, or at autopsy

Single or multifactorial insults to the liver ultimately lead to cirrhosis, of which most common being alcohol abuse, chronic hepatitis C, and obesity with concomitant nonalcoholic fatty liver disease Nonalcoholic fatty liver disease (NAFLD; formerly known as nonalcoholic steatohepatitis, or NASH) is an increasingly common cause of liver injury; risk factors include obesity, diabetes, hypertriglyceridemia, and profound weight loss after jejunoileal bypass.[6] some times the cause cannot be found.

EPIDEMIOLOGY

Cirrhosis of liver is an increasing cause of morbidity and mortality in more developed and developing countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide,[8] 170 000 per year in Europe,[9] and 33 539 per year in the USA.[10] Cirrhosis is the mainindication for 5500 liver transplants each year in Europe.[9] The prevelence is more in developed countries in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly], non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in subSaharan Africa and most parts of Asia.

The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic and patient do not present to the doctor so the disorder is undiagnosed. Prevalence was estimated at 0·3% in a French screening programme, and the annual incidence was 15·3–132·6 per 100 000 people in studies in the UK and Sweden.[9]

ETIOLOGY AND DEFINITION

The liver aids greatly in the maintenance of metabolic homeostasis by processing dietary amino acids, carbohydrates, lipids, and vitamins; metabolizing cholesterol and toxins; producing clotting factors; and storing glycogen.

Injury to the liver parenchyma associated with an influx of acute or chronic inflammatory cells is termed hepatitis, which might be reversible or irreversible.

Cirrhosis refers to a progressive, diffuse, fibrosing, nodular condition that disrupts the entire normal architecture of the liver. [3 4] Fibrosispreviously was thought to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence suggests that fibrosis may be reversible in some patients with chronic hepatitis B after newer antiretroviral therapy.[8]

Any chronic insult to the liver can cause progression to cirrhosis. Although numerous pathophysiologic mechanisms of injury exist, the final common pathway is persistent wound healing resulting in hepatic parenchymal fibrosis. In most persons, approximately 80 to] 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically].

ETIOLOGIES OF CIRRHOSIS

MOST COMMON CAUSES =

1) Alcohol (60 to 70 percent) ,
2) Biliary obstruction (5 to 10 percent)
3) Biliary atresia/neonatal hepatitis
4) Congenital biliary cysts
5) Cystic fibrosis Primary or secondary biliary cirrhosis

6) Chronic hepatitis B or C (10 percent)
7) Hemochromatosis (5 to 10 percent)
8) NAFLD (10 percent)—most commonly resulting from obesity; also can occur after jejunoileal bypass

LESS COMMON CAUSES =

1) Autoimmune chronic hepatitis types 1, 2, and 3
2) Drugs and toxins Alpha-methyldopa (Aldomet) Amiodarone (Cordarone) 3.Isoniazid (INH) Methotrexate Oxyphenisatin (Prulet)* Perhexiline* Troglitazone (Rezulin)*
3) Vitamin A Genetic metabolic disease a1-Antitrypsin deficiency Amino acid disorders (e.g., tyrosinemia) Bile acid disorders
4) Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)
5) Lipid disorders (e.g., abetalipoproteinemia)
6) Porphyria Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency) Wilson's disease Idiopathic miscellaneous
7) Granulomatous liver disease (e.g., sarcoidosis)
8) Idiopathic portal fibrosis
9) Indian childhood cirrhosis
10) Polycystic liver disease
11) Infection- Brucellosis Congenital or tertiary syphilis Echinococcosis Schistosomiasis
12) Vascular abnormalities Chronic, passive hepatic congestion caused by right-sided heart failure.
13) Pericarditis

14) Hereditary hemorrhagic telangiectasia (Osler-WeberRendu disease) Veno-occlusive disease When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma.[6]

PATHOPHYSIOLOGY

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion leading to shrunken liver and cirrhosis.[11]

This process leads to pronounced hepatic microvascular changes, characterised by sinusoidal remodelling, formation of intra hepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction.[12]

The endothelial dysfunction is characterised by insufficient release of vasodilators, of which nitric oxide is important. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-dependent phosphorylation, lack of cofactors, increased scavenging resulting from oxidative stress, and high concentrations ofendogenous inhibitors of nitric oxide), with concomitant increased production of vasoconstrictors (mainly adrenergic stimulation and thromboxane A2, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins).[13] Increased hepatic resistance to portal blood flow is the primary factor increasing portal pressure in cirrhosis and is responsible for the varices formation.

Portal hypertension results from the combination of structural disturbances associated with advanced liver disease (accounting for about 70% of total hepatic vascular resistance) and of functional abnormalities leading to endothelial dysfunction and increased hepatic vascular tone; portal pressure could perhaps therefore be decreased by 30% if this functional abnormality were antagonised. The molecular mechanisms of these abnormalities are being delineated and represent new targets for therapy. Splanchnic vasodilation increases in the inflow of blood into the portal venous system contributes to aggravate the increase in portal pressure.

Splanchnic vasodilation is an adaptive response to the changes in intrahepatic haemodynamics in cirrhosis; its mechanisms are directly opposite to those of the increased hepatic vascular tone. Because of vasodialtation, attempts to correct portal hypertension by acting on hepatic resistance or portal blood inflow should be ideally based on strategies acting as selectively as possible on the intrahepatic or the splanchnic circulation. In advanced cirrhosis, splanchnic vasodilation is so intense as to determine a hyper dynamic splanchnic and systemic circulation, which together with portal hypertension has a major role in the pathogenesis of ascites and hepatorenal syndrome.

Systemic vasodilation further causes ventilation perfusion mismatch that in severe cases leads to hepatopulmonary syndrome and arterial hypoxemia. Portopulmonary hypertension is characterized by pulmonary vasoconstriction, which is thought to be due to endothelial dysfunction in the pulmonary circulation. Formation and increase in size of varices is driven by anatomical factors, increased portal pressure and collateral blood flow, and by angiogenesis dependent on vascular endothelial growth factor, all of which contribute to variceal bleeding. Dilation of

gastric mucosal vessels leads to portalhypertensive gastropathy. In addition, the shunting of portal blood to the systemic circulation through the portosystemic collaterals is a major determinant of hepatic encephalopathy, of decreased first-pass effect of orally administered drugs, and of decreased reticuloendothelial system function. However, capillarisation of sinusoids and intrahepatic shunts are also important because these changes interfere with effective hepatocyte perfusion, which is a major determinant of liver failure.

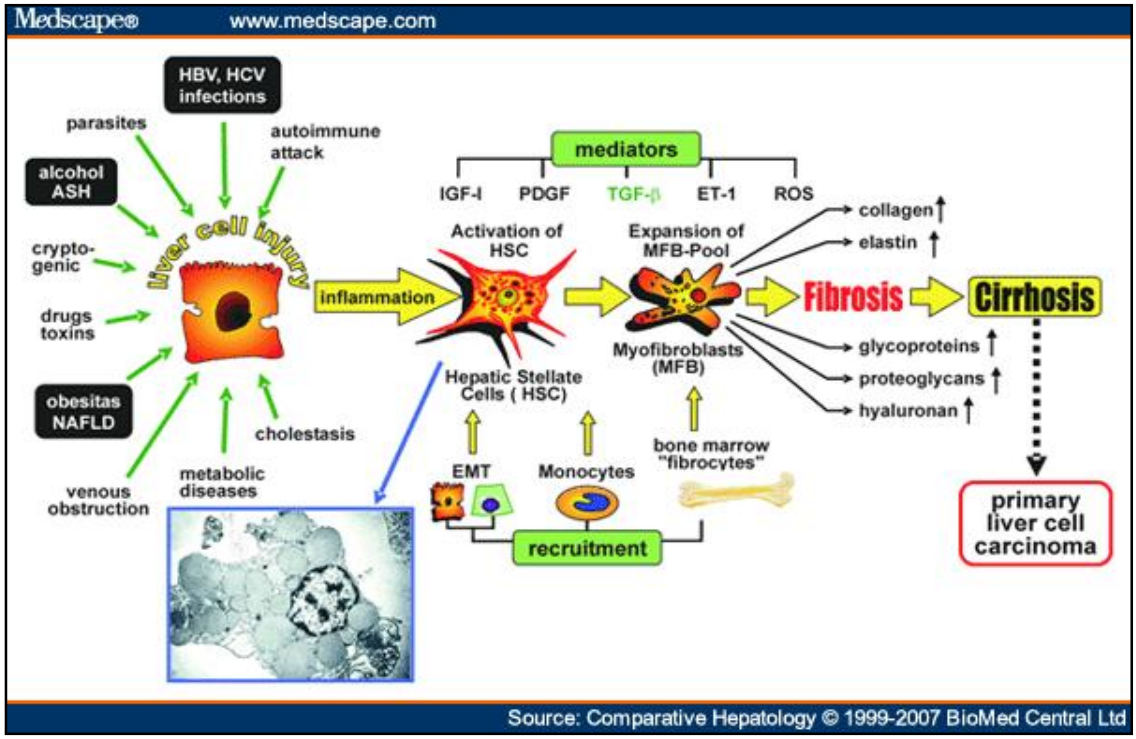


FIGURE-1 PATHOGENESIS OF CIRRHOSIS OF LIVER

NATURAL COURSE

Cirrhosis should no longer be believed as a terminal disease and the concept of a dynamic process is increasingly accepted. A prognostic clinical sub classification with four distinct stages has been proposed with substantially differing likelihoods of mortality:

Stage 1 (compensated with no oesophageal varices) has an estimated mortality of 1% per year,

Stage 2 (compensated with varices),

Stage 3 (decompensated with ascites),

Stage 4 (decompensated with gastrointestinal bleeding) have annual mortality rates of 3·4%, 20%, and 57%, respectively.[3]

Infections and renal failure have been considered as stage 5, with 67% 1-year mortality.[16,17]Acute decompensating events that lead to organ failure have mortality of 30%;[18] notably, mortality is higher in previously compensated patients than in those with previous decompensation, which suggests greater tolerance of the latter through the effects of the inflammatoryresponse.[18] Decompensating events are generally triggered by precipitating factors that include infection, portal-vein thrombosis, surgery, and hepatocellular carcinoma.

CLINICAL PRESENTATION

Cirrhosis often is a silent disease, with most patients will be asymptomatic until decompensation occurs. Physicians should inquire about risk factors that pre-dispose patients to cirrhosis,Quantity andduration of alcohol consumption is an important factor in the early diagnosis of cirrhosis.[3]

Other risk factors include those for hepatitis B and C transmission (e.g., birthplace in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body

fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases.[3]

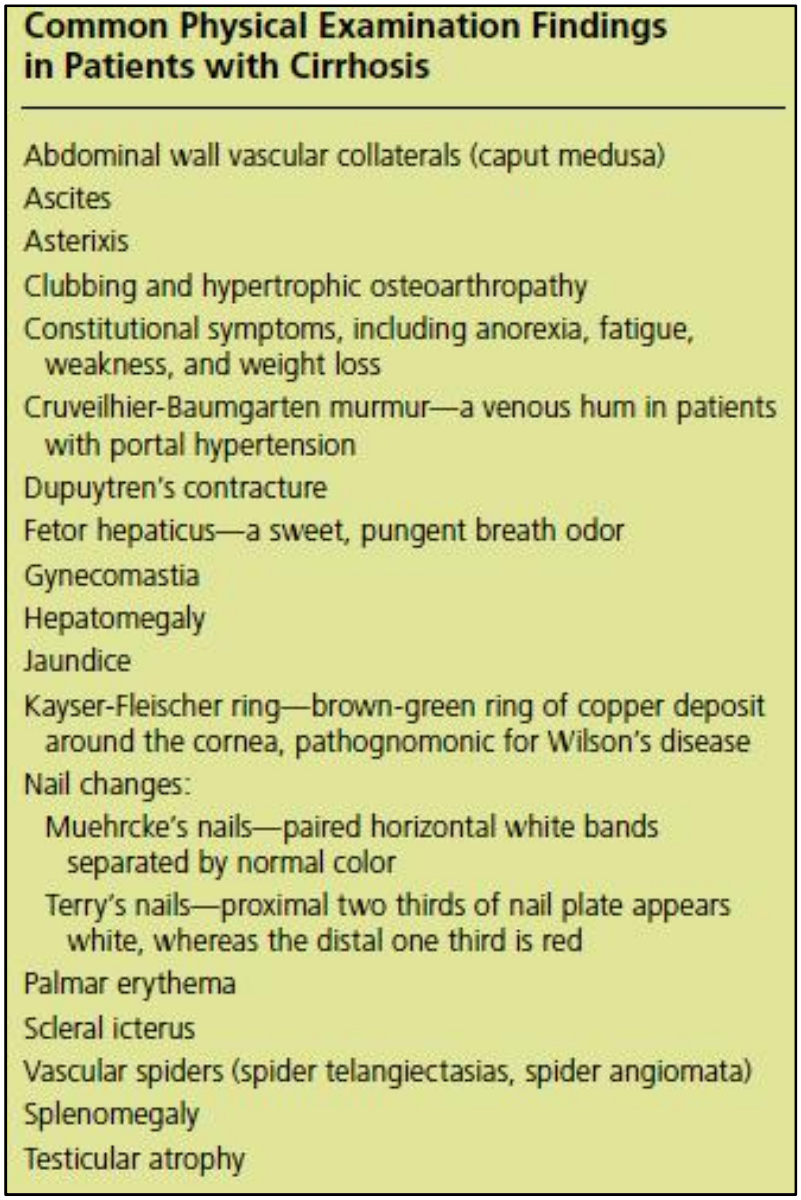
Early and well-compensated cirrhosis can present as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding from portal hypertension.

Clinical symptoms that are seen are jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Each of these clinical findings is the result of impaired hepatocellular function with or without physical obstruction secondary to cirrhosis. Because hepatic enzyme synthesis is requiredfor drug metabolism, heightened sensitivity and medication toxicity may occur in patients with impaired hepatic enzyme synthesis.[39]

PHYSICAL EXAMINATION

Physical examination of patients with cirrhosis may reveal a variety of findings that should lead to a targeted hepatic- or gastrointestinal-based work-up[10].

All patients will already have had serologic or radiographic tests or unrelated surgical procedure that incidentally uncovered signs of cirrhosis. Most patients with cirrhosis severe enough to lead to ascites have additional stigmata of cirrhosis on physical examination. Accurately diagnosing ascites depends upon the amount of fluid present in the abdomen, the technique used to examine the patient, and the patient's habitus.



Common Physical Examination Findings in Patients with Cirrhosis

Abdominal wall vascular collaterals (caput medusa)
Ascites
Asterixis
Clubbing and hypertrophic osteoarthropathy
Constitutional symptoms, including anorexia, fatigue, weakness, and weight loss
Cruveilhier-Baumgarten murmur—a venous hum in patients with portal hypertension
Dupuytren's contracture
Fetor hepaticus—a sweet, pungent breath odor
Gynecomastia
Hepatomegaly
Jaundice
Kayser-Fleischer ring—brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease
Nail changes:
Muehrcke's nails—paired horizontal white bands separated by normal color
Terry's nails—proximal two thirds of nail plate appears white, whereas the distal one third is red
Palmar erythema
Scleral icterus
Vascular spiders (spider telangiectasias, spider angiomata)
Splenomegaly
Testicular atrophy

FIGURE-2 PHYSICAL EXAMINATION FINDINGS IN PATIENBTS WITH CIRRHOSIS

DIAGNOSIS OF CIRRHOSIS OF LIVER

Most chronic liver disease are asymptomatic until cirrhosis with clinical decompensation occurs. Decompensating symptoms include ascites, sepsis, variceal bleeding, encephalopathy, and non-obstructive jaundice.

Imaging by ultrasound abdomen, CT, or MRI of an irregular and nodular liver together with impaired liver synthetic function is sufficient for the diagnosis of cirrhosis but liver biopsy is gold standard.

Other findings include small and shrunken liver, splenomegaly, and evidence of portosystemic collaterals. Differential diagnosis for cirrhosis of liver are congenital hepaticfibrosis (fibrosis without regenerative nodules), nodular regenerative hyperplasia (nodules but no fibrosis), and non-cirrhotic portal hypertension.

A liver biopsy is needed when a study of a sample can provide a definitive diagnosis and confirm the aetiology in cases of uncertainty. The transjugular approach yields samples of equal quality to the percutaneous one, is safe, and adds additional prognostic information through measurement of hepatic-vein pressure gradient (HVPG).[14] In early cirrhosis, however, conventional imaging can lead to false-negative diagnosis so other strategies are needed.

Non-invasive markers of fibrosis are increasingly used; they are more informative at the extremes of the liver fibrosis range—ie, little or no fibrosis, and cirrhosis.[15] They include indirect serum markers (simple, widely available indices), direct serum markers that measure biomarkers of fibrosis, and imaging modalities, such as transient elastography . These tests should be used and interpreted only once the aetiology is known.

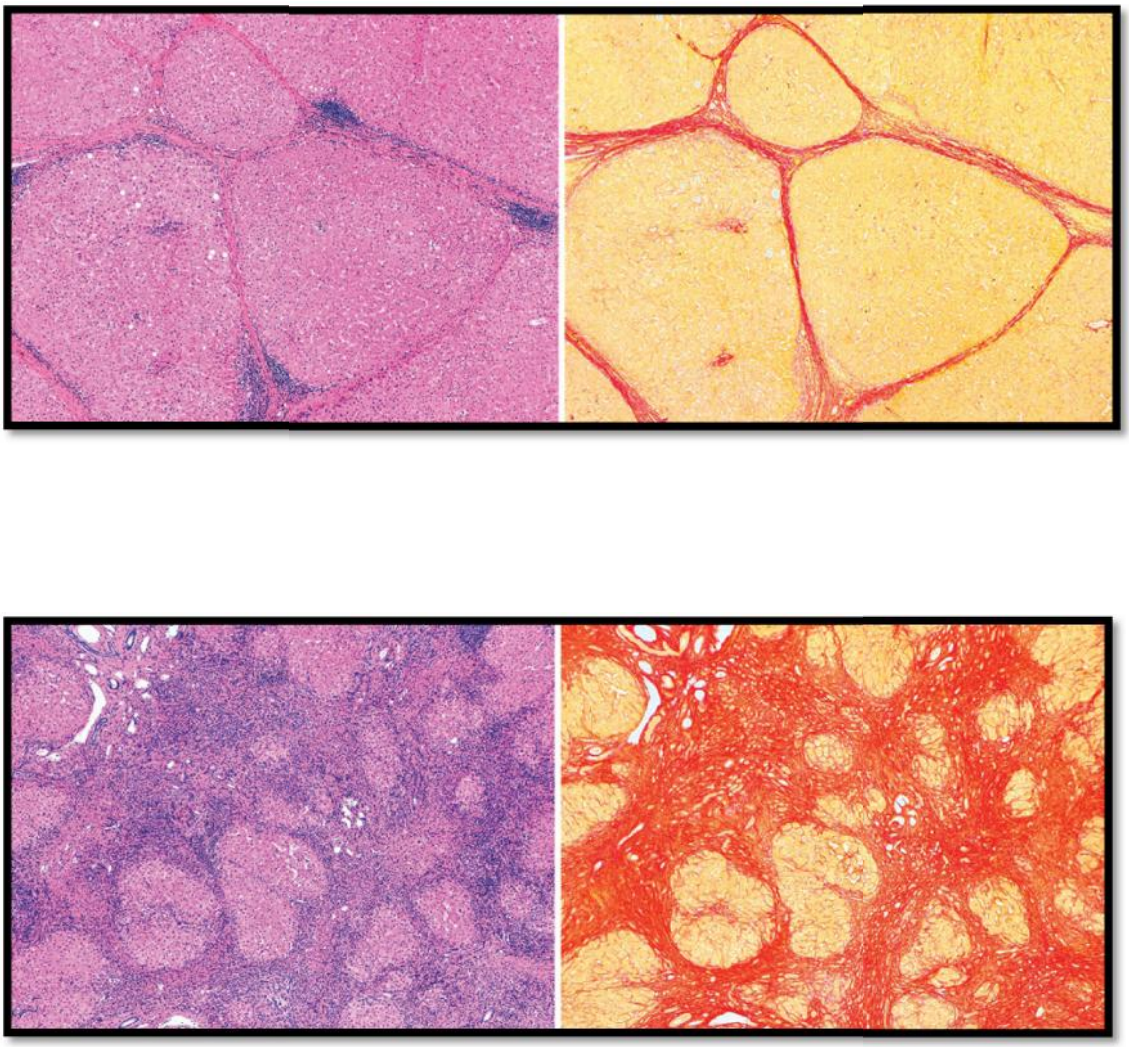


FIGURE-3 : HISTOPATHOLOGICAL APPEARANCE IN CIRRHOSIS

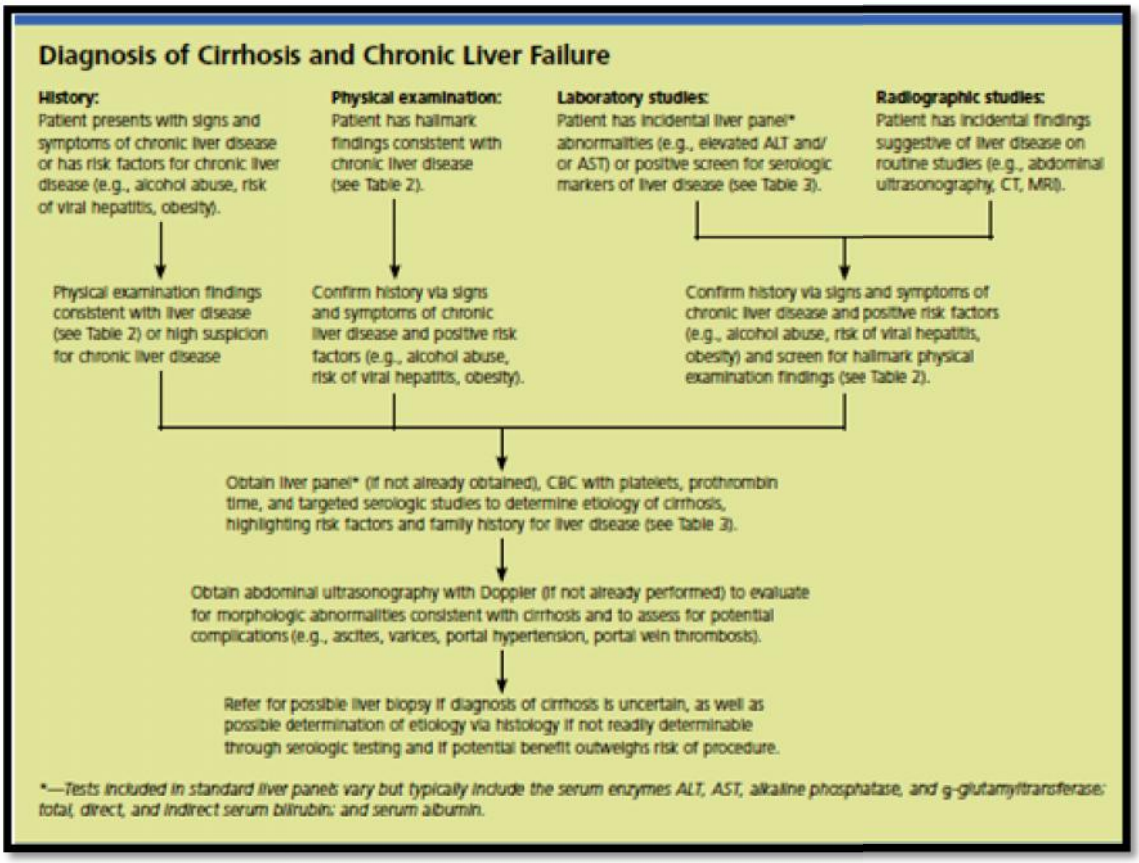


FIGURE-4 DIAGNOSIS OF CIRRHOSIS OF LIVER

LABORATORY EVALUATION

No serologic test is confirmatory for diagnosing cirrhosis accurately.[3] The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly.[10] Although liver function tests may not correlate exactly with hepatic function, interpreting abnormal biochemical patterns in conjunction with the clinical picture may suggest certain liver diseases.

When a liver pathology is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time test should be performed.[14]

Common tests in liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and g-

glutamyltransferase; total, direct, and indirect serum bilirubin; and serum albumin. The ALT is thought to be the most important test for identifying metabolic or drug-induced hepatic injury, but like other liver function tests, it is of limited use in predicting degree of inflammation and of no use in estimating severity of fibrosis.[15] One study found that a platelet count of less than 160 K per mm3 has a sensitivity of 80 percent for detecting cirrhosis in patients with chronic hepatitis C.[16]

If a patient has a persistently increased ALT level, viral hepatitis serologies should be assayed. If these are negative, the remaining serologic work-up should include an antinuclear antibodies test or anti–smooth muscle antibody test, or both, to evaluate for autoimmune hepatitis; and a fasting transferrin saturation level or unsaturated iron-binding capacity and ferritin level[18] to evaluate for hereditary hemochromatosis.[15] In patients younger than 40 years in whom Wilson's disease is suspected, serum ceruloplasmin and copper levels should be measured,[19] but screening all patients with chronic hepatic injury for Wilson's disease is not indicated.[15]

Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic cholestasis. Testing for a1-antitrypsin (A1AT) deficiency may be of benefit in patients with chronic hepatic injury and no cause. Although the role of A1AT deficiency in liver disease in adults is not clearly defined, testing is especially important in neonates with evidence of hepatic injury.[15] Ultrasonography or biopsy is necessary to establish the diagnosis of NAFLD.

LIVER BIOPSY

Referral for liver biopsy should be considered after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis of liver the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. The sensitivity and specificity for an accurate diagnosis of cirrhosis and its etiology range from 80 to 100 percent, depending on the number and size of the histologic samples and on the sampling method.[24]

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography- or CT-guided fine-needle approaches. Before the procedure, a CBC with platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding.

INVESTIGATION AT A GLANCE

	Components	Aetiology of liver disease	Comments
Imaging modalities			
Ultrasonography	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
CT/MRI	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
Fibroscan	Measurement of liver stiffness	All	Exact cutoffs for specific fibrosis stages and causes not established
Acoustic radiation force impulse imaging	Measurement of liver stiffness	All	Validation is still underway
MR elastography	Measurement of liver stiffness	All	Not widely available; further validation needed
Indirect serum non-invasive fibrosis tests			
APRI	AST, platelets	HBV, HCV	
FIB4	Age, ALT, AST, platelets	HBV, HCV, NAFLD	
AST/ALT	ALT, AST	All	
Forns index	Age, γGT, cholesterol, platelets	HBV, HCV	
Proprietary serum non-invasive fibrosis tests			
Fibrotest	γGT, haptoglobin, bilirubin, A1 apolipoprotein, α2-macroglobulin	HBV, HCV, NAFLD, ALD	Biopredictive, France
ELF	PIIINP, hyaluronate, TIMP-1	HBV, HCV, NAFLD	Siemens, UK
Hepascore	Age, sex, α2-macroglobulin, hyaluronate, bilirubin, γGT	HCV, NAFLD	Pathwest, Australia
Fibrospect II	Hyaluronate, TIMP-1, α2-macroglobulin	HCV	Prometheus, USA
Fibrometer	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	HBV, HCV, NAFLD, ALD	BioLiveScale, France
Combination strategies			
Ultrasonography and Fibroscan	As above	All	Done simultaneously
Fibrotest and Fibroscan	As above	HCV	Done simultaneously; liver biopsy if tests discordant on fibrosis classification
Fibrometer and Fibroscan	As above	HCV	Done simultaneously; results are introduced in a computer algorithm to assess severe fibrosis
APRI and Fibrotest	As above	HCV	Done sequentially; Fibrotest if indeterminate values of APRI

MR=magnetic resonance. APRI=AST-to-platelet ratio index. AST=aspartate aminotransferase. HBV=hepatitis B virus. HCV=hepatitis C virus. FIB4=fibrosis 4 index. ALT=alanine aminotransferase. NAFLD=non-alcoholic fatty liver disease. γGT= γglutamyltranspeptidase. ALD=alcoholic liver disease. PIIINP=N-terminal peptide of type III procollagen. TIMP-1=metallopeptidase inhibitor 1.

Table: **Most commonly used non-invasive tests for diagnosis of cirrhosis[15]**

FIGURE-5 LABORATORY INVESTIGATIONS

POPULATION SCREENING

The increasing burden of liver disease and the problemof late presentation with decompensation emphasise theneed for population screening to identify patients with chronic liver disease, similar to screening for cardiovascular risk factors. In the USA, screening for chronic hepatitis C is cost effective for people born between 1945 and 1965.[23]Non-invasive fibrosis markers could be screening tools in primary care, especially for non-alcoholic fatty liver disease and for alcohol misusers. The NAFLD fibrosis scores for non-alcoholic fatty liver disease is based on simple indices (age,

platelet count, serum albumin, aminotransferases, and diabetes) and has a negative predictive value of 96% for advanced fibrosis.[24] many tests have been used to class patients in the community into three prognostic groups to rationalise secondary referrals. [25] Transient elastograpy is now licensed in the USA, has also been used to classify patients,[26] although specifictest cutoff is yet to be established.[27]

LIFE STYLE CHANGES AND GENERAL MEASURES

Lifestyle changes tend to be overlooked in the management of cirrhosis, because life expectancy is short and the benefit is difficult to measure. Although evidence comes from cohort or case-control studies, lifestyle advice should still be offered to all patients, because it is easily implemented with little risk of side-effects or cost.

Insulin resistance, obesity, and the metabolic syndrome are pathophysiologically linked with non-alcoholic fatty liver disease, but they have deleterious effects irrespective of liver disease aetiology. Obesity is an predictor of cirrhosis in alcoholic liver disease,[28] and the presence of metabolic syndrome is associated with more severe fibrosis and cirrhosis in chronic liver disease.[29] In 161 patients with compensated cirrhosis who were studied and followed up prospectively, obesity was independently associated with clinical decompensation, together with HVPG and serum albumin.[30]

Moreover, insulin resistance and metabolic syndrome were independently associated with liver related mortality in acohort of more than 2500 patients with chronic liver disease.[31]Insulin resistance tells about occurrence of hepatocellular

carcinoma in cirrhosis,[32] and in large cohorts, bothdiabetes[33] and metabolic syndrome[34] increased the risk of hepatocellular carcinoma.

Overweight and obese patients with compensated cirrhosis (clinical stages I and II) should therefore be advised to lose weight to lower their long term risk of liver complications. In patients with decompensated cirrhosis, nutrition maintenance is important to avoid loss of muscle mass. Such patients have low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion, which can also contribute to development of hepatic encephalopathy. In a randomised In a randomised controlled trial (RCT),[35] a nutritional supplement given in the late evening over 12 months resulted in body protein accretion equivalent to 2 kg lean tissue; this approach should therefore be advised in such patients.

Alcohol intake is hazardous in patients with alcoholic cirrhosis but also in those with liver disease of other causes. In alcoholic cirrhosis, alcohol ingestion increases HVPG and portocollateral blood flow[36] these effects are likely also in cirrhosis of other causes thereby increasing the risk of variceal bleeding. Only abstinence from alcohol improves survival in alcoholic cirrhosis.[37]

In patients with chronic hepatitis C, alcohol intake increases the risk of cirrhosis and decompensated liver disease two to three times more, even with moderate intake.[38]Moreover, alcohol intake is an independent risk factor for hepatocellular carcinoma in chronic hepatitis C[39]and non-alcoholic steatohepatitis.[40] Therefore, all patients with cirrhosis irrespective of clinical stage should be advised to abstain from alcohol with relevant counselling if appropriate. Multidisciplinary alcohol care centres which help in deaddiction can lower the risk of acute hospital admission and improve the quality of care.[41]In many centres, avoiding alcohol

irrespective of liver disease aetiology is mandatory for the patient to be considered for liver transplantation.

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses.[42] smoking is independent risk factor with more severe fibrosis in chronic hepatitis C, non-alcoholic steatohepatitis, and primary biliary cirrhosis and possibly increases the risk of hepatocellular carcinoma in chronic hepatitis B.[43]

Cannabis use aggrevates fibrosisin patients with chronic hepatitis C.[44] Smoking cessation therefore should be advocated to prevent progression of liver disease and to facilitate eligibility for liver transplantation. Smoking also increases post-transplant morbidity and mortality.[45]

Antioxidant-rich foods and drinks have a potential preventive role in cirrhosis. Coffee consumption improves all-cause mortality[46]but is also associated with a significant reduction in fibrosis in liver disease of various causes[47] and with reduced risk of hepatocellular carcinomaas shown in a meta-analysis including 2260 patients with hepatocellular carcinoma.[48]For most of the benefits described, at least two cups of coffee daily are needed. In a RCT phase 2, ingestion of dark chocolate blunted the post-prandial HVPG increase in cirrhosis by improving flow-mediated hepatic vasorelaxation and ameliorated systemic hypotension.[49]The same effect on HVPG was noted with short-term administration of ascorbic acid.[50]

Physicians should always bear in mind drug interactions and the possible need for dose reductions when prescribing for patients with cirrhosis.[51]

CAUSE SPECIFIC TREATMENT

Patients with cirrhosis should be treated when possible for the underlying liver disease to stop disease progression; such treatment includes immuno suppression for auto autoimmune hepatitis, venesection for haemochromatosis, and copper chelators or zinc for Wilson's disease.

Patients with viral hepatitis should be assessed for antiviral treatment. All patients with cirrhosis who are positive for HBsAg should receive oral antiviral therapy with a potent antiviral (entecavir or tenofovir) irrespective of viral load.[52] Oral antiviral therapy reduces HVPG53 and delays clinical progression to decompensation in responders.[54] Treatment with tenofovir for 5 years resulted in regression of cirrhosis associated with hepatitis B virus in 71 (74%) of 96 treated patients.[5]

Inpatients with hepatitis-C-related cirrhosis withoutascites, achievement of low viral loadsignificantly reduced liver-related morbidity and mortality.[6] In a subgroup of patients, there was also regression of cirrhosis.[6]This strategy is also valid for patients with hepatitis C listed for liver transplantation because of hepatocellular carcinoma rather than complications of portal hypertension, because achievement of sustained virological response reduces post-transplant recurrence of hepatitis C, which is otherwise universal.[55] The newly licensed direct-acting antiviral drugs boceprevir and telaprevir increase rates of sustained virological response in patients with genotype 1.[56,57]

Supplementary strategies that can increase sustained response rates in this difficult-to-treat group of patients, as shown in cohort studies, include weight loss in

obese patients,[58] vitamin Dsupplementation when concentrations are low,[59] statinsin patients with diabetes,[60] and coffee drinking.[61]Patients with cirrhosis who respond to antiviral treatment still need regular surveillance for hepatocellular carcinoma, because the risk, although reduced, is not eliminated.[6,62]

PORTAL HYPERTENSION AND VARICEAL BLEED

Portal hypertension, rather than hepatocyte failure per se is cause for most of the complications of cirrhosis and subsequent mortality. HVPG is a good surrogate marker of portal hypertension and has robust prognostic power.[63]Portal hypertension is present when the HVPG is more than 5 mm Hg.

However, clinically significant portal hypertension andthe threshold for development of oesophageal varices isabove 10 mm Hg.[64]Patients with HVPG of less than 10 mm Hg had a 90% probability of not progressing to decompensation during median follow-up of 4 years,[65] whereas for those with HVPG of more than 10 mm Hg the incidence of hepatocellular carcinoma was six times higher than in patients with lower HVPG.[66]

Formation of oesophageal varices is the first clinically relevant consequence of portal hypertension and represents clinical stage 2 of cirrhosis. Current recommendations are that all patients with cirrhosis should be screened for varices.[67]The risk of development and growth of varices is 7% per year,[68] and that of first variceal bleeding is 12% per year.[69]

Non-selective β blockers and endoscopic band ligation are equally effective inprevention of bleeding and reduction of mortality, as shown in a meta-analysis that included only high-quality trials.[70] Results from a large meta-analysis of non-selective

β blockers versus placebo showed that the number of patients needed to treat with non-selective β blockers to prevent one death is 16.[71]Non-selective β blockers decrease cardiac output and cause splanchnic vasoconstriction thereby reducing portal inflow, as well as decreasing azygous vein blood flow and variceal pressure, which is more pronounced than the reduced portal inflow.[72] They can also reduce total effective vascular compliance.[73] Carvedilol is a β blocker with vasodilating properties resulting from α1-blockade; it decreases intrahepatic vascular resistance, which leads to a greater fall in HVPG than with conventional non-selectiveβ blockers.[74]

In one RCT, carvedilol was better than endoscopic band ligation for primary prophylaxis ofbleeding.[75] A decrease in HVPG of at least 20% or to less than 12 mm Hg is associated with a significant reduction in variceal re-bleeding compared with patients in whom these changes are not achieved, and defines patients receiving non-selective β blockers as responders.[76] assessing acute haemodynamic response to propranolol could be a substitute for repeated HVPG measurements, because it predicts the risk of first bleeding,[77] with HVPG reduction cut off s of 10%[77]and 12%[78] in prospective and retrospective studies, respectively.

HVPG is not measured routinely, so non-selective β blockers are generally titrated to the maximum tolerated dose, aiming at a heart rate of below 60 bpm.[69]Side-effects of fatigue, hypotension, and shortness of breath preclude their use in 15–20% of patients; however, specialised nurse-led clinics help to minimise withdrawal and enable successful dose titration.[79]

Endoscopic band ligation is done by placing rubber elastic bands on medium or large varices; it is repeated until the lesions are eradicated. We advocate use of non selective β blockers as primary prophylaxis, because they are cheap and effective and obviate the need for the expertise that endoscopic band ligation requires.[80]Moreover,

non-selective β blockers also prevent bleeding from portalhypertensive gastropathy and also have other beneficial effects. Endoscopic band ligation has a small iatrogenic risk of death, owing to bleeding from post-banding ulcers.[80]

In one RCT[81] simvastatin lowered HVPG and improvedliver haemodynamics in patients with cirrhosis andvarices, and this effect was additive to that of nonselective β blockers. Statins reduce the incidence of hepatocellular carcinoma in diabetes[82]and are not associated with an increased risk of hepatotoxicity in cirrhosis,[83]these drugs could be given to patients with cirrhosis and hyperlipidaemia. Trials in non-hyperlipidaemic patients are in progress.

ASCITIS

In cirrhosis, portal hypertension and splanchnic vasodilation, resulting mainly from increased production of nitric oxide,[90] is the main pathophysiological mechanism of ascites The effective blood volume is initially maintained and as a result of a compensatory increase in cardiac output. However, as cirrhosis progresses, this mechanism is not sufficient and homoeostatic activation of vasoconstrictor and antinatriuretic factors develops, with subsequent water and salt retention.[91]Fthus, the retained fluid accumulates in the peritoneal cavity as a result of increased portal pressure and forms ascitis. The development of renal vasoconstriction leads to the hepatorenal syndrome.

Type 1 hepatorenal syndrome is characterised by a doubling of serum creatinine concentrations within 2 weeks, whereas type 2 has a stable, less progressive course. The development of ascites is associated with a 1-year mortality rate of

20%.[3]Renal failure is an index of end-stage liver disease and increases the risk of mortality by seven times, with 50% of patients dying within a month.[17]

Reduction of the HVPG should prevent formation of ascites. In 83 patients with large varices followed up for a mean of 53 months, propranolol prevented ascites if it lowered the HVPG by 10% or more.[92]In patients with a new presentation of ascites, a diagnostic tap should be used to screen for underlying infection.[93] When no underlying cirrhosis is evident, a gradient between serum and ascites fluid in albumin concentration of 11 g/L or more is very accurate for diagnosis of portal hypertension.[91]

Treatment of ascits of education of the patient about limiting dietary sodium to 80–120 mmoles daily (4·0–6·9 g/day) and oral diuretic treatment. Diuretic therapy should start with a morning dose of spironolactone 100 mg with or without furosemide 40 mg. An RCT showed that combined therapy is associated with better responses than sequentialtherapy.[94]

Current European guidelines advices equential treatment for first presentation of ascites and combination therapy from presentation for recurrent ascites.[95] Renal function and serum electrolyte concentrations should be monitored during diuretic treatment, particularly when doses are being gradually increased to achieve adequate weight loss, which should not exceed 1 kg per day in patients with peripheral oedema or 0·5 kg per day in those without. Maximum doses of 400 mg spironolactone and 160 mg furosemide are suggested, but few patients tolerate these doses without developing renal dysfunction.

Random measurement of urinary sodium concentration in these patients is useful to monitor adherence to low-salt diet and response to diuretics.[91] Ascites that does not respond to maximum tolerated diuretic doses is termed refractory.[91]Midodrine together with standard medical treatment was superior to standard treatment alone in an RCT investigating recurrent or refractory ascites; it also improved systemic haemodynamics.[96] Refractory or difficult-to-control ascites necessitates an assessment for liver transplantation. Such patients should be treated by large-volume paracentesis with intravenous albumin administration (8 g/L) when the volume drained exceeds 5 L, to reduce the risk of postparacentesis circulatory syndrome.[97]

An alternative approach that significantly improves transplant-free survival is a transjugular intrahepatic portosystemic shunt for patients with refractory ascitesand preserved synthetic function.[98]A combination of serum bilirubin concentration below 50 μmol/L and a platelet count above 75 $\sim 10^9$/L was predictive of survival in 105 patients with refractory ascites treated in this way.[99]but the complication like hepatic encephalopathy should be kept in mind.

Non-steroidal anti-inflammatory drugs should not be given to patients with ascites, because their renal function is highly dependent on renal prostaglandin synthesis and it precipitates renal failure can be induced.[95]Similarly, although inhibitors of angiotensin-converting enzyme reduce portal pressure and can potentiate or substitute for non-selective β blockers in patients with varices and no ascites,100 they should be stopped if ascites develops.101 Aminoglycosides are associated with a high incidence of nephrotoxicity so other antibiotics should be used if possible.[95] A single retrospective study reported reduced survival in patients with refractory ascites

whoreceived propranolol, attributed to paracentesis-induced circulatory dysfunction.102 However, the doses used were large and rarely administered in routine clinical practice, so decisions should be made on an individual basis with close monitoring.[103]

INFECTION

Infection increases mortality in cirrhosis four times and has a poor prognosis, with 30% of patients dying within a month of infection and another 30% within a year.[16]

Most frequently seen are spontaneous bacterial peritonitis, urinary-tract infections, pneumonia, and skin infections; the incidence increases with worsening liver function.[93,104] Decreased bowel motility, bacterial overgrowth, and increased intestinal permeability all increase the risk of the translocation of intestinal microbiota to the mesenteric lymph nodes,[105] which predisposes patients to infection, most commonly spontaneous bacterial peritonitis, but is also the source of endotoxin and other bacterial products that influence systemic haemodynamics.[106] Genetic polymorphisms also predispose to spontaneous bacterial peritonitis and patients are at increased risk.[107] Bacterial DNA in non-infected patients with cirrhosis is associated with aggravation of peripheral vasodilation and worsening of intrahepatic endothelial dysfunction;[108] it is also associated with poor prognosis.[109] Defects in Kupffer cells and neutrophilfunction[110] and an exaggerated proinflammatory response of mononuclear cells[111]are commonly present and predispose to a poor outcome.

A meta-analysis showed that non-selective β blockers reduced the incidence of spontaneous bacterial peritonitis in patients with ascites, probably by increasing

bowel motility and thus decreasing bacterial translocation.[112] Intestinal permeability also improved and this effect is partly independent of the haemodynamic response.[113] Indeed, in a rat model of cirrhosis, splanchnic sympathectomy reduced bacterial translocation. [114]

An RCT showed that selective intestinal decontamination with oral norfloxacin for 2 weeks partly reverses the hyperdynamic circulation of cirrhosis, without influencing the hepatic and renal circulation. [115] Primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin improves survival in patients with advanced cirrhosis or impaired renal function and low ascites protein concentrations (<15 g/L).116 Since the risk of infections with quinolone-resistant bacteria is high, we advocate primary prophylaxis only in patients listed for liver transplantation, because the period of administration is short and patients can be maintained in better condition. By contrast, secondary prevention with oral quinolones to be given to all patients with a previous episode of spontaneous bacterial peritonitis.[91] No best strategy for prevention, if spontaneous bacterial peritonitis with quinolone-resistant organisms develops, has been established; available options include no prophylaxis or a rolling scheme of antibiotics.

Spontaneous bacterial peritonitis is diagnosed if ascetic neutrophil count is more than 250 per μL and can be asymptomatic.[95] Treatment consists of intravenous antibiotics and human albumin. The choice of antibioticsis influenced by previous quinolone prophylaxis, local prevalence of bacterial strains, and weather infection is community borne or hospital acquired . A 5-day course of intravenous cefotaxime is generally sufficient in most community-acquired cases.[117]An RCT showed that intravenous albumin (1·5 g/kg on day 1 and 1·0 g/kg on day 3) lowers the risk of

renal impairment and death from 30% to 10%.[118] This effect is possibly limited if bilirubin concentration is more than 68·4 μmol/L or creatinine more than 88·4 μmol/L.119In an RCT of 110 patients with infections that excluded spontaneous bacterial peritonitis, albumin also showed beneficial effects on renal and circulatory function, but not on survival.[120] Proton-pump inhibitor use is to be resistricted in cirrhosis with ascites, because the risk of spontaneous bacterial peritonitis is 4·3 times higher than without such treatment,[121]and should be avoided in inpatients (except for those with peptic ulcer bleeding), because the risk of infection with *Clostridium difficile* is increased.[122]

ENCEPHALOPATHY

The development of encephalopathy is an ominous sign in cirrhosis, because the associated 1-year mortality rateis up to 64%.123 Patients who develop encephalopathy despite preserved liver function have to be checked for presence of spontaneous portosystemic shunts. Embolisation of large shunts is safe and effective in selected patients.[124] Overt encephalopathy is generally transient and linked with a precipitating event, such as use of sedatives, constipation, dehydration, infection, or gastrointestinal bleeding or infection. Lactulose is the first-choice drug for prevention of recurrent encephalopathy; in an RCT, the risk of recurrent encephalopathy was 20% compared with 47% in placebo-treated patients ients.[125] L-ornithine-l-aspartate is equivalent to lactulose as a first-line treatment.[126]Rifaximin, a non-absorbable antibiotic, is effective when added to lactulose if encephalopathy recurs; it reduces the risk of further recurrence from 46% to 21%.[127] Subclinical encephalopathy or minimal hepatic encephalopathy is more common than overt encephalopathy, and influences co-ordination of patient and hinders skilful work , leading to increased risks of

accidents.128 A cost-effectiveness analysis concluded that patients with cirrhosis who drive should be screened for minimal hepatic encephalopathy, and treated with lactulose if necessary.[129] Rifaximin significantly improved driving simulation skills in an RCT of 42 patients with the disorder,[128] but it is not currently cost effective. [129] Minimal hepatic encephalopathy is significantly associated with risk of falling.[1] and should be detected early and treated

HEPATOCELLULAR CARCINOMA

Guidelines recommend 6-monthly ultrasonographic screening, it is commonly associated with cirrhosis secondary to hepatotropic viruses because it results in more effective treatment of smaller hepatocellular carcinomas, although this approach has been inadequately assessed by RCTinvestigations. However, routine surveillance occurred inonly 12% of a US cohort of 13 002 patients with cirrhosis.[131] The carcinoma can develop in all stages of cirrhosis, of all causes.[39]

LIVER TRANSPLANTATION

Liver transplantation is a therapeutic option in patients who develop decompensation or hepatocellular carcinoma with cirrhosis. Listing, prioritisation, and organ allocation are decided on the basis of scores for reasons of equity, owing to the shortage of donor organs.The indications and contraindications for transplantation are given in the panel. The most commonly used scores are MELD in the USA and UKELD in the UK. It has its own advantages and disadvantages.

Indications

Cirrhosis with decompensation

Generally for patients with clinical stage 3 and above—ie, at least with ascites as assessed by disease-severity scores; intractable pruritus, recurrent cholangitis, and hepatopulmonary syndrome are potential exceptions of listing on the basis of such scores.

Hepatocellular carcinoma with background cirrhosis

Most centres use the Milan criteria for listing—one lesion ≤5 cm or no more than three lesions ≤3 cm each with no macrovascular invasion and no extrahepatic disease.

Contraindications

Active illicit substance misuse

Patients on drug substitution such as methadone are not generally excluded.

AIDS

Controlled HIV infection alone is not a contraindication. HIV and hepatitis C virus co-infection is a contraindication in some centres.

Extrahepatic malignancy

Neuroendocrine tumours and haemangio endotheliomas are a possible exception in selected cases.

Uncontrolled sepsis

Transplantation contraindicated until infection is successfully treated.

Extrahepatic organ failure (lungs, heart)

Echocardiography and if needed catheterisation are essentialin liver transplant work-up; pulmonary pressure of >50 mm Hg despite medical treatment is an absolute contraindication.

Extensive splanchnic thrombosis extending to the superior mesenteric vein

AUTONOMIC DYSFUNCTION IN CIRRHOSIS OF LIVER

Liver cirrhosis is associated with complex cardiovascular changes, including hyperdynamic circulation with increased blood volume, increased cardiac output and reduced peripheral vascular resistance [15,67]

Autonomic dysfunction is common in liver cirrhosis, both in alcoholic and non-alcoholic and is associated with the severity of hepatic dysfunction and survival

The pathogenesis of autonomic neuropathy in cirrhosis is not fully known and several mechanisms are suggested:

1) circulatory changes in cirrhosis,
2) metabolic and neurohormonal alterations including renin angiotensin aldosterone system
3) excessive nitric oxide production,
4) oxidative stress and inflammatory mediators (interleukines)

The prevalence autonomic dysfunction (AD) in cirrhosis has varied from 8% - 80% in different series. Its occurrence is irrespective of the etiology of chronic liver disease: ethanol or non ethanol related.[9-14]and increases in parallel with the severity of

liver disease. Other factors contributing to AD in cirrhosis include that affecting nerve integrity such as alterations in lipid metabolism, vitamin E deficiency, alcohol consumption, immunologic mechanisms and retention of toxic metabolites.[15,16] Vagal dysfunction due to elevated angiotensin II production and sympathetic dysfunction due to blunted responsiveness owing to either a production of weak neurotransmitters or a receptorial & postreceptorial defect has been documented.[4,17,20] Presence of AD irrespective of the cause is often associated with an adverse prognosis.[16,21,23]

DOES AUTONOMIC DYSFUNCTION INFLUENCE VARICIEAL BLEED

How does AD influence a bleed? Normally in ahealthy individual, following a bleed, primarily there is a reduction in the splanchnic blood pool, and redistribution of the blood into the systemic circulation. This stimulates the cardiovascular responses by increasing the heart rate and blood pressure. In presence of AD, the vasoconstrictivephenomenon of the splanchnic circulationis lost and the secondary cardiovascular responses are ineffective. In cirrhosis of the liver, there is primarily an increase in splanchnic blood pool. In presence of AD, a variceal bleed will fail to elicit cardiovascular response reflex and in fact may further increase the splanchnic blood pool further increasing the risk of further variceal bleed. To test this hypothesis, we under took a study to determine the risk of variceal bleed and bleed related mortality in cirrhotics with AD, with a basic understanding that the splanchnic vascular bed is richly innervated and is the major site of autonomic regulation during orthostatic stress.

MEASURMENT OF AUTONOMIC DYSFUNCTION

	Method
Active standing (parasympathetic) ≥ 1.04 normal 1.01–1.03 borderline < 1.0 abnormal	Wearing an ECG monitor the subject rests supine to achieve stable baseline HR levels. The subject then stands and the ratio is calculated of the longest RRI (around the thirtieth beat) to the shortest RRI (around the fifteenth beat)
Deep breathing (parasympathetic) > 9 bpm normal (age > 60) ≥ 15 bpm normal (age < 60) 11–14 bpm borderline ≤ 10 bpm abnormal	With ECG monitoring in a sitting position the patient breathes deeply and evenly at 6 breaths per minute. The maximum and minimum HR during each cycle is noted for 3 consective cycles. The mean difference between maximum and minimum HR is calculated
Valsalva (parasympathetic) ≥ 1.11 normal (age > 60) 1.11–1.2 borderline ≥ 1.21 normal (age < 60)	After resting, the patient expires for 15 seconds against a closed glottis (pressure of 40 mmHg). The ratio of the longest RRI just after the valsalva, and the short RRI during the strain, is calculated
Valsalva (sympathetic) In normal patients there will be a BP overshoot shortly after releasing the strain	The same method as for valsalva (parasympathetic) but BP is recorded
Isometric exercise (sympathetic) ≥ 16 mmHg normal 11–15 mmHg borderline ≤ 10 mmHg abnormal	Using a dynamometer, hand grip is maintained at 30% of maximum grip for 5 minutes. Diastolic pressure is measured before exercise and just before release, the difference is calculated
Cold pressor (sympathetic) ≥ 15 mmHg normal 11–14 mmHg borderline ≤ 10 mmHg abnormal	One hand is held in iced water for 1 minute. Diastolic BP is measured, before and after, the increase is calculated
Dysautonomia may be classified as: • None: all tests normal or borderline • Early: one abnormal HR test or two borderline • Definite: two or more abnormal HR tests • Severe: two or more HR rate tests abnormal, plus one borderline or abnormal BP test • Atypical: any other combination of abnormal tests	

FIGUER -6 MEASURMENT OF AUTONOMIC DYSFUNCTION

METHODOLOGY

The present study was conducted in the department of General Medicine at KLES Dr Prabhakar Kore Hospital and Medical Research Centre Belagavi from January 2015 to December 2015.

STUDT DESIGN

The study design was a One year Cross-Sectional study

STUDY PERIOD

The present study was carried out from January 2015 to December 2015

SOURCE OF DATA

All patients admitted with cirrhosis of liver with various aetiology in department of General Medicine.

SAMPLE SIZE

A total of 100 patient with cirrhosis of liver were included in the study

SAMPLINIG PROCEDURE

Based on this formula a sample size of 100 patients was considered

Sample size : 100

Sample size calculation : $4pq/d^2$

56% sensitivity

10% error

0.6% prevalence

p-sensitivity (80)-as obtained from previous studies , q(100-p),

d-absolute error

INCLUSION CRITERIA

- All patients with CIRRHOSIS OF LIVER diagnosed either by clinical examination, laboratory parameters, ultrasonographic findings and admitted in KLE hospital Belagavi.

EXCLUSION CRITERIA

Coronary heart disease/ Heart failure

Arrhythmias

pericardial effusion

Diabetes mellitus

Hypertension

Chronic obstructive pulmonary Disease

Renal failure

Drugs known to produce autonomic abnormalities such as tranquilizers, antidepressants, calcium channel blockers but not limited to

ETHICAL CLEARENCE

Prior to the beginning, the study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College Belagavi.

INFORMRED CONSENT

The patients who fulfilled the selection criteria were informed about the nature of study and a written informed consent was obtained (annexure-1)

DATA COLLECTION

Patients were interviewed and demographic data, history of present illness, other co-morbid conditions, personal history were obtained. Further these patients underwent clinical examination followed by systemic examination. These findings were noted on a predesigned and pretested proforma (annexure-2)

INVESTIGATIONS CARRIED OUT

- Complete haemogram/peripheral smear
- Liver function tests
- Renal function tests
- Urine routine
- Electrocardiography
- HCV/ HbsAg

AUTONOMIC FUNCTION TESTS[1]

- Active standing
- Deep breathing
- Valsalva
- Isometric exercise
- Cold pressor
- Valsalva-BP

STATISTICAL METHODS

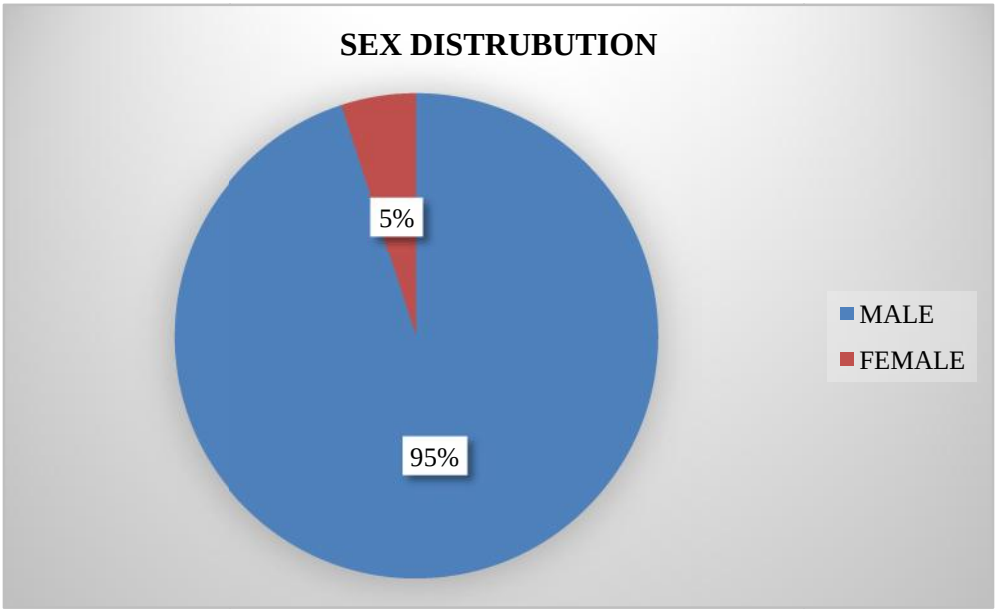
The data obtained was entered into the Microsoft excel spreadsheet (annexure-3). The categorial data was expressed in terms of rates, ratios and percentages and comparision was done using chi-square test. The continuous data was expressed as mean +- standard deviation and comparison was done using independent 't' test. A Probability value (p- value) of less than or equal to 0.05 was considered as statistically significant.

RESULTS

TABLE 1 : SEX DISTRUBUTION

SEX	NUMBER	PERCENT
MALE	95	95
FEMALE	5	5
TOTAL	100	100

GRAPH 1- GENDER DISTRIBUTION



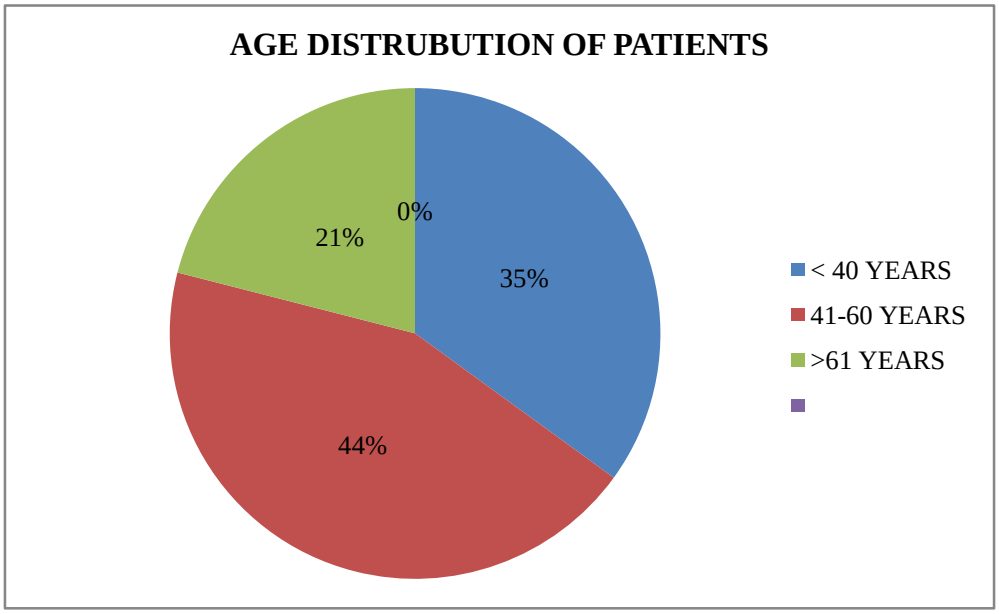
Out of 100 patients, 95 (95%) were males and 5 (5%) were females, accounting a ratio of male to female 19:1

INFERENCE : Male predominance was seen

TABLE 2 : AGE DISRUBUTION

AGE GROUPS	NUMBER	PERCENT
<40 YEARS	35	35
41-60 YEARS	44	44
>60 YEARS	21	21
TOTAL	100	100.0

GRAPH 2 – AGE DISTRUBUTION

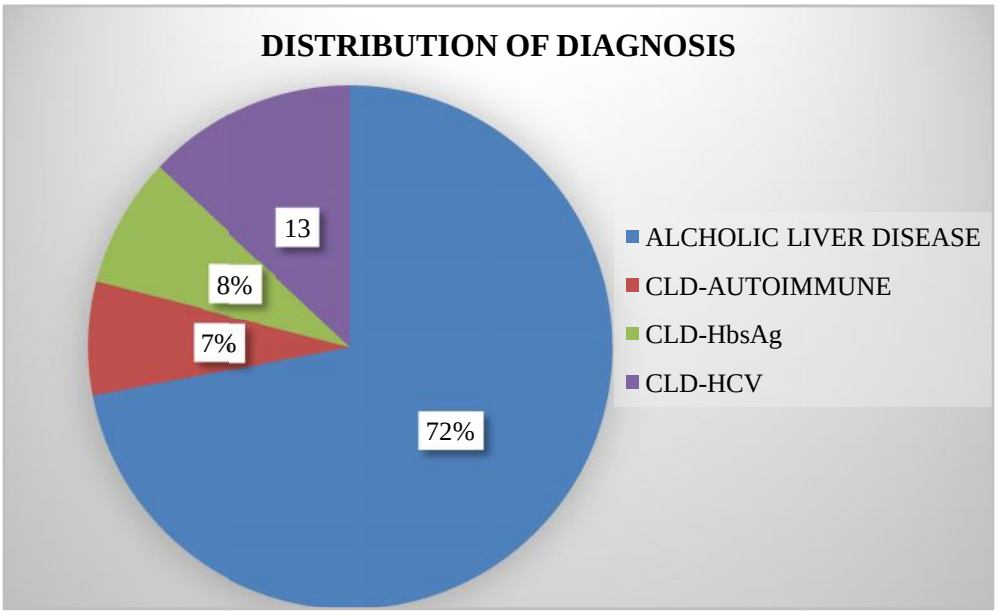


Patients age ranged from 22-80 years, maximum number of cases were in age group of 41-60 years that is 44 patients (44%) between age group below 40 years 35 patients (35%) and above 60 years 21 patients (21%).

TABLE-3 DIAGNOSIS OF PATIENTS

Diagnosis	male	female	Total
ALD	72	0	72
CLD-autoimmune	6	1	7
CLD-HBSAG	6	2	8
CLD-HCV	11	2	13

GRAPH-3 DIAGNOSIS OF PATIENTS

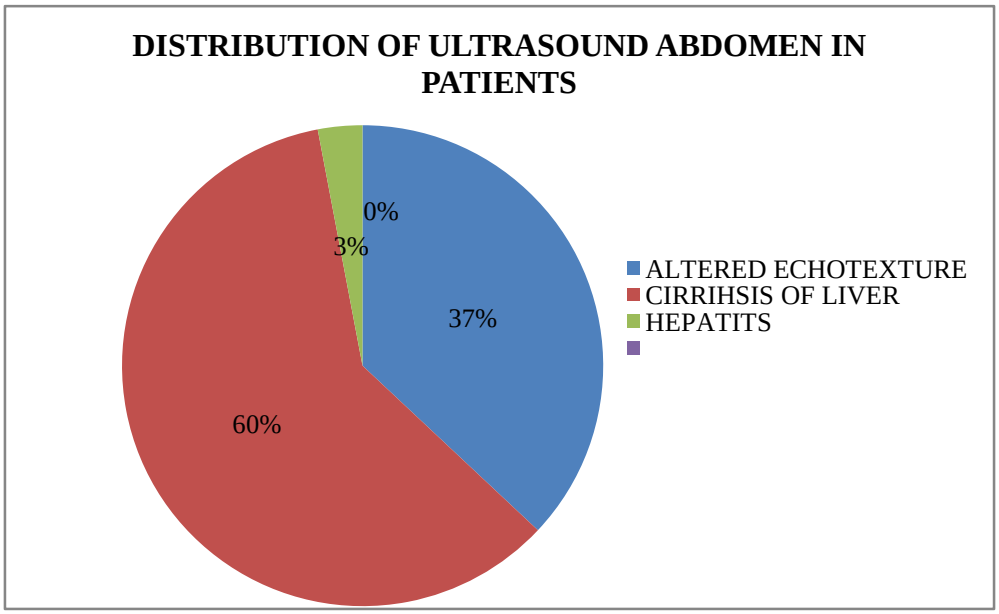


In our study majority of of patients, that is 72 (72%) were of alcoholic liver disease, 11 patients (11%) were of CLD-HCV , 8 patients were of CD-HBV and 7 patients were of CLD due to autoimmune cause.

TABLE-4 DISTRIBUTION OF ULTRASOUND ABDOMEN REPORT

ULTRASOUND-FINDING	NUMBER	PERCENT
ALTERED ECHOTEXTURE	37	37
CIRRHOSIS OF LIVER	60	60
HEPATITIS	3	3
TOTAL	100	100

GRAPH- 4 : ULTRASOUND ABDOMEN FINDINGS

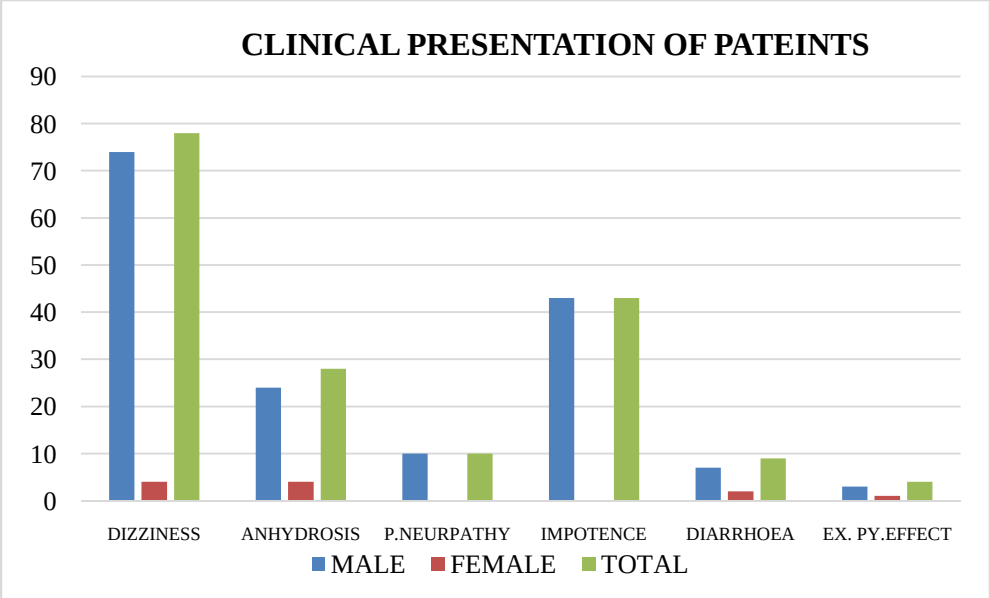


In our study 60 patients (60%) had cirrhosis of liver as their USG finding, 37 patients (37%) had altered echotexture and 3 patients had hepatitis as their USG finding but they were chronic alcholics.

TABLE -5 CLINICAL PRESENTATION

SYMPTOMS	MALES	FEMALES	TOTAL
DIZZINESS	74	4	78
ANHYDROSIS	24	4	28
P.NEURPATHY	10	0	10
IMPOTENCE	43	0	43
DIARRHOEA	7	2	9
EX. PY.EFFECT	3	1	4

GRAPH- 5 : CLINICAL PRESENTATION



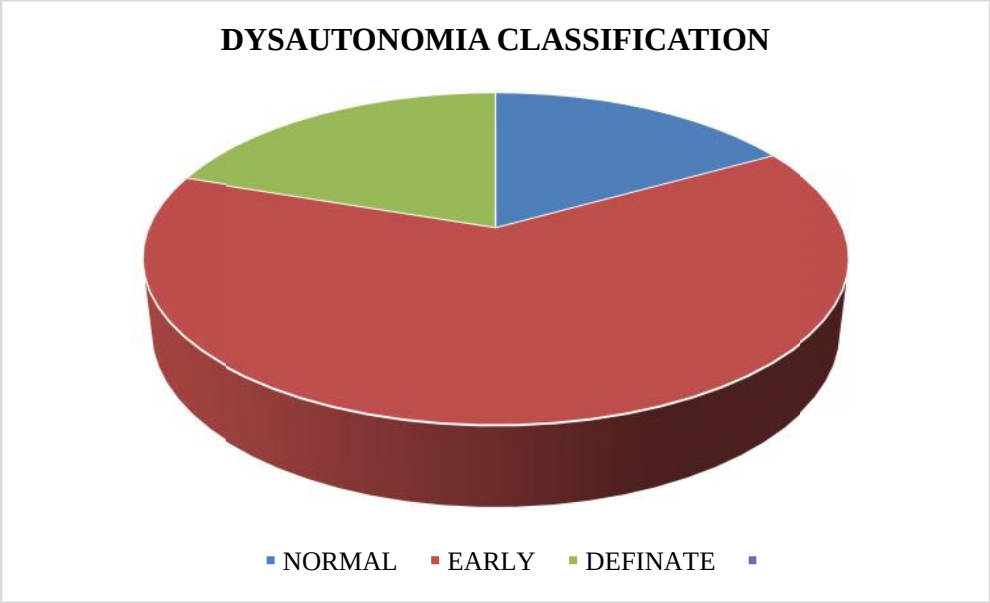
In our study 78 patients had dizziness as their main complaint , followed by impotence in 45 patients and 28 patients had anhydrosis as their complaint , 10 patients had peripheral neuropathy, 9 patients had diarrhoea which was not related to lactulose intake, and 4 patients had extra-pyramidal sympotoms.

TABLE-6 DISTRIBUTION OF PATIENYS BASED ON THEIR SEVERITY GRADING OF DYSAUTONOMIA

DYSAUTONOMIA CLASSIFICATION	NO. OF PATIENTS	% OF PATIENTS
NORMAL	17	17
EARLY	63	63
DEFINATE	20	20
TOTAL	100	100

P value- <0.05

GRAPH-6 : DYSAUTONOMIA CLASSIFICATION



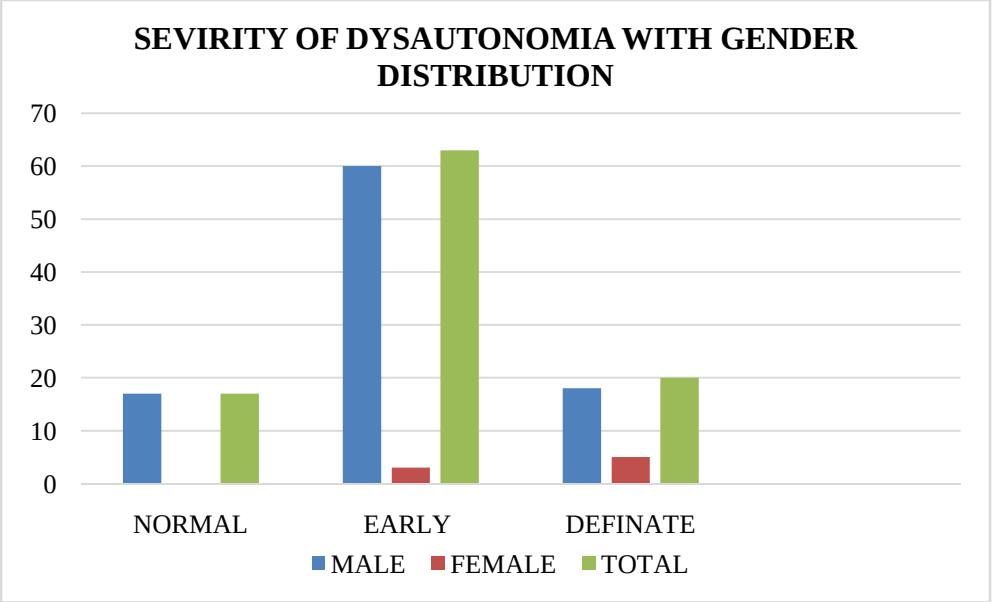
In the present study amoung 100 patients, 63 patients(63%) had early dysautonomia, 20 patients(20%) had definite dysautonomia and 17 patients(17%) were normal. P value being stastically significant

TABLE-7 CORELATION OF SEVIRITY OF DYSAUTONOMIA WITH GENDER DISTRIBUTION

DYSAUTONOMIA CLASSIFICATION	MALE	FEMALE	TOTAL
NORMAL	17	0	17
EARLY	60	3	63
DEFINATE	18	2	20
TOTAL	95	5	100

P value- 0.372

GRAPH-7 : DYSAUTONOMIA WITH GENDER DISTRIBUTION



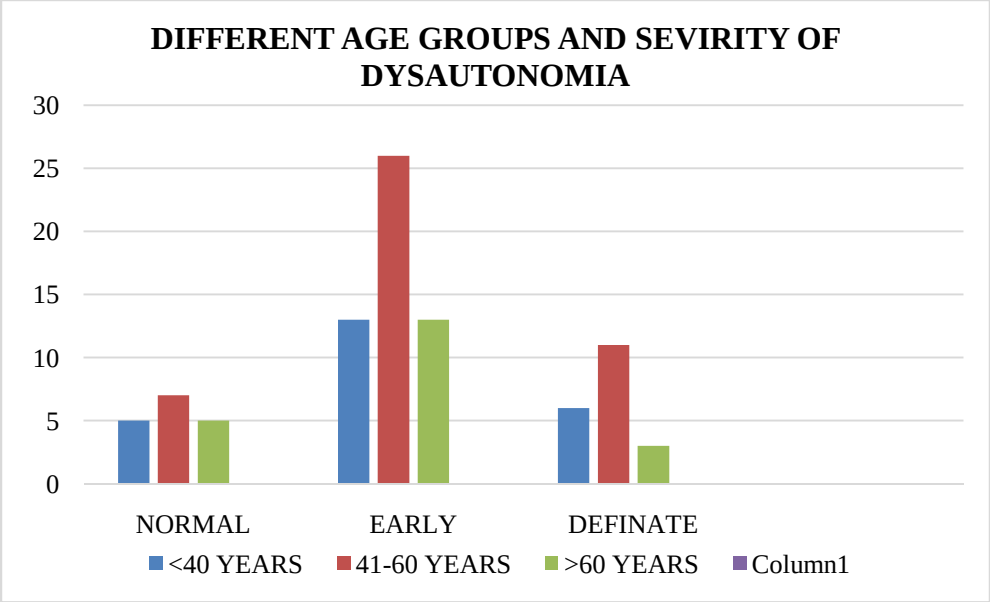
In our study we found out that 63 patients had early dysautonomia amoung them 60 were male patients and 3 were female patients,20 patients had definite dysautonomia, with 18 male and 2 female patients, 17 were absolutely normal.

TABLE-8 CORELATION BETWEEN DIFFERENT AGE GROUPS AND SEVIRITY OF DYSAUTONOMIA

DYSAUTONNOMIA CLASSIFICATION	<40 YEARS	41-60 YEARS	>60 YEARS	TOTAL
NORMAL	5	7	5	17
EARLY	24	26	13	63
DEFINATE	6	11	3	20
TOTAL	35	44	21	100

P value- 0.002

GRAPH-8 : DYSAUTONOMIA WITH DIFFERENT AGE GROUPS



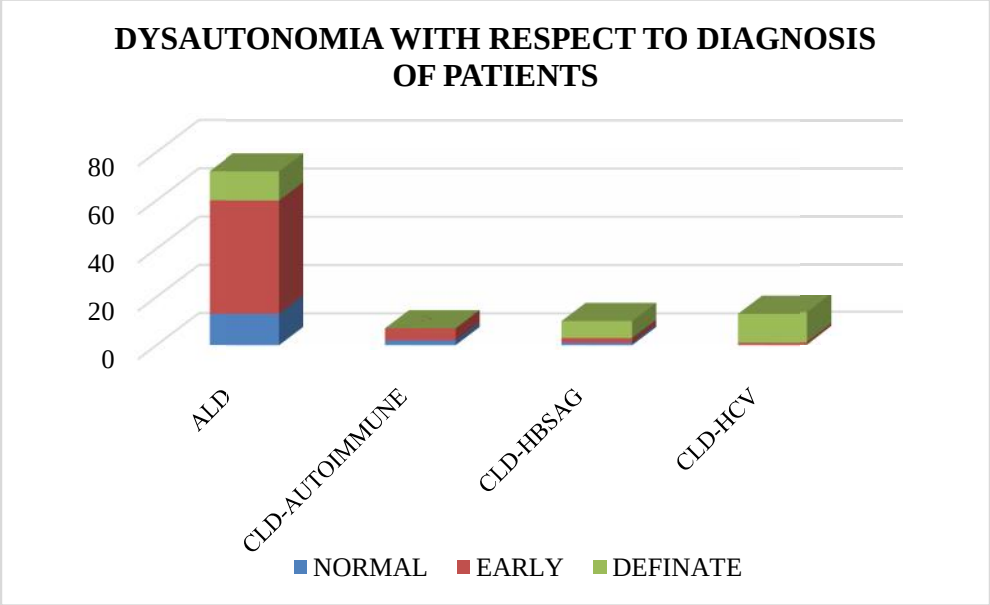
In this study we found that maximum number of patients with dysautonomia were from age group of 41-60 years, then were patients belonging to age group <40 years and last was patients age above 60 years

TABLE-9 ASSOCIATION BETWEEN SEVIRITY OF DYSAUTONOMIA WITH DIAGNOSIS

DIAGNOSIS	NORMAL	EARLY	DEFINATE	TOTAL
ALD	13	47	12	72
CLD-AUTOIMMUNE	2	5	0	7
CLD-HBSAG	1	1	6	8
CLD-HCV	0	1	12	13

P value-0.03

GRAPH-9: DYSAUTONOMIA WITH RESECT TO DIAGNOSIS OF PATIENTS



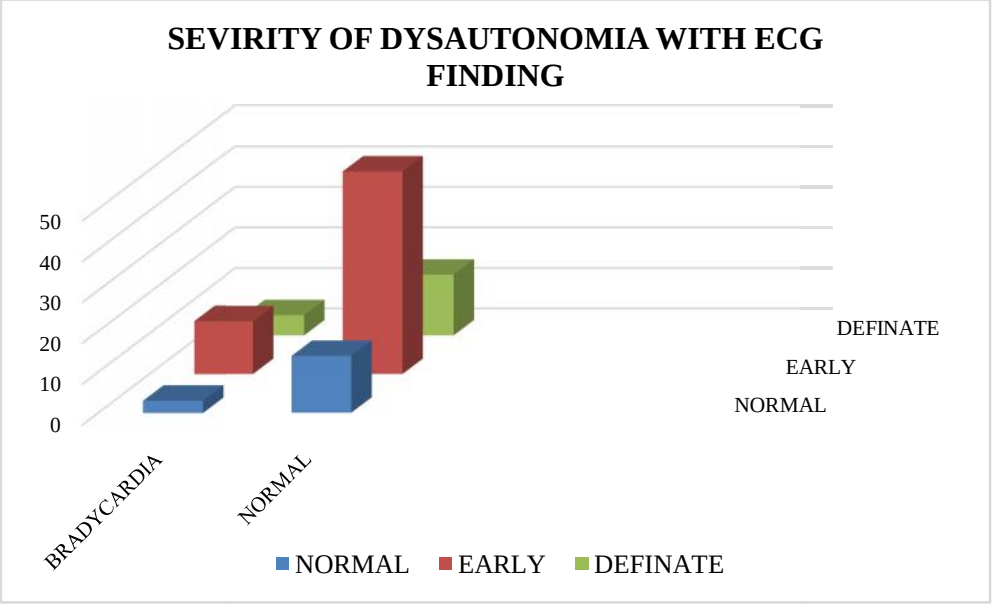
In our study we observed that out of 72 ALD patients 47 had early dysautonomia, 13 had definite dysautonomia. Out of 7 patients with CLD-AUTOIMMUNE 5 had earl dysautonomia, in 8 patients with CLD-HBSAG, 6 had definite dysautonomia, 1 had early dysautonomia. In 13 patients with CLD-HCV 12 had definite dysautonomia and 1 had early dysautonomia.

TABLE-10 SEVIRITY OF DYSAUTONOMIA WITH RESPECT TO ECG FINDING

ECG	NORMAL	EARLY	DEFINATE	TOTAL
BRADY	3	13	5	21
NORMAL	14	50	15	79

P value- 0.234

GRAPH-`10: DYSAUTONOMIA WITH RESPECT TO ECG FINDINGS

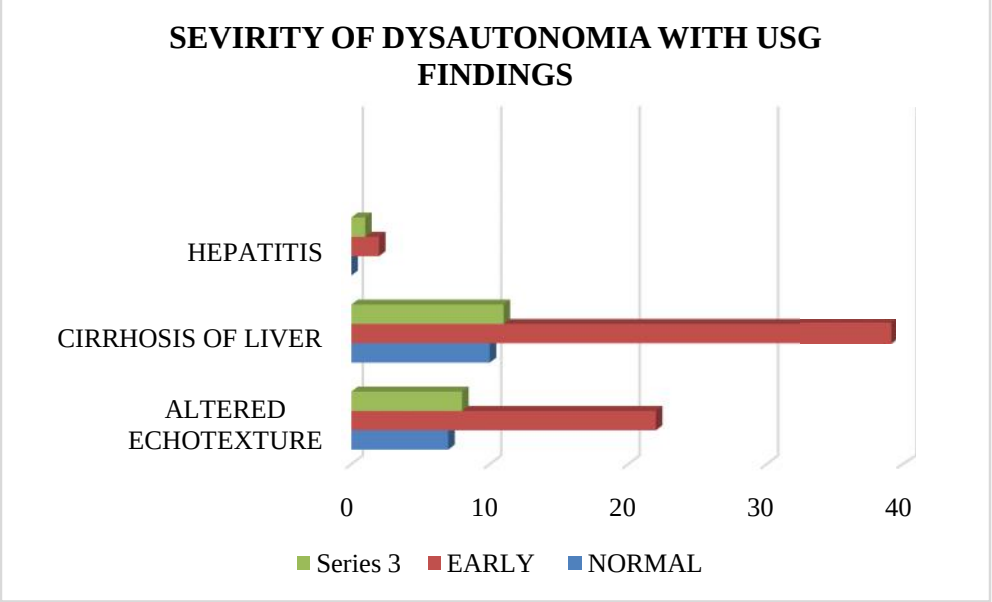


In this study we found that 21 patients had bradycardia, of that 13 patients had early dysautonomia, 3 had definite dysautonomia. 79 patients had normal ECG

TABLE-11 CORELATION OF SEVIRITY OF DYSAUTONOMIA WITH USG FINDINGS

USG ABD	NORMAL	EARLY	DEFINATE	TOTAL
ALTERED ECHOTEXTURE	7	22	8	37
CIRRHOSIS OF LIVER	10	39	11	60
HEPATITIS	0	2	1	3
Chi-square=1.1114 p=0.8925				

GRAPH 11 : DYSAUTONOMIA WITH USG ABDOMEN FINDINGS



From the USG findings of all patients, out of 60 patients with cirrhosis of liver, 39 had early dysautonomia, 11 had severe dysautonmia .37 patients had altered echotexture of liver with fatty infiltration, in them 22 had early dysautonomia and 8 had definite dysautonomia, 2 patients with hepatitis had early dysautonomia and 1 had definite dysautonomia.

TABLE-12 : CLINICAL OBSERVATIONS

			<=40yrs	41-60yrs	>=61yrs	Total	F-value	P-value
Pulse rate	Lying	Mean	71.74	68.43	62.76	68.40	9.1573	0.0002*
		SD	7.11	7.96	7.63	8.21		
	Sitting	Mean	70.51	66.93	61.57	67.06	9.3928	0.0002*
		SD	6.87	8.15	6.96	8.09		
	Standing	Mean	68.11	65.66	59.48	65.22	5.1494	0.0075*
		SD	12.89	7.99	6.98	10.23		
SBP	Lying	Mean	113.14	109.00	106.19	109.86	3.1886	0.0456*
		SD	12.40	9.42	8.65	10.65		
	Sitting	Mean	70.34	68.18	65.71	68.42	2.6096	0.0787
		SD	7.93	7.24	6.76	7.52		
	Standing	Mean	110.46	105.00	102.19	106.32	4.5633	0.0128*
		SD	12.32	10.22	8.17	11.02		
DBP	Lying	Mean	68.63	65.45	62.38	65.92	4.6933	0.0113*
		SD	7.67	7.61	7.00	7.78		
	Sitting	Mean	106.06	102.41	99.43	103.06	2.7821	0.0669
		SD	13.31	9.01	7.49	10.66		
	Standing	Mean	64.86	62.05	58.38	62.26	4.0404	0.0206*

In our study we found that the clinical parameters like pulse rate, systolic blood pressure, diastolic blood pressure were decreasing with respect to increasing age in all positions like sitting, standing and lying down position.

Table-13: COMPARING DYSAUTONOMIA WITH CLINICAL OBSERVATIONS

			NORMAL	EARLY	DEFINATE	Total	F-value	P-value
Pulse rate	Lying	Mean	69.41	69.16	65.15	68.40	2.0073	0.1399
		SD	5.86	8.94	6.85	8.21		
	Sitting	Mean	67.88	67.76	64.15	67.06	1.6402	0.1993
		SD	6.38	8.79	6.57	8.09		
	Standing	Mean	63.29	66.62	62.45	65.22	1.6446	0.1984
		SD	15.95	9.00	6.98	10.23		
SBP	Lying	Mean	108.24	110.86	108.10	109.86	0.7434	0.4782
		SD	10.15	10.59	11.38	10.65		
	Sitting	Mean	65.88	69.21	68.10	68.42	1.3406	0.2665
		SD	7.12	7.25	8.50	7.52		
	Standing	Mean	104.00	107.02	106.10	106.32	0.5013	0.6073
		SD	10.42	10.82	12.35	11.02		
DBP	Lying	Mean	64.71	66.22	66.00	65.92	0.2514	0.7782
		SD	7.17	7.90	8.21	7.78		
	Sitting	Mean	102.35	103.75	101.50	103.06	0.3774	0.6866
		SD	11.30	10.76	10.09	10.66		
	Standing	Mean	61.53	63.02	60.50	62.26	0.7312	0.4839
		SD	8.93	8.35	8.87	8.53		

We observed that the on examination the parameters like pulse rate, blood pressure(systolic and diastolic) were comparatively less as the evidence of dysautonomia increased in patients.

TABLE-14 : COMPARING DYSAUTONOMIA WITH LABORATORY PARAMETES

		NORMAL	EARLY	DEFINATE	Total	F-value	P-value
Hemoglobin	Mean	8.49	8.1	7.6	8.20	0.3120	0.7327
	SD	1.86	2.51	2.77	2.45		
Bilirubin-total	Mean	4.34	5.57	4.89	5.23	0.3220	0.7255
	SD	3.97	6.67	5.19	5.98		
Bilirubun-direct	Mean	2.72	4.54	2.99	3.92	0.5566	0.5750
	SD	2.67	9.26	3.86	7.64		
ALK PHOS	Mean	140.41	150.56	133.45	145.41	0.1852	0.8312
	SD	71.97	136.20	58.24	114.70		
SGOT	Mean	68.71	82.44	67.80	77.18	0.4689	0.6271
	SD	72.65	78.11	37.09	70.61		
SGPT	Mean	49.06	57.21	50.90	54.56	0.2773	0.7585
	SD	40.46	53.54	23.05	46.63		

In our study we found that hemoglobin was comparatively lower in patients with definite dysautonomia than early or normal patients, there was no correlation between liver function test with respect to dysautonomia.

TABLE-15: COMPARING CLINCAL PRESENTATION WITH SEVIRITY OF DYSAUTONOMIA

Variables	NORMAL	%	EARLY	%	DEFINATE	%	Chi-square	p-value
Dizziness								
Positive	13	16.67	49	62.82	16	20.51	0.0720	0.9650
Negative	4	18.18	14	63.64	4	18.18		
Anhydrosis								
Positive	5	17.86	15	53.57	8	28.57	1.9940	0.3690
Negative	12	16.67	48	66.67	12	16.67		
P.neuropathy								
Positive	2	20.00	5	50.00	3	30.00	0.9120	0.6340
Negative	15	16.67	58	64.44	17	18.89		
Impotence								
Positive	6	13.33	31	68.89	8	17.78	1.2990	0.5220
Negative	11	20.00	32	58.18	12	21.82		
Diarrhoea								
Positive	3	33.33	5	55.56	1	11.11	2.0300	0.3620
Negative	14	15.38	58	63.74	19	20.88		
Extra-pyramidal effects								
Positive	1	25.00	0	0.00	3	75.00	9.0840	0.0110*
Negative	16	16.67	63	65.63	17	17.71		

In our study the presence of various dysautonomic symptom's were enquired and their relation to severity of dysautonomia was compared but was not statistically significant

TABLE 16: CORELLATION BETWEEN DYSAUTONOMIA AND TESTS USED

ACTIVE STANDING	NORMAL	%	EARLY	%	DEFIINATE	%	CHI-SQUARE	P-VALUE
ABNORMAL	3	12.00	17	68.00	5	20.00	1.3500	0.8530
BODERLINE	13	18.84	43	62.32	13	18.84		
NORMAL	1	16.67	3	50.00	2	33.33		
Deep breathing								
ABNORMAL	4	16.00	18	72.00	3	12.00	3.8420	0.4280
BODERLINE	11	18.97	36	62.07	11	18.97		
NORMAL	2	11.76	9	52.94	6	35.29		
Valsalva								
ABNORMAL	7	18.92	24	64.86	6	16.22	14.9060	0.0050*
BODERLINE	9	17.31	36	69.23	7	13.46		
NORMAL	1	9.09	3	27.27	7	63.64		
Isometric exercise								
ABNORMAL	6	16.67	26	72.22	4	11.11	3.5030	0.4770
BODERLINE	10	18.52	31	57.41	13	24.07		
NORMAL	1	10.00	6	60.00	3	30.00		
Cold pressor								
ABNORMAL	6	17.65	24	70.59	4	11.76	5.4620	0.2430
BODERLINE	10	20.00	30	60.00	10	20.00		
NORMAL	1	6.25	9	56.25	6	37.50		
Total	17	17.00	63	63.00	20	20.00		

P<0.05

From the tests used to detect autonomic dysfunction we found that only Valsalva(parasympathetic) was more evident in our patients. While other were positive in many patients but did not have individual significance.

DISCUSSION

In the present study of 100 patients with cirrhosis of liver of various aetiologies were studied for autonomic dysfunction .

In our study the patient age ranged from 22- 80 years, the maximum number of patients that is 44 (44%) were in the age group of 41-60 years, between the age <40 years 35 (35%) patients and below >60 years 21 (21%) patients were there. There were more number of cases between the age group of 41-60 as compared to above 60 years. This is almost similar to study done by Jaquelynet al[13]and Branislav et al[17]

Taking gender into consideration we observed in our study that males (95%) were more compared to females (5%), with male to female ratio of 19:1.similar conclusion was drawn from Branislav et all[13] .

On comparing the ultrasound abdomen findings of all patients we found that 60 patients (60%) had cirrhosis of liver, 37 patients(37%) had altered echotexture of liver with fatty infiltration and 3 patients(3%) had hepatitis all were chronic alcholics. Many authors have not mentioned the clinical or USG findings in their study and their sample size was not more than 60 cases. In our study we have 100 cases and have made an attempt of defining USG findings.

We made an attempt to find out the aetiologies of various cirrhosis of liver we found 72% had cause of alcoholism, 13% HCV related, 8% HbsAg and 7% autoimmune cause. This is similar to study done by Chaudrye all[15]

We observed that of all 100 patients 90% had complaints of abdominal distention, pedal edema and icterus as their clinical presentation, 10% had altered

sensorium, increased sleepiness and bleeding manifestation at the time of presentation.this is similar to study by Franco et al[12], Branslav et al[15]

In our study the maximum number of patients were alcohol relatedcirrhosis of liver (72%) . This is in sharp contrast to Chaudre et al [13]who observed hepatotropic viruses as main cause of cirrhosis of liver.

On comparing the clinical presentation of patients we found that78 patients (78%) had dizziness as their presenting complaint, followed by 45patients(45%) had impotence and 66 patients(66%) had both dizziness and impotence as their complaints. andanhydrosis 28%, gastroparesis 9%, peripheral neuropathy 10% and last in the line was extra pyramidal symptoms of 4%. To the best of our knowledge where we tried to search for various studies to compare clinical presentation the information is lacking.

On comparing the presence of dysautonomia in our patients, 63 patients(63%) had early dysautonomia, 20 patients(20%) had definite dysautonomia and 17 patients (17%) were normal p value being stastically significant<0.001. This is similar to study done by Bajaj et all[1], Franco et al[12].

When an attempt was made to compare the degree of dysautonomia with respect to gender distribution, 63 patients had early dysautonomia, amoung them 60 were male and 3 were female patients, 20 patients had definite dysautonomia with 18 males and 2 females. In our study more number of male patients were present as compared to females with dysautonomia and most of them were alcohol related cirrhosis of liver with dysautonomia, as we know that female gender are not indulged in alchol abuse in our country (total number of females-5 , all were non alcoholics)

When an attempt was made to correlate age with dysautonomia, we observed that 37 patients were in age group between 41-60 years, 16 patients were in age above 60 years. This is similar to study done by Trevisaniet all [13]who also noticed maximum number of patients with dysautonomia in age below 60 years.

We have tried to compare the association of degree of dysautonomia with diagnosis of patients, in 72 alcoholic liver disease patients 47 had early dysautonomia,13 had definite dysautonomia. Out of 13 CLD-HCV patients, 12 had definite dysautonomia and 1 had early. 8 patients with CLD-HBV cause, 6 had definite dysautonomia, 1 had early. Out of 7 patients with CLD-AUTOIMMUNE, 5 patients had early dysautonomia 2 were normal. Though we had maximum number of patient in alcohol related group, there was evidence of early dysautonomia (47 patients) and only 13 had definite dysautonomia. Where as patients with HCV, HBV related cirrhosis of liver had definite evidence of dysutonomia. These finding were similar to study done by Jaquelin et al[13] this could be because of direct viral etiology leading to dysautonomia by hypoyhesis.

Our all 100 patients were subjected to ECG tracing and we found 21 patients had bradycardia of which 13 patients had early dysautonomia followed by 5 patients had definite dysautonomia, remaining 3 were normal without evidence of dysautonomia (79 patients had dysautonomia without ECG abnormality).

When we correlated the degree of dysautonomia with with patient USG findings we found that maximum number of patients with cirrhosis of liver(60 patients) had dysautonomia compared to patients with altered echotexture 37 patients. The literature regarding this comparison is lacking.

On comparing other symptoms of dysautonomia like dizziness, anhydrosis peripheral neuropathy, impotence, diarrhoea, extra-pyramidal symptoms we found evidence of dysautonomia with p value being statistically significant,(p value-0.003)however comparison of these variables was not attempted reason being overlapping of these symptoms and which may not give true association.

We tried to compare other variables for evidence of dysautonomia like pulse rate (sitting standing and lying down position) blood pressure – systolic and diastolic blood pressure in sitting standing and lying down position, we found the variation of pulse rate, systolic blood pressure, diastolic blood pressure in patients with dysautonomia with increasing age and severity of dysautonomia, which is in contrast to study done by Trevisani et al [12]

Lastly we tried to compare the patients with dysautonomia with laboratory parameters, most of patients had evidence of anaemia (most were iron deficiency anaemia) reason being due to chronic blood loss, bone marrow suppression [4]. Majority had leucopenia and thrombocytopenia, most of these patients with abnormality of haemoglobin, total count, and platelet had evidence of dysautonomia with p value being not significant.

We have tried to find out the proposed cause for these abnomality which might be because of direct bone marrow suppression, nutritional deficiency, malabsorption and chronic blood loss and altered coagulation factors due to cirrhosis of liver.

Evidence of parasympathetic damage was more than sympathetic damage in our patients. Which is similar to study done by Fancoet al[13], Chaudry et al [15]

Other laboratory parameters like liver function tests which showed abnormality of protein and albumin did not have statistical significance and did not correlate with dysautonomia.

CONCLUSION

In the present study of 100 patients with cirrhosis of liver we observed significant correlation with various factors

Based on the findings of the present study the prominent features are:

- In patients with aetiology like HBV, HVC, autoimmune, had more autonomic dysfunction as compared to alcohol related cirrhosis of liver
- There is strong evidence of dysautonomia in majority of patients with various aetiology
- The evidence of dysautonomia was more observed with patient with increasing age.
- Comparison with haemoglobin, TC, platelet, Liver function test majority of patients had these abnormality
- We did not find significant correlation with gender and clinical presentation
- We feel its worth to study co-morbid conditions / confounding factors with various other dysautonomic symptoms or tests to know these factors have true association or not
- We have not compared varecial bleed with autonomic dysfunction and mortality associated with autonomic dysfunction
- Owing to small sample size (100 patients) a large sample size is required to overcome these biasis.

SUMMARY

In the present study of 100 patients titled 'AUTONOMIC DYSFUNCTION IN CIRRHOSIS OF LIVER' during the period from January 2015 to December 2015 in the department of general medicine, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi. The findings of the study has been summarized as follows:

- There were more cases of dysautonomia in age group of 41-60 years.
- In our study there were 95% males and 5% females
- Clinical presentation of dysautonomia was dizziness and impotence
- Majority of patients had early dysautonomia rather than definite dysautonomia
- Out of 100 patients maximum number of patients were alcoholic liver disease
- In our study 83 patients had evidence of dysautonomia with various aetiology, remaining were normal
- Out of 100 patients majority had anaemia, leukopenia, thrombocytopenia and abnormality of liver function test- decreased protein and albumin.
- Evidence of dysautonomia was more common with cirrhosis secondary to HBV,HCV as compared to alcoholics
- Patients with cirrhosis of liver as compared to other USG findings (altered echotexture, fatty liver, hepatitis) had evidence of dysautonomia more
- There was more of sympathetic damage than para-sympathetic damage amoung the patients.

BIBLIOGRAPHY

1. National Center for Health Statistics. National Vital Statistics Report. Chronic liver disease/cirrhosis. Accessed May 2, 2006, at: www.cdc.gov/nchs/fastats/liverdis.htm.
2. Heidelbaugh JJ, Sherbondy M. Cirrhosis and chronic liver failure. Part II: Complications and treatment. Am Fam Physician 2006;74:765-74, 779.
3. Friedman S, Schiano T. Cirrhosis and its sequelae. In: Goldman L, Ausiello D, eds. Cecil Textbook of Medicine. 22nd ed. Philadelphia, Pa.: Saunders, 2004:936-44
4. Crawford JM. Liver and biliary tract. In: Kumar V, Abbas AK, Fausto N, eds. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Philadelphia, Pa.: Elsevier Saunders, 2005:877-938.
5. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. Gastroenterology 2002;123:1702-4.
6. United Network for Organ Sharing. Data. Accessed May 2, 2006, at: www.unos.org/data/.
7. Centers for Disease Control and Prevention. Alcohol-attributable deaths and years of potential life lost—United States, 2001. MMWR Morb Mortal Wkly Rep 2004;53:866-70.
8. Malekzadeh R, Mohamadnejad M, Rakhshani N, Nasseri-Moghaddam S, Merat S, Tavangar SM, et al. Reversibility of cirrhosis in chronic hepatitis B. Clin Gastroenterol Hepatol 2004;2:344-7.
9. Diehl A. Alcoholic and nonalcoholic steatohepatitis. Goldman L, Ausiello D, eds. Cecil Textbook of Medicine. 22nd ed. Philadelphia, Pa.: Saunders, 2004:935-6.

10. Yee HF, Lidofsky SD. Acute liver failure. In: Feldman M, Friedman LS, Sleisenger MH, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. 7th ed. Philadelphia, Pa.: Saunders, 2002:1567-74.
11. Cattau EL Jr, Benjamin SB, Knuff TE, Castell DO. The accuracy of the physical examination in the diagnosis of suspected ascites. JAMA 1982;247:1164-6.
12. .Franco T, Guiseppe S, Paulo C, journal of hepatology sept 1999,935-6
13. Jaquelin F, Fleckenstein, Steven M journal of hepatology june 2000
14. Joye V, Balan A, Naveen B et al. annals of hepatology april 2007 issue 23 225-75
15. Vinay C, Ander C, Rishard O et al. journal of hepatology june 1999 issue 45,54:69
16. Bajaj B, Agarwal M, Krishna ram B postgraduate medical journal 2001:408-411
17. Branslav M, Nikola M, Danjeila T et al. gen. Physiol.Biophys- 2009 special issue 28, 251-261
18. Fede G, D'Amico G, Arvaniti V, et al. Renal failure and cirrhosis: a systematic review of mortality and prognosis. *J Hepatol*2012; 56: 810–18.
19. Moreau R, Jalan R, Gines P, et al, and the CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; 144: 1426–37, e1–9.

20. Kim SU, Oh HJ, Wanless IR, Lee S, Han KH, Park YN. The Laennec staging system for histological sub-classifi cation of cirrhosis is useful for stratifi cation of prognosis in patients with liver cirrhosis. *J Hepatol*2012; 57: 556–63.
21. Manousou P, Dhillon AP, Isgro G, et al. Digital image analysis of liver collagen predicts clinical outcome of recurrent hepatitis C virus 1 year after liver transplantation. *Liver Transpl*2011; 17: 178–88.
22. Parkes J, Roderick P, Harris S, et al. Enhanced liver fi brosis test can predict clinical outcomes in patients with chronic liver disease. *Gut* 2010; 59: 1245–51.
23. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fi brosis and liver stiff ness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 1970–79, e1–3.
24. Rein DB, Smith BD, Wittenborn JS, et al. The cost-eff ectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med* 2012; 156: 263–70.
25. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fi brosis score: a noninvasive system that identifies liver fi brosis in patients with NAFLD. *Hepatology* 2007; 45: 846–54.
26. Sheron N, Moore M, Ansett S, Parsons C, Bateman A. Developing a 'traffi c light' test with potential for rational early diagnosis of liver fi brosis and cirrhosis in the community. *Br J Gen Pract*2012; 62: 616–24.
27. Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fi brosis and cirrhosis in a community-based population aged over 45 years. *Gut* 2011; 60: 977–84.

28. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fi brosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol*2011; 54: 650–59.
29. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology* 1997; 25: 108–11.
30. Tsochatzis E, Papatheodoridis GV, Manesis EK, Kafiri G, Tiniakos DG, Archimandritis AJ. Metabolic syndrome is associated with severe fi brosis in chronic viral hepatitis and non-alcoholic steatohepatitis. *Aliment PharmacolTher*2008; 27: 80–89.
31. Berzigotti A, Garcia-Tsao G, Bosch J, et al, and the Portal Hypertension Collaborative Group. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* 2011; 54: 555–61.
32. Stepanova M, Rafi q N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. *Gut* 2010; 59: 1410–15.
33. Nkontchou G, Bastard JP, Ziol M, et al. Insulin resistance, serum leptin, and adiponectin levels and outcomes of viral hepatitis C cirrhosis. *J Hepatol*2010; 53: 827–33.
34. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126: 460–68.
35. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology* 2011; 54: 463–71.

36. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. *Hepatology* 2008; 48: 557–66.
37. Luca A, García-Pagán JC, Bosch J, et al. Eff ects of ethanol consumption on hepatic hemodynamics in patients with alcoholic cirrhosis. *Gastroenterology* 1997; 112: 1284–89.
38. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol*2012; 57: 399–420
39. Westin J, Lagging LM, Spak F, et al. Moderate alcohol intake increases fi brosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat*2002; 9: 235–41.
40. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379: 1245–55.
41. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; 51: 1972–78.
42. Moriarty K, Cassidy P, Dalton D, et al. Alcohol-related disease: meeting the challenge of improved quality of care and better use of resources. http://www alcohollearningcentre org uk/Topics/ Browse/AHW/?parent=6057&child=6382 2013 (accessed May 1, 2013).
43. Tsochatzis EA, Bosch J, Burroughs AK. New therapeutic paradigm for patients with cirrhosis. *Hepatology* 2012; 56: 1983–92.
44. Zein CO. Clearing the smoke in chronic liver diseases. *Hepatology* 2010; 51: 1487–90.

45. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fi brosis in chronic hepatitis C. *Hepatology* 2005; 42: 63–71.
46. Leithead JA, Ferguson JW, Hayes PC. Smoking-related morbidity and mortality following liver transplantation. *Liver Transpl*2008; 14: 1159–64.
47. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specifi c mortality. *N Engl J Med* 2012; 366: 1891–904.
48. Torres DM, Harrison SA. Is it time to write a prescription for coffee? Coffee and liver disease. *Gastroenterology* 2013; 144: 670–72.
49. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology* 2007; 132: 1740–45.
50. De Gottardi A, Berzigotti A, Seijo S, et al. Postprandial eff ects of dark chocolate on portal hypertension in patients with cirrhosis: results of a phase 2, double-blind, randomized controlled trial. *Am J ClinNutr*2012; 96: 584–90.
51. Hernández-Guerra M, García-Pagán JC, Turnes J, et al. Ascorbic acid improves the intrahepatic endothelial dysfunction of patients with cirrhosis and portal hypertension. *Hepatology* 2006; 43: 485–91.
52. Lewis JH, Stine JG. Review article: prescribing medications in patients with cirrhosis—a practical guide. *Aliment PharmacolTher* 2013; 37: 1132–56.
53. European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*2012; 57: 167–85.
54. Manolakopoulos S, Triantos C, Theodoropoulos J, et al. Antiviral therapy reduces portal pressure in patients with cirrhosis due to HBeAg-negative

chronic hepatitis B and signifi cant portal hypertension. *J Hepatol*2009; 51: 468–74.

55. Liaw YF, Sung JJ, Chow WC, et al, and the Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351: 1521–31.
56. Everson GT, Terrault NA, Lok AS, et al, and the Adult-to-Adult Living Donor Liver Transplantation Cohort Study. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. *Hepatology* 2013; 57: 1752–62.
57. McHutchison JG, Everson GT, Gordon SC, et al, and the PROVE1 Study Team. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827–38.
58. Poordad F, McCone J Jr, Bacon BR, et al, and the SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195–206.
59. Charlton MR, Pockros PJ, Harrison SA. Impact of obesity on treatment of chronic hepatitis C. *Hepatology* 2006; 43: 1177–86.
60. Cholongitas E, Theocharidou E, Goulis J, Tsochatzis E, Akriviadis E, Burroughs K. Review article: the extra-skeletal eff ects of vitamin D in chronic hepatitis C infection. *Aliment PharmacolTher*2012; 35: 634–46.
61. Rao GA, Pandya PK. Statin therapy improves sustained virologic response among diabetic patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 144–52.
62. Freedman ND, Curto TM, Lindsay KL, Wright EC, Sinha R, Everhart JE, and the HALT-C TRIAL GROUP. Coffee consumption is associated with

response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 1961–69.

63. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al, and the HEPNET. Greece Cohort Study Group. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011; 60: 1109–16.
64. Burroughs AK, Thalheimer U. Hepatic venous pressure gradient in 2010: optimal measurement is key. *Hepatology* 2010; 51: 1894–96.
65. Groszmann RJ, Garcia-Tsao G, Bosch J, et al, and the Portal Hypertension Collaborative Group. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; 353: 2254–61.
66. Ripoll C, Groszmann R, Garcia-Tsao G, et al, and the Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; 133: 481–88.
67. Ripoll C, Groszmann RJ, Garcia-Tsao G, et al, and the Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol*2009; 50: 923–28.
68. de Franchis R, and the Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*2010; 53: 762–68.

69. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol*2003; 38: 266–72.
70. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med* 2010; 362: 823–32.
71. Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol*2007; 102: 2842–48.
72. Poynard T, Calès P, Pasta L, et al, and the Franco-Italian Multicenter Study Group. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. *N Engl J Med* 1991; 324: 1532–38.
73. Bosch J, Masti R, Kravetz D, et al. Eff ects of propranolol on azygos venous blood fl ow and hepatic and systemic hemodynamics in cirrhosis. *Hepatology* 1984; 4: 1200–05.\
74. Andreu V, Perello A, Moitinho E, et al. Total eff ective vascular compliance in patients with cirrhosis. Eff ects of propranolol. *J Hepatol*2002; 36: 356–61.
75. Bosch J. Carvedilol for portal hypertension in patients with cirrhosis. *Hepatology* 2010; 51: 2214–18.
76. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the fi rst variceal bleed. *Hepatology* 2009; 50: 825–33.
77. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; 37: 902–08.

78. Villanueva C, Aracil C, Colomo A, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. *Gastroenterology* 2009; 137: 119–28.
79. La Mura V, Abraldes JG, Raff a S, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol*2009; 51: 279–87.
80. Tandon P, Saez R, Berzigotti A, Abraldes JG, Garcia-Pagan JC, Bosch J. A specialized, nurse-run titration clinic: a feasible option for optimizing beta-blockade in non-clinical trial patients. *Am J Gastroenterol*2010; 105: 1917–21.
81. Burroughs AK, Tsochatzis EA, Triantos C. Primary prevention of variceal haemorrhage: a pharmacological approach. *J Hepatol*2010; 52: 946–48.
82. Abraldes JG, Albillos A, Bañares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009; 136: 1651–58.
83. El-Serag HB, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology* 2009; 136: 1601–08.
84. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R, and the Pravastatin in Chronic Liver Disease Study Investigators. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology* 2007; 46: 1453–63.

85. Bañares R, Albillos A, Rincón D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology* 2002; 35: 609–15.
86. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999; 353: 139–42.
87. Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004; 39: 746–53.
88. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; 368: 11–21.
89. García-Pagán JC, Caca K, Bureau C, et al, and the Early TIPS(Transjugular Intrahepatic Portosystemic Shunt) Cooperative StudyGroup. Early use of TIPS in patients with cirrhosis and varicealbleeding. *N Engl J Med* 2010; 362: 2370–79.
90. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM,Bañares R, Albillos A. Meta-analysis: combination endoscopic anddrug therapy to prevent variceal rebleeding in cirrhosis.*Ann Intern Med* 2008; 149: 109–22.
91. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosisand portal hypertension: too much, not enough. *Hepatology* 2002;35: 478–91.
92. Runyon BA, and the AASLD Practice Guidelines Committee.Management of adult patients with ascites due to cirrhosis: anupdate. *Hepatology* 2009; 49: 2087–107.
93. Hernández-Gea V, Aracil C, Colomo A, et al. Development of ascitesin compensated cirrhosis with severe portal hypertension treatedwith β-blockers. *Am J Gastroenterol*2012; 107: 418–27.

94. Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patientswith advanced cirrhosis: a multicentre prospective study.*Dig Liver Dis* 2001; 33: 41–48.
95. Angeli P, Fasolato S, Mazza E, et al. Combined versus sequentialdiuretic treatment of ascites in non-azotaemic patients with cirrhosis:results of an open randomised clinical trial. *Gut* 2010; 59: 98–104.
96. European Association for the Study of the Liver. EASL clinicalpractice guidelines on the management of ascites, spontaneousbacterial peritonitis, and hepatorenal syndrome in cirrhosis.*J Hepatol*2010; 53: 397–417.
97. Singh V, Dhungana SP, Singh B, et al. Midodrine in patients withcirrhosis and refractory or recurrent ascites: a randomized pilotstudy. *J Hepatol*2012; 56: 348–54.
98. Ginès P, Titó L, Arroyo V, et al. Randomized comparative study oftherapeutic paracentesis with and without intravenous albumin incirrhosis. *Gastroenterology* 1988; 94: 1493–502.98 Salerno F, Cammà C, Enea M, Rössle M, Wong F. Transjugularintrahepatic portosystemic shunt for refractory ascites: ameta-analysis of individual patient data. *Gastroenterology* 2007;133: 825–34.
99. Bureau C, Métivier S, D'Amico M, et al. Serum bilirubin andplatelet count: a simple predictive model for survival in patientswith refractory ascites treated by TIPS. *J Hepatol*2011; 54: 901–07.
100. Tandon P, Abraldes JG, Berzigotti A, Garcia-Pagan JC, Bosch J.Renin-angiotensin-aldosterone inhibitors in the reduction of portalpressure: a systematic review and meta-analysis. *J Hepatol*2010;53: 273–82.

101. Vlachogiannakos J, Tang AK, Patch D, Burroughs AK. Angiotensinconverting enzyme inhibitors and angiotensin II antagonists astherapy in chronic liver disease. *Gut* 2001; 49: 303–08.

102. Sersté T, Melot C, Francoz C, et al. Deleterious eff ects ofbeta-blockers on survival in patients with cirrhosis and refractoryascites. *Hepatology* 2010; 52: 1017–22.

103. Senzolo M, Nadal E, Cholongitas E, Burroughs AK. Is hydrophobia necessary for the hepatologist prescribing nonselective beta-blockers in cirrhosis? *Hepatology* 2011; 53: 2149–50.

104. Fernández J, Navasa M, Gómez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; 35: 140–48.

105. Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. *Gut* 2005; 54: 556–63.

106. Albillos A, de la Hera A, González M, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* 2003; 37: 208–17.

107. Nischalke HD, Berger C, Aldenhoff K, et al. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol*2011; 55: 1010–16.

108. Bellot P, García-Pagán JC, Francés R, et al. Bacterial DNA translocation is associated with systemic circulatory abnormalities and intrahepatic endothelial dysfunction in patients with cirrhosis. *Hepatology* 2010; 52: 2044–52.

109. Zapater P, Francés R, González-Navajas JM, et al. Serum and ascetic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. *Hepatology* 2008; 48: 1924–31.

110. Tritto G, Bechlis Z, Stadlbauer V, et al. Evidence of neutrophil functional defect despite inflammation in stable cirrhosis. *J Hepatol* 2011; 55: 574–81.

111. Coant N, Simon-Rudler M, Gustot T, et al. Glycogen synthase kinase 3 involvement in the excessive proinflammatory response to LPS in patients with decompensated cirrhosis. *J Hepatol*2011; 55: 784–93.

112. Senzolo M, Cholongitas E, Burra P, et al. β-blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a metaanalysis. *Liver Int*2009; 29: 1189–93.

113. Reiberger T, Ferlitsch A, Payer BA, et al, and the Vienna Hepatic Hemodynamic Lab. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol*2013; 58: 911–21.

114. Worlicek M, Knebel K, Linde HJ, et al. Splanchnic sympathectomy prevents translocation and spreading of *E coli* but not *S aureus* in liver cirrhosis. *Gut* 2010; 59: 1127–34.

115. Rasaratnam B, Kaye D, Jennings G, Dudley F, Chin-Dusting J. The eff ect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: a randomized trial. *Ann Intern Med* 2003; 139: 186–93.

116. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; 133: 818–24.

117. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis: a randomized controlled study of 100 patients. *Gastroenterology* 1991; 100: 1737–42.

118. Sort P, Navasa M, Arroyo V, et al. Eff ect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; 341: 403–09.

119. Sigal SH, Stanca CM, Fernandez J, Arroyo V, Navasa M. Restricted use of albumin for spontaneous bacterial peritonitis. *Gut* 2007; 56: 597–99.

120. Guevara M, Terra C, Nazar A, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis: a randomized, controlled study. *J Hepatol*2012; 57: 759–65.

121. Bajaj JS, Zadvornova Y, Heuman DM, et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Am J Gastroenterol*2009; 104: 1130–34.

122. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, et al. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. *Am J Gastroenterol*2010; 105: 106–13.

123. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; 51: 1675–82.

124. Laleman W, Simon-Talero M, Maleux G, et al, and the EASL-CLIFConsortium. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. *Hepatology* 2013; 57: 2448–57.

125. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology* 2009; 137: 885-91, 891.
126. Bai M, Yang Z, Qi X, Fan D, Han G. l-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. *J GastroenterolHepatol*2013; 28: 783–92.
127. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; 362: 1071–81.
128. Bajaj JS, Heuman DM, Wade JB, et al. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. *Gastroenterology* 2011; 140: 478–87, e1.
129. Bajaj JS, Pinkerton SD, Sanyal AJ, Heuman DM. Diagnosis and treatment of minimal hepatic encephalopathy to prevent motor vehicle accidents: a cost-eff ectiveness analysis. *Hepatology* 2012; 55: 1164–71.
130. Soriano G, Román E, Córdoba J, et al. Cognitive dysfunction in cirrhosis is associated with falls: a prospective study. *Hepatology* 2012; 55: 1922–30.
131. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med* 2011; 154: 85–93.
132. Tsochatzis EA, Bosch J, Burroughs AK. Prolonging survival in patients with cirrhosis: old drugs with new indications. *Gastroenterology* 2010; 139: 1813–15, e1.
133. Lisman T, Caldwell SH, Burroughs AK, et al, and the Coagulation in Liver Disease Study Group. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol*2010; 53: 362–71.

134. Tsochatzis EA, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. *Aliment PharmacolTher*2010; 31: 366–74.

135. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012; 143: 1253–60, e1–4.

136. Bellot P, Welker MW, Soriano G, et al. Automated low fl ow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. *J Hepatol*2013; 58: 922–27.

137. Vlachogiannakos J, Saveriadis AS, Viazis N, et al. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment PharmacolTher* 2009; 29: 992–99.

138. Kalambokis GN, Mouzaki A, Rodi M, et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *ClinGastroenterolHepatol*2012; 10: 815–18. 139 Nkontchou G, Cosson E, Aout M, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. *J ClinEndocrinolMetab*2011; 96: 2601–08.

139. Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013; 62: 606–15.

ANNEXURE-I

INFORMED CONSENT FORM

AUTONOMIC DYSFUNCTION IN CIRRHOSIS OF LIVER – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY

Objective and purpose of the study:

This research is intended to assess **autonomic dysfunction in cirrhosis of liver** The principal investigator of the study is **Dr. SHIVAKUMAR VEERANNA TURAMARI** under the guidance **of Dr. VIJAY G SOMANNNAVAR**

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsorer may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

.**Financial incentives for participation**

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant you may call :

1. **Dr. GANGA PILLI**,

   Chairman,

   J.N.M.C Ethical Committee for Human Research,

   Professor and Head , Department of Pathology , JNMC Belagavi

   Phone number: 0831-2471350.

   Extn: 1527

2. **Dr. REKHA PATIL**

   Professor & HOD,

   Department of Medicine,

   JNMC, Belagavi.

   Phone No: 09448371125,

   Extn: 1371/1520

3. **Dr. SHIVAKUMAR. V.TURAMARI**

   Investigator,

   PG in General Medicine,

   JNMC, Belgaum.

   Phone No.: 9591666830

CONSENT FORM

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

Signature /Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ : …….

Signature/ Left Thumb

Impression of the participant's : …….

Name of the legally

authorized representative/ Guardian : …….

Signature/ Left Thumb Impression. : …….

Witness's Name : …….

Signature/ Left Thumb Impression. :…….

Investigators name and Signature : …….

Date and Place : …….

ANNEXURE-II

PROFORMA

IP No: **Date:**

Name:

Age & sex

Unit

IP/OP No:

Marital Status

Educational status:

Brief History:

Occupation:

History of drug intake:

1. Antihypertensives
2. Tranquilizers
3. Antidepressants
4. Calcium channel blockers

General physical examination:

Parameter	**Lying**	**Sitting**	**Standing**
Pulse			

Blood Pressure

SYSTEMIC EXAMINATION

CVS

RESPIRATIORY SYSTEM

PER ABDOMEN

CNS

INVESTIGATIONS

Hb

Bilirubim

Alkaline phosphate

SGOT

SGPT

ECG

USG

HCV

HBsAg

Others

ASSESSMENT OF AUTONOMIC FUNCTION

1. History and clinical examination

H/O Dizziness/Syncope Impotence

Anhidrosis Diarrhoea

Peripheral neuropathy Extrapyramidal defects

2. Autonomic Function Tests

3.

These tests are performed using ECG and ratio is calculated for longest and shortest RR interval and following interpretation is made=

Active standing = 1) more than or equal to 1.04=

2) 1.01-1.03 =

3) <1=

Deep breathing = 1)>9 bpm(age>60)=

2)>15bpm (age<60)=

3) 11-14=

Valsalva = 1) more than or equal 1.11=

2) 1.11-1.2=

3) >1.21=

Isometric exercise = 1) >16=

2) 11-15=

3) <10=

Cold pressor 1) >15=

2) 11-14 =

3) < 10 =

Valsalva-BP =

CLASSIFICATION OF DYSAUTONOMIA

1. **ABSENT= all tests are normal**
2. **EARLY= one abnormal HR test or two borderline**
3. **DEFINITE=two or more abnormal HR tests**
4. **SEVERE= two or more abnormal HR tests abnormal plus one borderline or abnormal BP test**
5. **ATYPICAL= any other combination of abnormal tests**

MASTER CHART

SL.NO	IP.NO	AGE	SEX	DIAGOSIS	PULSE-LYING	PULSE-SITTING	PULSE-STANDING	BP-LYING	BP-SITTING	BP-STANDING	HEMOGLOBIN	BILIRUBIN-TOTAL	BILIRUBUN-DIRECT	ALK PHOS	SGOT	SGPT	ECG	USG ABD	DIZZINESS	ANHYDROSIS	P.NEUROPATHY	IMPOTENCE	DIARRHOEA	EXTRA-PYRAMIDAL EFFFECTS	ACTIVE STANDING	DEEP BREATHING	VALSALVA	ISOMETRIC EXERSISE	COLD PRESSOR	VALASVA BP	DYSAUTONMIA CLASSIFICATION
1	644924	53	M	ALD	70	70	70	110/70	110/70	110/70	8	4.81	3.97	166	88	77	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	2	2	2	1	1	110/70	2
2	645613	35	M	ALD	87	86	86	110/70	100/60	100/60	8	5.05	3.14	133	93	47	M	CIRRHOSIS OF LIVER	+	-	-	-	-	-	1	1	1	1	1	100/60	2
3	644950	46	M	ALD	60	60	60	110/70	110/70	100/50	11	6.19	2.91	104	104	56	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	2	1	1	1	120/60	2
4	645216	29	M	CLD-HBSAG	70	70	67	100/60	106/60	100/60	7.5	1.1	0.53	60	26	29	N	CIRRHOSIS OF LIVER	-	-	-	-	-	-	1	1	1	1	1	110/6	2
5	644633	55	M	ALD	68	66	66	100/60	100/60	94/60	8	7.53	5.33	145	87	35	BRADY	ALTERED ECHOTEXTURE	+	+	-	+	-	-	2	2	1	2	1	96/60	2
6	3297182	42	M	CLD-HCV	74	74	70	110/70	100/60	100/60	11	5.39	4.5	165	31	27	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	1	2	2	2	100/60	1
7	2479616	58	M	ALD	70	74	74	100/60	96/60	96/60	7.8	12.7	7.73	87	45	33	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	90/60	1
8	644087	58	M	ALD	70	68	60	110/70	100/60	100/60	8	0.66	0.86	263	26	38	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	1	2	2	1	2	100/60	2
9	3292332	54	M	ALD	66	64	63	100/60	100/60	90/50	6.8	2.31	1.2	129	24	19	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	2	2	2	2	100/60	1
10	661974	63	M	ALD	80	80	72	110/70	100/60	100/60	6.8	2.38	0.76	75	38	28	N	CIRRHOSIS OF LIVER	+	+	+	+	-	-	2	2	2	2	2	90/50	2
11	681332	17	M	CLD-AUTOIMMUNE	70	68	66	100/60	96/60	90/50	11	10.6	3.8	206	60	76	N	CIRRHOSIS OF LIVER	-	-	-	-	-	-	1	2	1	2	1	100/60	2
12	2479616	58	M	ALD	70	68	68	100/60	100/60	98/60	8	12.8	7.73	87	45	33	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	100/60	1
13	643634	54	M	ALD	76	74	70	110/60	100/60	100/60	6.8	0.3	0.74	74	87	87	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	1	2	1	2	100/60	2
14	643879	44	M	ALD	74	70	68	110/70	100/70	100/60	11	0.68	0.32	80	33	30	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	1	2	1	1	2	100/60	2
15	643543	54	M	ALD	84	80	80	130/80	110/70	100/60	6	3.42	1.93	97	34	35	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	2	2	2	2	100/60	2
16	672092	38	M	CLD-HBSAG	72	66	68	110/60	100/60	100/60	0.35	0.1	67	22	24	55	N	HEPATITIS	-	-	-	-	-	-	1	2	1	2	2	110/70	2
17	670748	34	M	ALD	72	70	70	124/80	120/80	120/80	15.4	1.11	1.2	75	16	28	N	CIRRHOSIS OF LIVER	-	-	-	-	-		2	2	2	2	2	100/60	2
18	676295	88	M	ALD	62	60	60	100/70	100/70	100/60	9.4	0.8	1	120	47	32	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	90/60	2
19	673476	58	M	ALD	66	66	66	130/80	130/80	120/70	15.4	2.3	1.6	190	61	41	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	2	1	2	1	100/60	3
20	673555	34	M	ALD	68	66	68	110/70	110/70	110/70	12.2	12.2	8.49	162	245	58	N	CIRRHOSIS OF LIVER	+	-	-	+	+	-	2	2	2	2	2	100/60	2
21	676360	68	M	ALD	56	58	58	100/60	100/60	100/60	11	11.4	1.6	1.06	78	110	BRADY	CIRRHOSIS OF LIVER	-	-	-	-	-	-	2	1	2	2	2	100/60	2

22	642779	65	M	ALD	68	60	60	110/60	106/60	100/50	10.4	0.35	0.21	184	34	37	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	2	2	2	2	100/70	1
23	642962	38	M	ALD	66	64	66	100/60	94/60	90/60	11	3.47	1.7	106	95	41	N	CIRRHOSIS OF LIVER	+	-	+	-	-	-	2	2	2	1	1	100/60	1
24	700736	38	M	ALD	76	74	74	110/70	100/70	110/70	7	8.36	6.37	158	42	22	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	2	1	1	1	100/60	1
25	641450	63	M	ALD	68	66	66	130/80	120/80	120/80	6	4.03	2.96	107	322	87	N	CIRRHOSIS OF LIVER	+	-	-	+	+	-	2	2	2	2	2	90/50	1
26	655244	58	M	CLD-HCV	60	60	60	100/60	110/60	100/50	10	0.6	0.2	113	38	36	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	1	1	1	100/60	2
27	2611931	51	M	ALD	70	70	70	100/60	90/60	100/60	11	2.99	1.93	301	69	94	BRADY	CIRRHOSIS OF LIVER	+	+	-	-	-	-	1	1	1	1	2	80/50	1
28	641935	18	M	CLD-AUTIMMUNE	70	66	66	100/60	98/60	90/60	6	8.37	5.9	299	145	182	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	2	2	1	2	2	100/60	1
29	642082	47	M	ALD	68	60	60	110/70	100/60	100/60	6	5.13	4.36	113	29	28	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	1	1	1	1	100/60	2
30	642287	37	M	CLD-AUTOIMMUNE	70	68	68	110/70	110/70	110/70	8	8.86	4.97	230	286	69	BRADY	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	100/70	2
31	692257	39	M	ALD	88	86	88	130/80	110/70	110/70	9.6	1.05	0.49	133	36	20	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	1	2	1	2	100/70	2
32	642090	48	M	ALD	70	68	70	110/70	100/70	100/70	10.2	5.59	2.25	125	111	110	N	CIRRHOSIS OF LIVER	-	-	-	-	-	-	2	2	2	2	2	110/70	4
33	641887	61	M	ALD	74	70	70	120/70	100/60	100/60	11.3	1.08	0.85	65	40	45	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	2	2	2	90/60	2
34	6713865	57	M	ALD	70	66	66	100/60	100/60	100/60	7	0.94	0.32	124	20	24	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	1	1	2	1	100/60	2
35	647026	46	M	ALD	70	70	70	110/70	110/70	104/70	11	3.4	0.24	0.49	159	56	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	1	1	110/70	2
36	740824	51	M	ALD	70	66	68	120/80	120/70	110/70	11	1.04	0.4	110	159	90	BRADY	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	1	1	90/50	2
37	740917	37	M	ALD	78	78	76	130/80	120/80	120/70	6	7.25	4.6	116	57	20	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	1	2	2	1	2	100/60	2
38	3423990	59	M	CLD-HCV	70	68	66	100/60	100/60	100/60	8	4.18	2.24	124	72	42	N	CIRRHOSIS OF LIVER	+	+	-	-	+	-	1	1	1	1	1	90/50	1
39	669004	44	M	ALD	68	68	68	110/70	110/70	104/60	10.4	8.95	7.05	139	74	40	N	CIRRHOSIS OF LIVER	+	-	-	+	+	-	2	2	2	1	1	100/60	2
40	666691	49	M	CLD-HBSAG	74	70	70	110/70	110/70	110/70	9	1.62	0.52	121	40	21	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	1	1	1	1	2	100/50	2
41	666460	27	M	CLD-AUTOIMMUNE	76	76	7	120/70	120/70	120/70	11	0.83	0.14	86	21	35	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	1	1	100/60	1
42	665093	62	M	ALD	74	70	70	110/70	100/60	100/56	8	0.86	0.57	202	69	59	BRADY	CIRRHOSIS OF LIVER	+	+	+	+	-	-	2	2	1	2	1	96/60	1
43	334870	45	M	ALD	70	66	66	110/70	106/60	100/60	7	7.29	5.21	187	80	86	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	1	2	1	1	1	100/60	2
44	652420	38	M	ALD	76	76	76	110/70	110/70	106/70	14	0.68	0.25	62	75	24	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	1	2	100/60	2
45	652191	49	M	CLD-HBSAG	90	90	86	110/70	90/60	90/60	6	5.19	1.7	115	63	45	TACHY	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	1	1	90/60	2
46	651347	54	M	ALD	60	54	54	100/60	90/50	90/50	7	4.3	2.09	169	153	64	BRADY	CIRRHOSIS OF LIVER	+	+	+	+	-	-	2	2	2	2	3	100/60	2
47	651093	22	M	CLD-AUTOIMMUNE	70	70	70	130/80	130/70	110/60	13	1.81	1.21	185	33	34	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	1	1	110/60	2
48	730191	51	M	ALD	70	66	66	120/70	110/80	116/80	11	1.82	0.83	102	27	25	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	2	2	2	2	100/60	2
49	646018	36	M	ALD	74	70	70	110/70	106/70	100/60	11	4.09	2.01	104	54	49	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	3	3	2	3	94/50	4
50	650438	28	M	CLD-HBSAG	66	60	60	100/80	104/60	96/50	11	1.04	0.16	85	56	85	N	HEPATITIS	-	-	-	-	-	-	1	1	1	1	1	100/60	3
51	3330154	41	M	ALD	70	66	67	100/60	100/60	100/60	7	3.48	1.83	305	28	16	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	2	2	3	2	100/60	3
52	649108	33	M	CLD-HBSAG	70	70	70	110/70	110/70	110/70	11	1.23	0.3	100	31	36	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	1	1	2	1	2	120/70	3

53	752220	65	M	ALD	60	60	60	120/70	120/70	110/70	7	4.49	2.36	61	37	17	BRADY	CIRRHOSIS OF LIVER	+	+	+	-	-	-	2	3	3	2	3	104/60	3
54	648139	70	M	CLD-HCV	70	70	68	100/60	90/60	90/60	2.6	0.36	0.07	121	24	46	BRADY	CIRRHOSIS OF LIVER	+	+	+	+	-	-	3	2	3	2	3	90/50	3
55	3317510	58	M	ALD	60	60	56	100/80	90/60	90/60	8	2.25	0.75	163	47	40	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	2	1	1	2	100/60	3
56	648031	61	F	CLD-HBSAG	60	60	56	100/60	90/50	86/50	8	1.8	0.82	139	59	45	N	CIRRHOSIS OF LIVER	+	+	-	-	-	-	2	3	2	2	2	110/70	3
57	3302336	52	M	ALD	70	66	66	100/60	100/60	100/60	8	0.92	0.03	103	23	20	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	1	1	120/80	2
58	645613	35	M	ALD	70	70	68	100/60	90/60	90/60	6	2.87	2.23	101	66	44	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	100/60	2
59	646082	62	M	ALD	60	60	60	100/80	100/60	100/60	11	1.6	0.41	74	41	34	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	1	1	1	1	100/60	2
60	666123	31	M	CLD-HCV	68	66	66	110/70	10+6/62	100/60	7.8	0.51	0.18	211	15	30	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	2	2	2	2	1	100/60	2
61	642945	55	M	ALD	60	60	60	110/70	106/60	106/70	14	24.9	10.9	299	444	249	BRADY	ALTERED ECHOTEXTURE	+	-	-	-	-	-	1	1	1	13	3	90/50	2
62	692257	39	M	ALD	66	64	66	110/70	104/70	100/60	7	1.05	0.49	133	36	20	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2	3	1	1	1	100/60	1
63	2555835	60	M	ALD	68	66	66	100/70	94/60	90/60	7.8	6.31	3.62	146	59	59	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	3	2	3	2	100/60	2
64	734842	39	M	CLD-HCV	74	70	70	120/80	120/80	116/70	10	8.49	6.69	137	96	49	BRADY	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	90/50	2
65	653038	30	M	ALD	74	70	70	110/70	110/70	110/70	7.8	19.7	14.2	156	169	75	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	3	2	2	2	3	104/50	2
66	336823	43	M	ALD	70	70	70	110/70	110/70	110/70	10.4	2.16	1.09	233	36	24	N	CIRRHOSIS OF LIVER	-	-	-	-	-	-	1	1	1	1	1	110/70	2
67	656599	31	M	ALD	66	64	66	100/60	110/70	100/50	8	0.48	0.07	100	42	56	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	1	1	1	2	2	100/60	3
68	656707	60	M	ALD	60	56	56	110/70	100/60	100/60	6.4	17.4	14.2	392	55	44	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	3	2	3	2	90/40	2
69	667545	36	M	ALD	80	78	80	130/80	126/80	120/70	9	16.5	12	122	94	37	N	CIRRHOSIS OF LIVER	+	-	-	-	-	-	2	2	2	2	2	100/60	2
70	657946	27	M	CLD-AUTOIMMUNE	70	70	70	110/70	110/70	110/70	8.4	11	2.38	0.63	204	199	N	HEPATITIS	-	-	-	-	-	-	1	1	1	1	1	110/70	2
71	658138	72	M	ALD	60	56	56	110/70	110/70	100/50	6.8	6.9	0.89	50	39	44	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	2	2	2	2	100/60	2
72	659562	43	M	ALD	76	76	74	130/80	126/80	120/70	7.8	1.42	0.84	152	63	33	BRADY	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	2	2	2	100/50	2
73	665386	69	M	ALD	68	66	64	100/60	100/60	90/50	9	6.36	5.49	1049	74	51	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	3	2	2	3	100/50	2
74	3395980	38	M	CLD-HCV	56	66	60	140/80	140/80	140/80	8	2.41	0.91	181	100	57	N	ALTERED ECHOTEXTURE	+	+	-	-	+	-	2	2	2	2	2	100/50	2
75	660689	38	M	ALD	64	64	60	100/60	96/60	64/50	7.4	17.2	12.1	168	163	63	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	1	1	1	1	1	100/50	2
76	2501122	62	F	CLD-HBSAG	50	50	48	100/60	90/50	90/50	6.4	2.96	0.44	137	42	28	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	-	-	3	3	2	3	3	90/50	2
77	661703	60	F	CLD-HCV	50	50	48	100/60	96/60	90/50	8.4	21.9	14.6	72	72	63	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	+	+	3	3	3	3	3	90/50	3
78	661800	45	M	ALD	68	68	66	110/70	110/70	106/60	9.4	3.81	2.22	59	109	45	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	1	2	1	1	1	100/50	4
79	663844	33	M	CLD-HCV	78	76	70	136/82	130/80	120/80	6.4	8.27	6.07	121	88	39	N	CIRRHOSIS OF LIVER	+	-	+	-	-	-	2	3	2	2	2	100/60	3
80	666290	55	M	ALD	64	64	60	100/60	100/60	96/60	9.8	7.04	2.81	225	99	90	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	2	3	2	2	104/60	3
81	677846	46	M	ALD	50	48	46	100/60	100/60	96/50	7.8	13.8	12	168	154	49	TACHY	CIRRHOSIS OF LIVER	+	+	-	+	-	+	2	2	3	3	3	96/50	3
82	6798224	43	M	ALD	65	66	60	110/70	110/70	100/50	14	3.77	3	150	76	51	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	1	2	1	2	1	110/70	3
83	679464	40	M	ALD	70	70	70	110/70	110/70	100/50	10.4	2.04	0.58	130	49	39	N	CIRRHOSIS OF LIVER	+	+	+	-	+	-	2	2	3	2	2	100/60	2
84	676922	35	M	CLD-HCV	66	66	66	100/60	100/60	100/60	7.8	1.93	1.36	123	131	66	N	ALTERED	+		-	-	-	-	2	2	2	2	2	100/60	3

																		ECHOTEXTURE														
85	700631	66	M	ALD	56	56	50	100/60	100/60	96/50	6.5	1.52	1.14	61	20	19	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	-	+	3	3	3	3	33	96/60	1
86	679863	63	M	ALD	60	60	60	110/70	110/70	100/60	9.4	1.13	0.46	84	29	39	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	2	2	2	100/60	1
87	667056	52	M	ALD	80	80	80	130/80	130/80	130/80	9.5	3.36	1.05	74	69	45	N	CIRRHOSIS OF LIVER	+	+	-	-	+	-	2	2	2	2	2	100/60	1
88	681247	54	M	CLD-HCV	64	65	60	100/60	100/60	100/60	8.4	8.28	4.59	145	56	43	BRADY	CIRRHOSIS OF LIVER	+	+	-	+	-	+	2	3	2	2	3	100/50	3
89	682023	24	F	CLD-AUTOIMMUNE	70	70	70	110/70	110/60	110/60	14	11.3	9.6	286	16	342	N	ALTERED ECHOTEXTURE	-	-	-	-	-	-	2		1	1	1	100/60	2
90	653545	44	M	ALD	66	66	64	126/80	126/80	120/70	11	1.91	0.97	113	21	31	N	ALTERED ECHOTEXTURE	+	-	-	+	-	-	2	2	3	2	2	100/60	3
91	3539512	38	M	ALD	70	70	70	120/80	120/80	120/80	9.4	36.9	24.8	109	186	140	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	2	2	2	110/70	2
92	685533	65	F	CLD-HCV	66	66	60	100/60	100/60	96/50	6.5	1.68	1.66	160	27	33	BRADY	CIRRHOSIS OF LIVER	+	+	-	-	+	-	2	3	2	2	2	100/60	2
93	689370	34	M	ALD	90	90	90	140/80	140/80	120/80	9.6	3.66	1.7	166	51	38	TACHY	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	2	2	2	1	110/70	2
94	672550	59	M	ALD	86	86	80	110/70	100/70	110/70	12	1.7	13.2	232	11	26	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	3	2	2	3	100/60	2
95	672269	39	M	ALD	60	60	56	100/60	100/60	100/60	8.6	3.69	1.54	120	89	55	N	ALTERED ECHOTEXTURE	+	-	-	-	-	-	2	1	1	1	1	110/70	2
96	2875090	56	M	CLD-HCV	56	56	55	120/80	120/80	110/70	6.4	2.58	1.06	215	48	36	BRADY	CIRRHOSIS OF LIVER	+	-	+	-	-	-	2	3	2	2	3	100/60	2
97	672827	61	M	ALD	54	54	50	100/60	100/60	100/60	8.9	4.54	1.88	71	235	79	N	CIRRHOSIS OF LIVER	+	+	-	+	-	-	2	3	3	3	3	100/60	2
98	672594	82	M	ALD	60	60	55	100/60	100/60	100/60	9	0.36	0.16	66	14	26	BRADY	CIRRHOSIS OF LIVER	+	+	+	+	-	-	3	3	3	3	3	90/60	2
99	675210	74	M	ALD	56	55	50	100/60	100/60	100/60	8.9	3.32	2.17	244	201	66	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	2	2	2	100/60	2
100	674923	68	M	ALD	56	56	56	110/70	110/70	110/70	10	0.55	0.07	107	29	36	N	CIRRHOSIS OF LIVER	+	-	-	+	-	-	2	2	1	2	2	96/60	2

ANNEXURE-IV

KEY TO MASTER CHART

-	-	ABSENT
+	-	PRESENT
N	-	NIL
M	-	MALE
F	-	FEMALE
DOA	-	DATE OF ADMISSION
DOD	-	DATE OF DISCHARGE
IP NO	-	INPATIENT NUMBER

1- NORMAL

2- BORDERLINE

3- PRESENT/ ABNORMAL