CARDIAC FUNCTIONS IN ALCOHOLIC AND NON – ALCOHOLIC CIRRHOSIS

DISSERTATION SUBMITTED FOR

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CHENNAI

CERTIFICATE

This is to certify that the dissertation entitled ***" CARDIAC FUNCTIONS IN ALCOHOLIC AND NON – ALCOHOLIC CIRRHOSIS"*** *submitted by* ***Dr. Bindu Varghese*** *to the Faculty of Medicine, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch I (General Medicine) is a bonafide research work carried out by her under our direct supervision and guidance.*

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DECLARATION

This is a consolidated report on ***"Cardiac functions in alcoholic and non – alcoholic cirrhosis"****, a bonafide study conducted at the Department of General Medicine in Government Rajaji Hospital, Madurai, during the period June 2004 to May 2005 by me. It was not submitted earlier for any award, degree or diploma..*

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in General Medicine.

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PROFORMA

CARDIAC FUNCTIONS IN ALCOHOLIC AND NON - ALCOHOLIC CIRRHOSIS

Case No : Name : Age : Sex :

Occupation: Address: IP No.:

Height : Weight :

Alcoholism : Y/N Type : Amount : D/W Duration :

Habits : Smoking / drug addiction

Bleeding : Haematemesis / Melena / Per rectum

Abdominal distension Pedal Edema

Treatment History :

General Examination :

Anemia Jaundice Cyanosis Clubbing LNE
P/R- /mt B.P. mm Hg

CVS :

JVP
Apical Impulse
Pulsations :
LP Epigastric Second LICS
S1 S2 Addtl. Sounds Murmur

GIT :

Distension Dilated veins
Liver Spleen Fluid thrill Shifting dullness
Bowel sounds Bruit

R/S

Breath sounds Added sounds

CNS

Higher functions Sensory system
Cerebellar signs Motor system

Investigations

Hb	TC	DC	ESR	Platelet count
Urine	Albumin	Sugar	Deposits	
RBS	Blood Urea	S. Creatinine		
ECG				

ECHOCARDIOGRAPHY

TR Jet velocity - m/s Gradient - mm Hg PAH– Mild/Mod/Severe

Systolic function indices :

IVSd	LVPWd	LVIDd
IVSs	LVPWs	LVIDs
EF- %	LV Mass	

Diastolic function indices:

IVRT	Mitral E-	m/s	A-	m/s	E/A-	
	Tricuspid E-	m/s	A-	m/s	E/A-	

Deceleration Time (DT):

Pulmonary venous Doppler - S - D- AR-

USG Abdomen :

S. bilirubin	T-	D-	Total protein-	Albumin-	Globulin-
SALP	SGOT		SGPT		

OGD-

Viral Markers-

INTRODUCTION

Cirrhosis is associated with a spectrum of characteristic clinical manifestations. Clinical features of cirrhosis derive from the morphologic alterations and often reflect the severity of hepatic damage rather than the etiology of the underlying liver disease[1].

Loss of functioning hepatocellular mass may lead to jaundice, edema, coagulopathy and a variety of metabolic abnormalities: Fibrosis and distorted vasculature leads to portal hypertension and its sequelae, including gastro-esophageal varies and splenomegaly[1].

Involvement of the cardiovascular system is crucial during the course of cirrhosis due to its pathophysiological, clinical and therapeutic relationships with the liver.

Cardiovascular alterations are frequently observed in the late stages of cirrhosis. It may result in subclinical latent cardiomyopathy with hyperdynamic circulation characterised by increased cardiac output and decreased peripheral resistance. The pathogenesis of these hemodynamic alterations is still uncertain[2].

It was previously reported that chronic alcoholism may have an effect on heart[3]. Hence, it is worth comparing the cardiac parameters between alcoholic and non-alcoholic cirrhosis.

The cardiovascular changes should be taken into serious consideration during programming of therapy for the complications of cirrhosis, in particular ascites (diuretic treatment, paracentesis, Le Veen peritoneo – venous shunt) and portal hypertension.

A stable cardiac status is important before the performance of interventional procedures or liver transplantation. Perioperative cardiac dysfunction has been observed in upto 50 percent of patients after transplantation[4], with overt heart failure occurring in 1 percent to 2 percent of patients[4,5]. Some reports have suggested that this cardiac dysfunction may be reversible[5]. However, cardiac failure is a cause of mortality in upto 7 percent to 20 percent of transplants recipients [6,7]. Hence it is relevant to perform a detailed study of cardiovascular system in cirrhosis patients.

OBJECTIVES OF THE STUDY

1. *To assess the cardiac functions of alcoholic and non – alcoholic cirrhosis patients and controls.*

2. *To compare the cardiac functional status between alcoholic and non-alcoholic cirrhosis patients.*

REVIEW OF LITERATURE

Definition

Cirrhosis is defined pathologically as a diffuse process with fibrosis and nodule formation. Although the causes are many, the end results are the same.[8]

Evolution of Cirrhosis[9]

The responses of the liver to necrosis are limited; the most important are collapse of hepatic lobules, formation of diffuse fibrous septae and nodular regrowth of liver cells. Fibrosis follows hepatocellular necrosis. Nodules, which disturb the hepatic architecture follow cell death and full cirrhosis develops.

Fibrogenesis

The transformation of normal liver to a fibrotic liver and eventually cirrhosis is a complex process involving several key components, in particular stellate cells, cytokines, proteinases and their inhibitors.

The hepatic stellate cell (also called lipocyte, fat storing cell, Ito cell, pericyte) is the principal cell involved in fibrogenesis. Imbalance between matrix synthesis and degradation plays a major role in hepatic fibrogenesis.

With continued alcohol intake and destruction of hepatocytes, fibroblasts appear at the site of injury and deposit collagen. Web like septae of connective tissue appear in periportal and pericentral zones and eventually connect portal triads and central veins. This fine connective tissue network surrounds small masses of remaining liver cells, which regenerate and form nodules. With continuing hepatocyte destruction and collagen deposition, the liver shrinks in size, and acquires a nodular appearance as end-stage cirrhosis develops.[9]

Classification of cirrhosis[9]

Three anatomical types of cirrhosis are recognised micro nodular, macro nodular and mixed. Micronodular cirrhosis is characterised by thick regular septae, by regenerating small nodules varying little in size, and by involvement of every lobule. The macronodular liver may represent impaired capacity for regrowth as in alcoholism, malnutrition, old age or anaemia. Regeneration in a micronodular cirrhosis results in a macronodular or mixed appearance. With time, micronodular cirrhosis often converts to macronodular.

Aetiology[9]

- Viral hepatitis type B $\pm$ delta; C
- Alcohol

- Metabolic, e.g. haemochromatosis, Wilson's disease, α1-antitrypsin deficiency, type IV glycogenosis, galactosemia, congential tyrosinosis and non-alcoholic steatohepatitis.
- Prolonged cholestasis, intra and extra – hepatic.
- Hepatic venous outflow obstruction, e.g. venoocculsive disease, Budd-Chiari syndrome, constrictive pericarditis.
- Disturbed immunity (autoimmune hepatitis)
- Toxins and therapeutic agents, eg. Methotrexate, amiodarone.
- Indian childhood cirrhosis
- Cryptogenic cirrhosis

Diagnosis of Cirrhosis[9]

Clinical History

Fatigue and weight loss, loss of libido, anorexia and flatulent dyspepsia, abdominal pain, colour of urine and faeces, swelling of legs or abdomen, haemorrhage – nose, gums, skin, alimentary tract. Past health : jaundice, hepatitis, drugs ingested, blood transfusion. Social : alcohol consumption.

Examination

Nutrition, fever, fetor hepaticus, jaundice, pigmentation, purpura, clubbing, white nails, vascular spider, palmar erythema, gynaecomastia, testicular atrophy, distribution of body hair.

Abdomen

Ascites, abdominal wall veins, liver, spleen, oedema.

Neurological changes

Mental functions, stupor, tremor

Investigations

Haematology

- Haemoglobin
- Platelet count
- Leucocyte count
- Prothrombin time

Serum biochemistry

- Bilirubin
- Alkaline Phosphatase
- Transaminases
- γ- glutamyl transpeptidase (γ - GT)

- Immunoglobulins
- Albumin and globulin

If ascites present

- Serum electrolytes
- Daily weight
- Urea and creatinine
- 24 hours urinary volume and sodium

Serum immunological investigations

- Hepatitis B Ag, Anti HCV
- Alpha fetoprotein
- Smooth muscle, mitochondrial, nuclear antibodies

Endoscopy

Hepatic CT scan or ultrasound

Using ultrasound, cirrhosis is suggested by fine surface nodularity and portal vein mean flow velocity. The caudate lobe is enlarged relative to the right lobe. Regeneration nodules may be shown as focal lesions. CT scan is cost – effective for the diagnosis of cirrhosis and its complications. Liver size can be assessed and the irregular nodular surface seen. After intravenous contrast, the portal vein and hepatic veins can be identified in the liver, and

a collateral circulation with splenomegaly may give confirmation to the diagnosis of portal hypertension. Ascites can be seen.

Laparotomy

Laparotomy should never be used to diagnose cirrhosis because it may precipitate liver failure even in those with very well compensated disease.

Laparoscopy

Laparoscopy visualizes the nodular liver and allows directed liver biopsy.

Liver biopsy

Biopsy diagnosis of cirrhosis may be difficult. Reticulin and collagen stains are essential for the demonstration of a rim of fibrosis around the nodule.

EEG

EEG indicated if neuropsychiatric changes are present and to detect early changes in pre coma.

Clinical and pathological associations[9]

- Δ Nutrition : Protein – calorie malnutrition is commonly seen in chronic liver disease, present in 20% of patients with

compensated cirrhosis and more than 60% of those with severe hepatic dysfunction. Malnutrition also is an independent predictor for the first variceal bleed and survival in patients with oesophageal varices.

- Δ Parotid gland enlargement and Dupuytren's contracture are seen in some alcoholic patients with cirrhosis.
- Δ Digital clubbing and hypertrophic oesteroarthropathy may be seen in cirrhosis, especially biliary cirrhosis.
- Δ Muscle cramps occur significantly more frequently in cirrhotic patients and correlated with the presence of ascites, low mean arterial pressure.
- Δ Steatorrhoea is frequent due to reduced hepatic bile salt secretion even in the absence of pancreatitis or alcoholism.
- Δ Splenomegaly and abdominal wall venous collaterals usually indicate portal hypertension.
- Δ Abdominal herniae are common with ascites.
- Δ Gastrointestinal: Peptic ulceration has been found in cirrhosis more frequently than in those who are HBsAg positive. Duodenal ulcers were more frequent than gastric ulcers.
- Δ Primary liver cancer is frequent with all forms of cirrhosis except the biliary and cardiac types with an overall 60-fold increased risk.
- Δ Cardiovascular: Cirrhotics are less liable to coronary and aortic atheroma. Cirrhosis is associated with an increased cardiac output

and heart rate, decreased systemic peripheral vascular resistance and blood pressure. Cirrhotic cardiomyopathy is recognised with abnormal cardiac contractility.

- Δ Pulmonary: Hypoxemia may be due to the hepatopulmonary syndrome and right heart failure due to porto pulmonary hypertension. α1- Antitrypsin deficiency may cause childhood liver disease, and later emphysema and silent cirrhosis.
- Δ Renal: Changes in intrarenal circulation, and particularly a redistribution of blood flow away from the cortex, are found in all forms of cirrhosis. This predisposes to the hepato-renal syndrome.
- Δ Infections: Bacterial infections are frequent due to reduced immune defence mechanisms and impaired reticuloendothelial cell phagocytic activity. Patients with ascites are prone to spontaneous bacterial peritonitis (SBP). Sepsis should always be suspected in cirrhotic patients with unexplained pyrexia or deterioration. After gastrointestinal haemorrhage the risk of sepsis is greater in Child C rather than Child A/B grade cirrhotics. There is increased occurrence of tuberculosis, in cirrhotics and tuberculous peritonitis is therefore still encountered but often not suspected.
- Δ Diabetes Mellitus: While upto 80% of cirrhotics are glucose intolerant, only 10-20% are truly diabetic.

Compensated cirrhosis[9]

The disease may be discovered at a routine examination or biochemical screen, or at operation undertaken for some other condition. Cirrhosis may be suspected if the patient has mild pyrexia, vascular spiders, palmar erythema, or unexplained epistaxis or oedema of the ankles. Firm enlargement of the liver and splenomegaly are helpful diagnostic signs. Vague morning indigestion and flatulent dyspepsia may be early features in the alcoholic cirrhotic. Confirmation should be sought by biochemical tests, scanning and if necessary, by liver biopsy. Biochemical tests may be quite normal in this group. The most frequent changes are a slight increase in the serum transaminase or γ– GT level. Diagnosis is confirmed by needle biopsy of liver.

Decompensated Cirrhosis

The patient usually seeks medical advice because of ascites and or jaundice. General health fails with weakness, muscle wasting and weight loss. Continuous mild fever (37.5-38^{0}C) is often due to gram-negative bacteremia, continuing hepatic cell necrosis or liver cell carcinoma. A liver flap may be present. The deeper the jaundice, the greater the liver cell dysfunction.

Pigmentation of the skin and clubbing of the fingers are occasionally seen. Purpura over the arms, shoulders and shins may be associated with a

low platelet count. Spontaneous bruising and epistaxis reflect a prothrombin deficiency. The blood pressure is low. Sparse body hair, vascular spiders, palmar erythema, white nails and gonadal atrophy are common. Ascites and oedema of the legs are frequently associated. The liver may be enlarged (early stages), with a firm regular edge, or contracted and impalpable (late stages). The spleen may be palpable.

Laboratory findings

Haematology

There is usually a mild normocytic, normochromic anaemia; it is occasionally macrocytic. Gastrointestinal bleeding leads to hypochromic anaemia. The leucocyte and platelet counts are reduced ('hypersplenism'). The prothrombin time is prolonged and does not return to normal with vitamin K therapy. The bone marrow is macro normoblastic.

Serum biochemical changes

In addition to the raised serum bilirubin level, albumin is depressed and γ–globulin raised. The serum alkaline phosphatase is usually raised to about twice normal; very high readings are occasionally found, particularly with alcoholic cirrhosis. Serum transaminase values may be increased.

Urine

Urobilinogen and bilirubin are detected if the patient is jaundiced.

Needle biopsy diagnosis

This may give a clue to the aetiology and inflammatory activity. If there are contraindications, such as ascites or a coagulation defect, the transjugular approach should be used.

Child Pugh Classification[9]

Points			
	1	**2**	**3**
Encephalopathy (grade)	None	1 – 2	3 – 4
Ascites	Absent	Slight	Moderate–Severe
Bilirubin (mg/dl)	<2	2 – 3	> 3
Albumin (g/dl)	>3.5	2.8 – 3.5	< 2.8
Prothrombin time (sec prolonged)	<4	4 – 6	> 6
INR	<1.7	1.7 – 2.3	>2.3

The total score classified patients into grade A (5-7) B (7-9) or C (>10). Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, advanced age, high daily alcohol

consumption, high serum bilirubin and alkaline phosphatase, low albumin values, and poor nutrition. Patients with compensated cirrhosis become decompensated at the rate of 10% per year. Ascites is the usual first sign. Decompensated patients have around a 20% 5 year survival.

The following points are useful prognositically:

- Liver size: A large liver carries a better prognosis than a small one because it is likely to contain more functioning cells.
- Haemorrhage from oesophageal varices: If liver function is good, haemorrhage may be tolerated; if poor, hepatic coma and death are probable.
- Persistent hypotension (systolic BP < 100 mm-Hg) is serious.
- Ascites worsens the prognosis.
- If decompensation has followed haemorrhage, infection or alcoholism, the prognosis is better than if it is spontaneous, because the precipitating factor is correctable.
- Jaundice, especially if persistent, is a serious sign.
- Neurological complication. The significance of encephalopathy depends on clinical circumstances. Developing in the course of progressive hepatocellular failure, it carries a bad prognosis. Chronic and those with an extensive portal – systemic collateral circulation who respond well to medical treatment carries good prognosis.

- Biochemical tests: If the serum albumin is less than 25g/l the outlook is poor. Hyponatremia (serum sodium < 120 mmol/l), if unrelated to diuretic therapy, is grave. Serum transaminase and globulin levels give no guide to prognosis.
- Alcoholic cirrhotics, if they abstain, respond better than those with 'cryptogenic' cirrhosis.
- The response to therapy: If the patient has failed to improve within 1 month of starting hospital treatment, the outlook is poor.
- Hepatic histological changes: Section are useful in evaluating the extent of necrosis and of inflammatory infiltration. A fatty liver responds well to treatment.

CIRRHOSIS AND CARDIOVASCULAR INVOLVEMENT

Cardiovascular alterations are frequently observed in the late stages of cirrhosis. The patient with hepatocellular dysfunction in cirrhosis shows marked vasodilatation accompanied by hyperdynamic circulation and opening of arteriovenous shunts[2]. The effect of these circulatory changes and especially the profound vasodilatation has only recently been investigated in detail[1,2].

Hyperdynamic Circulatory State

Systemic hemodynamic alterations have been recognised in patients with chronic liver disease and may occur in more than 30 percent of cirrhotics [10,11]. This hyperdynamic circulatory state is characterised by splanchnic and systemic vasodilatation and an elevated cardiac output. Clinically, patients may present with low blood pressure, tachycardia, and a cardiac flow murmur. Cutaneous stigmata of vasodilatation in chronic liver disease including spider angiomata and palmar erythema may also be present. The usefulness of cutaneous findings in predicting the presence or absence of a hyperdynamic state is unknown. When measured, cardiac output is elevated and systemic vascular resistance is low. The clinical and hemodynamic alterations in the hyperdynamic circulatory state of cirrhosis are similar to those seen in endotoxemia and sepsis. This observation contributed to the initial hypothesis by Vallance and Moncada that endotoxin and cytokine mediated nitric oxide production contributes to the hyperdynamic circulation in cirrhosis [12]. In addition, it is now increasingly recognised that the vascular alterations associated with the hyperdynamic circulatory state may also occur in other organs and contribute to pulmonary, renal and central nervous system complications seen in liver disease.[13]

The pathogenesis of cardiovascular complications in chronic liver disease remains an area of intense study. Significant experimental data have

implicated excess nitric oxide production as a major contributor to the splanchnic and systemic vasodilatation underlying the hyperdynamic circulatory state [14,15]. The majority of information suggests that nitric oxide production is generated from the endothelial form of nitric oxide synthase found in the vasculature rather than from the inducible form of nitric oxide synthase found more commonly in parenchymal, smooth muscle, and inflammatory cells, as originally hypothesized [12]. This concept has recently been supported by experimental work demonstrating that mediators, classically known to up-regulate inducible nitric oxide synthase, also modulate endothelial nitric oxide synthase, in experimental cirrhosis [16]. However, the pathogenesis of the hyperdynamic circulatory state is likely multi-factorial and other mediators, including glucagon, prostaglandins and bile acids may contribute to vasodilatation [17]. Vasodilatation is accompanied by sodium and water retention and leads to total body fluid overload and an elevated cardiac output. However, the primary stimulus for vascular nitric oxide production remains unknown.

The relative importance of hepatic dysfunction and portal hypertension in triggering the hyperdynamic circulatory state is also unknown. Although the hyperdynamic circulatory state is generally more pronounced in more severe liver disease[18], a similar state is seen in experimental animals[14] and in humans[20] with extrahepatic portal hypertension. These findings suggest that both hepatic dysfunction and

portal hypertension may trigger changes in the splanchnic and systemic vasculature leading to nitric oxide overproduction. The observation that the hyperdynamic circulatory state worsens for a period of at least 1 to 3 months after portal pressure is acutely lowered by transjugular intrahepatic portosystemic shunt (TIPS)[21] suggests that the interactions between portal pressure, hepatic synthetic function and portosystemic shunting that lead to the hyperdynamic circulatory state are complex.

Cirrhotic Cardiomyopathy

Shortly after the recognition of the hyperdynamic circulatory state in liver disease, studies suggested that the cardiac response during increased demand was subnormal in cirrhosis [22]. Initial studies were performed in alcoholic cirrhosis [23, 24] and led to the assumption that alcohol was the cause of the cardiac dysfunction. More recently, it has been established that the cardiac response to physiologic and pharmacologic stresses may be impaired in many different types of cirrhosis. This finding has resulted in the recognition that a unique form of high output cardiac dysfunction occurs in liver disease [22]. Clinically, cardiac dysfunction is often mild or latent in cirrhosis, a finding some have attributed to the after load reducing effects of systemic vasodilatation that decrease cardiac work[22]. However, in the setting of increased cardiac stress such as liver transplantation [4,25] and TIPS, [21] overt cardiac dysfunction may occur. Perioperative cardiac dysfunction has been observed in upto 50 percent of patients after transplantation [4], with

overt heart failure occurring in 1 percent to 2 percent of patients [4,5]. Some reports have suggested that this cardiac dysfunction may be reversible[5]. However, cardiac failure is a cause of mortality in upto 7 percent to 20 percent of transplant recipients[1,7]. No studies have identified reliable screening methods to define which patients have latent cardiac dysfunction and may be at risk for overt heart failure under stress[26].

The pathogenesis of the cardiac dysfunction in liver disease has largely been investigated in experimental models and likely involves a number of abnormalities. Alterations in cardiac β– adrenergic signaling [27-29], decreased plasma membrane fluidity[29], increased cardiac nitric oxide production[30-31] and elevated circulating levels of catecholamines[32] have all been suggested to contribute to cardiac dysfunction. However, how these abnormalities relate to the hyperdynamic circulatory state and the degree of hepatic synthetic dysfunction and whether similar abnormalities contribute to human disease remain unknown. The pathophysiologic mechanisms in alcoholic cardiomyopathy appear to be different from cirrhotic cardiomyopathy[33], supporting the idea that the two entities are distinct. In addition, the common perception that alcoholic cardiomyopathy is infrequent in alcoholic cirrhosis appears to be incorrect, because the two entities commonly co-exist[3]. Finally, genetic hemochromatosis may also result in the development of a dilated cardiomyopathy secondary to iron mediated myocardial injury[34].

Pulmonary Complications

Pulmonary symptoms and abnormalities occur commonly in patients with chronic liver disease. As many as 70 percent of cirrhotic patients undergoing evaluation for liver transplantation, if asked, complain of dyspnoea[35]. Arterial blood gas and pulmonary function abnormalities also are common and are found in as many as 45 percent to 50 percent of patients[36]. A variety of causes for pulmonary dysfunction in liver disease have been identified and include intrinsic cardiopulmonary disorders not specifically related to liver disease and unique problems associated with the presence of liver disease or portal hypertension. The recognition that a subset of patients with hepatic disease develop significant pulmonary vascular alterations, either microvascular dilation leading to the hepato pulmonary syndrome (HPS) or arteriolar vasoconstriction leading to portopulmonary hypertension, indicates that unique changes in the pulmonary vasculature may occur in liver disease. These pulmonary vascular syndromes significantly impact morbidity and mortality in affected patients and may influence candidacy for liver transplantation.

Hepatopulmonary syndrome

HPS result from intrapulmonary microvascular dilation that occurs in a subgroup of patients with liver disease or portal hypertension. It is commonly defined by the presence of hepatic dysfunction or portal hypertension, a widened age corrected alveolar arterial oxygen gradient on

room air with or without hypoxemia, and intra pulmonary vasodilation[11]. Presently, studies demonstrate that as many as 40 percent of cirrhotic patients have detectable intrapulmonary vasodilatation[38] and that upto 8 to 15 percent will develop impaired oxygenation leading to significant functional limitations [37].

The pathogenesis of intrapulmonary vasodilatation in HPS is an area of active investigation. Studies in humans have implicated enhanced pulmonary production of nitric oxide in the development of vasodilatation by assessing exhaled nitric oxide production[39]. However, the cause of the increased pulmonary nitric oxide production and its relationship to the presence of portal hypertension, the hyperdynamic circulation, and the degree of liver injury remains undefined. Animal studies suggest that low level production and release of endothelin – 1 during liver injury may increase the levels and activity of pulmonary vascular endothelial nitric oxide synthase in the setting of portal hypertension, which leads to excess local nitric oxide production and vasodilatation[40]. However, whether hepatic endothelin – 1 production contributes to the development of human disease is unknown.

Portopulmonary Hypertension

The association between pulmonary artery hypertension and portal hypertension has been termed 'portopulmonary hypertension'. It is defined

by the National Institute of Health Patient Registry for the characterisation of primary pulmonary hypertension as a mean pulmonary artery pressure greater than 25 mm Hg and a pulmonary capillary wedge pressure lower than 15 mm Hg in the setting of portal hypertension[41].

Portopulmonary hypertension frequently presents with progressive symptoms that may begin as non specific complaints of fatigue, dyspnea, and peripheral edema. The severity of these symptoms worsens with increasing pulmonary hypertension[42]. However, similar symptoms are common in cirrhosis without pulmonary hypertension and are also seen in HPS.

The prevalence and severity of portopulmonary hypertension do not appear to correlate with the degree of hepatic synthetic dysfunction; azygos blood flow, or the severity of portal hypertension. However, survival in pulmonary hypertension correlates with the severity of right-sided cardiac dysfunction as assessed by the degree of elevation in the right atrial pressure and the degree of decline in the cardiac output. Accordingly, survival appears to be prolonged in portopulmonary hypertension relative to primary pulmonary hypertension (5 year survival, 50 present versus 25 percent), possibly related to the beneficial effects of the hyperdynamic circulatory state. Nonetheless, portopulmonary hypertension is generally

progressive and has a high likelihood of contributing to morbidity and mortality in affected cirrhotics[42].

The pulmonary histologic abnormalities in portopulmonary hypertension are identical to those found in primary pulmonary hypertension and include smooth muscle proliferation and hypertrophy, concentric intimal fibrosis, plexogenic arteriopathy and necrotizing vasculitis. The cause of these abnormalities remains incompletely understood.

Studies that have evaluated the diagnostic utility of various clinical predictors of portopulmonary hypertension including systemic hypertension, accentuated P_2, echocardiographic measurement of pulmonary artery pressures and right ventricular dilation, and electrocardiographic and chest radiographic abnormalities have shown that these predictors are in general specific but of low sensitivity. Many transplant centers will routinely perform echocardiography in transplant candidates more than 40 years of age and proceed to right heart catheterization if the estimated pulmonary arterial pressure is greater than 50 mm Hg or when right ventricular dilation or hypertrophy is present[42].

L-carnitine, cirrhosis of liver and cardiac involvement

L-carnitine is an essential co-factor in the transfer of long chain fatty acids across the inner mitochondrial membrane for oxidation. Fatty acids

have an important role in myocardial metabolism. There have been previous reports that deficiency of L-carnitine may have an effect on myocardial fatty acid metabolism and subsequent development of dilated cardiomyopathy[43]. Since L-carnitine levels and metabolism were altered in cirrhosis, it may contribute to cardiac dysfunction.

INVESTIGATIONS FOR ASSESSING CARDIAC INVOLVEMENT[47]

The assessment of left ventricular function is an essential component of the evaluation of any patient with suspected heart disease. Echocardiography is an excellent tool for non –invasive assessment of left ventricle.

Intracavity dimensions

Measurements can be made on an M-mode (motion mode) echocardiogram during diastole (d) and systole (s). (Figure 1). These measurements reflect the chamber dimensions of the heart.

All M mode measurements be made from leading edge to leading edge. From M mode measurements taken at the tip of the mitral valve level in parasternal long axis view, ejection fraction can be measured. Ejection fraction represents the percent or fractions of left ventricular diastolic volume that is ejected in systole.

LV Diastolic function

Spectral Doppler is currently the technique of choice for evaluating left ventricular diastolic functions.

Figure 2 illustrates the left ventricular inflow velocities and measurements for assessing the diastolic function of the left ventricle. Figure 2(A) shows the normal situation. The early inflow of blood reaches a peak at the E point. Flow then decelerates until atrial systole, at which time the left atrial pressure rises above the left ventricular pressure and flow again passes through the mitral valve.

Alterations in left ventricular diastolic function may reduce the height of the E wave and increase the height of the 'A' wave. This type of abnormality is usually accompanied by prolongation of the isovolumic relaxation time (IVRT) and prolongation of the decelaration time (DT). [Figure 2 (B)] The hemodynamic abnormalities responsible for this pattern usually are reduced left ventricular relaxation and slower fall in left ventricular pressure.

The other pathologic pattern that is seen with mitral flow velocities is the reverse – a tall E wave and a short A wave. This pattern is accompanied by short isovolumic relaxation and deceleration times. [Figure 2 (D)] This type of mitral inflow can be produced by elevated left ventricular filling

pressures. With elevated early diastolic pressure, the flow into the left ventricle is accelerated and there may be relatively little blood to propel with atrial systole.

In some disease states, the initial pathologic pattern in abnormal relaxation with a short E wave and tall A wave. If mitral regurgitation or congestive heart failure raises the left ventricular filling pressure, then the pattern may reverse and the E wave will become taller and A wave will become shorter. Thus a transition situation can occur whereby 'pseudonormalisation' of the mitral inflow can occur. [Figure 2 (C)]

Pulmonary venous flow also reflects changes in left ventricular diastolic function. With reduced early relaxation, the diastolic component decreases and the reversed 'A' wave increases. When early filling is rapid, the pulmonary venous flow exhibits almost no systolic phase and tall diastolic and atrial components.

Estimation of the systolic pressure in pulmonary artery (PA)

This measurement can be done using modified Bernoulli equation. With the transducer in the apical position, tricuspid regurgitation jet velocity is measured. Pressure gradient is given by the modified Bernoulli equation $\Delta P = 4V^2$ in which V is the peak velocity of the tricuspid regurgitation jet. PA systolic pressure is calculated by adding ten to the estimated pressure gradient.

MATERIALS AND METHODS

1. Type of Study : Prospective Observational Analytical Study

2. Place : Government Rajaji Hospital, Madurai

3. Collaborating Departments : Department of Medical Gastroenterology and Department of Cardiology.

4. Duration of Study : June 2004 to May 2005

5. Ethical clearance : Ethical clearance was obtained and the study was initiated

6. Consent : Informed consent was obtained before taking up the case for study

7. Inclusion Criteria

All newly diagnosed cases of cirrhosis of liver based on physical examination, biochemical parameters, ultrasonogram of abdomen and upper GI endoscopy.

8. Exclusion Criteria

- Δ Age < 20 years and > 60 years
- Δ Sex : Female
- Δ CVS
    - o Systemic arterial hypertension
    - o Primary cardiac / pulmonary diseases
    - o Hemodynamic instability
- Δ GIT
    - o Hepatic encephalopathy
    - o Gross ascites
    - o Viral hepatitis
- Δ Haematological
    - o Anemia
- Δ Metabolic
    - o Diabetes Mellitus
    - o Thyroid dysfunction
- Δ Active infection / Septicemia
- Δ Collagen vascular diseases
- Δ Malignancies
- Δ Habits
    - o Smoking
    - o Drug addiction

- Drugs
    - Hepatotoxic drug intake
    - Cardiac drug intake
- Un co-operative patients

9. Materials :

A total of one hundred consecutive adult male patients of cirrhosis of liver, admitted to the medical and gastroenterology wards of Government Rajaji Hospital, Madurai were selected based on inclusion and exclusion criteria.

All patients in the study underwent full clinical evaluation. Clinical history and physical examination findings were recorded with particular attention to present or previous haematemesis, melena, bleeding PR, other bleeding tendencies, alcoholism, blood transfusion, intake of hepatotoxic drugs, jaundice, anemia, edema, stigmata of chronic liver disease, dilated abdominal veins, splenomegaly, ascites and encephalopathy.

All patients were subjected to the following haematological, biochemical and microbiological studies.

Blood

- Hb, TC, DC, ESR
- Platelet count
- Random blood sugar
- Blood urea and serum creatinine
- Liver function tests
    - Serum bilirubin (total and direct)
    - Total protein, albumin and globulin
    - Serum alkaline phosphatase
    - ALT and AST
- Viral markers

Each one of them was subjected to ultrasonogram of abdomen to confirm the presence of cirrhosis. Upper GI endoscopy was done in all patients, after overnight fasting early in the morning. Single channel electro cardiogram (using Alpha 99 trans health care) was done to measure the electrical activity of the heart. Colour Doppler Echocardiogram (using Aloka, Philips system) was done to assess the cardiac involvement. The parameters studied were :

- **Systolic function indices**
    - Left ventricular internal dimension in systole (LVIDs)
    - Left ventricular internal dimension in diastole (LVIDd)

- Interventricular septal diameter in diastole (IVSd)
- Left ventricular posterior wall thickness in diastole (LVPWd)
- Ejection Fraction % (EF)

o **LV Mass**

o **TR Jet velocity and gradient**

o **Diastolic function indices**

- Isovolumic relaxation time (IVRT)
- Mitral E Deceleration time (DT)
- Mitral E and A velocities

10. Conflicting interests **:** Nil

11. Financial Supply **:** Nil

Data were collected in a predetermined proforma (section 10) and later in Microsoft excel spreadsheet of a computer.

Age and sex matched forty healthy subjects served as the control group.

12. Statistical analysis

Computer analysis of data was done using the software – Epidemiological Information Package, 2002 (Epi Info 2002) developed by the Centre for Disease Control and Prevention, Atlanta; U.S.A. for World Health Organisation. The range, median, standard deviation and statistical significance were calculated. Wherever p value was found to be less than 0.05, it was considered significant.

Results

The results of the present study are presented in the ensuing pages.

Table 1 : Age distribution

Age (years)	Alcoholic cirrhotics	Non - alcoholic cirrhotics	Total	Controls
20-40	3 (8%)	38 (56%)	41 (41%)	16 (40%)
41-60	35 (92%)	24 (44%)	59 (59%)	24 (60%)
Total	38 (38%)	62 (62%)	100	40

- Out of the hundred patients selected, 38% were having alcoholic cirrhosis.

- Most of the alcoholic cirrhotics were above the age of forty years while majority of non alcoholic cirrhotics in the study were young ($\leq$ 40 years).

I. CIRRHOSIS (N = 100 CASES) AND CONTROLS (n = 40)

Table 2: LV Systolic Function Parameters (in cms)

The LV systolic function parameters (LVIDs LVIDd, EF, IVSd, LVPWd) studied are presented in the table given below

Parameter	Type of cases	Range	Mean	Std. Deviation	P value
LVIDs	a) Cirrhosis cases	2.51-4.35	3.19	0.48	0.683
	b) Controls	2.91-3.41	3.14	0.15	
LVIDd	a) Cirrhosis cases	3.59-5.7	4.79	0.5	0.301
	b) Controls	4.13-5.22	4.71	0.35	
EF (%)	a) Cirrhosis cases	50-86	67.66	8.67	0.1802
	b) Controls	60-71	66.28	3.43	
IVSd	a) Cirrhosis cases	0.45-1.4	0.86	0.19	0.366
	b) Controls	0.67-1.04	0.89	0.09	
LVPWd	a) Cirrhosis cases	0.5-1.9	0.88	0.25	0.9613
	b) Controls	0.6-1.15	0.85	0.15	

When the left ventricular systolic function parameters were compared between cirrhosis patients and controls, there was no statistically significant difference.

Table 3: PA systolic Pressure (PASP in mm Hg)

The PA systolic pressures of cirrhosis and controls are given in the following table

Type of Cases	Range	Mean	Std. Deviation
Cirrhosis Cases	12.5-56	28.64	9.06
Controls	13-29	20.4	4.21

'p'=0.0001

There was significant difference between the PA systolic pressures of cirrhosis cases and controls.

Table 4: LV Mass (in grams)

The LV mass estimated in cirrhotics and controls are presented in the table given below

Type of Cases	Range	Mean	Std. Deviation
Cirrhosis Cases	74-271	162.26	50.65
Controls	90-210	159.33	41.77

'p'=0.8917

The difference between LV Mass values of cirrhosis cases and controls were not statistically significant.

II. ALCOHOLIC CIRRHOSIS (A=38) AND NON-ALCOHOLIC CIRRHOSIS (n=62) cases

Table 5: LV Systolic function indices (in cms)

LV systolic function indices (LVIDs, LVIDd, EF, IVSd, LVPWd) studied in alcoholic and non - alcoholic cirrhotic patients are presented in the tabular column below.

Parameter	Type of cases	Range	Mean	Std. Deviation	P value
LVIDs	Alcoholic cirrhosis	2.56-4.35	3.25	0.58	0.5938
	Non–alcoholic cirrhosis	2.51-4.1	3.17	0.41	
LVIDd	Alcoholic cirrhosis	3.59-5.7	4.77	0.55	0.7596
	Non–alcoholic cirrhosis	4.04-5.6	4.81	0.48	
EF (%)	Alcoholic cirrhosis	50-81	65.42	8.94	0.654
	Non –alcoholic cirrhosis	52-86	69.03	8.23	
IVSd	Alcoholic cirrhosis	0.58-1.4	0.91	0.21	0.3701
	Non –alcoholic cirrhosis	0.45-1.12	0.84	0.17	
LVPWd	Alcoholic cirrhosis	0.54-1.21	0.89	0.19	0.2086
	Non –alcoholic cirrhosis	0.5-1.9	0.88	0.3	0.2026

There was no statistically significant difference, when the LV systolic functions parameters were compared between alcoholic and non-alcoholic cirrhotics.

Table 6: PA Systolic Pressure (in mm Hg)

PA systolic pressure measured in the alcoholic and non-alcoholic cirrhosis patients is tabulated below.

Type of Cases	Range	Mean	Std. Deviation
Alcoholic Cirrhosis Cases	13.4-37.8	28.24	8.54
Non Alcoholic Cirrhosis cases	12.5-56	28.88	9.42

'p'=0.9405

Statistically significant difference does not exist between the PA systolic pressure values of alcoholic cirrhosis cases and Non alcoholic cirrhosis cases.

Table 7: LV Mass (in grams)

The estimated LV mass of alcoholic and non – alcoholic cirrhosis patients are listed below

Type of Cases	Range	Mean	Std. Deviation
Alcoholic Cirrhosis Cases	74-262	175.5	57.4
Non Alcoholic Cirrhosis cases	76-271	154.1	44.6

'p'=0.1148

The difference between LV Mass values of Alcoholic cirrhosis cases and non alcoholic cirrhosis cases was not statistically significant.

III. ALCOHOLIC CIRRHOSIS (N=38) AND CONTROLS (N=40)

Table 8: LV systolic function parameters (in cms)

LV systolic function parameters (LVIDs, LVIDd, EF, IVSd, LVPWd) are compared between the alcoholic cirrhotics and controls in the following table.

Parameter	Type of cases	Range	Mean	Std. Deviation	P value
LVIDs	Alcoholic cirrhosis cases	2.56-4.35	3.25	0.58	0.4622
	Controls	2.91-3.41	3.14	0.15	
LVIDd	Alcoholic cirrhosis cases	3.59-5.7	4.77	0.55	0.2937
	Controls	4.13-5.22	4.71	0.35	
EF (%)	Alcoholic cirrhosis cases	50-81	65.42	8.94	0.7751
	Controls	60-71	66.28	3.43	
IVSd	Alcoholic cirrhosis cases	0.58-1.4	0.91	0.21	0.9322
	Controls	0.67-1.04	0.89	0.09	
LVPWd	Alcoholic cirrhosis cases	0.54-1.21	0.89	0.19	0.3813
	Controls	0.6-1.15	0.85	0.15	

There was no significant difference between cirrhosis patients and controls when the LV systolic function parameters were compared.

Table 9: PA systolic pressure (in mm Hg)

The PA systolic pressures calculated in the alcoholic cirrhotic patients and controls are furnished in the table given below.

Type of Cases	Range	Mean	Std. Deviation
Alcoholic Cirrhosis Cases	13.4-46	28.24	8.54
Controls	13-29	20.4	4.21

'p'=0.0001

Statistically significant difference exists between the PA systolic pressure values of alcoholic cirrhosis cases and controls.

Table 10: LV Mass (in grams)

LV mass measurements of alcoholic cirrhosis cases and controls are compared below.

Type of Cases	Range	Mean	Std. Deviation
Alcoholic Cirrhosis Cases	74-262	175.53	57.4
Controls	90-210	159.33	41.77

'p'=0.3371

The difference between LV Mass values of alcoholic cirrhosis cases and control cases was not statistically significant.

IV. NON – ALCOHOLIC CIRRHOSIS (N=62) CASES AND CONTROLS (N=40).

Table 11: LV systolic function parameters (in cms)

The LV systolic function parameters of non-alcoholic cirrhosis patients and controls are furnished in the table below.

Parameter	Type of cases	Range	Mean	Std. Deviation	P value
LVIDs	Non -alcoholic cirrhosis cases	2.51-4.1	3.17	0.4	0.9181
	Controls	2.91-3.41	3.14	0.15	
LVIDd	Non -alcoholic cirrhosis cases	4.04-5.6	4.81	0.48	0.4143
	Controls	4.13-5.22	4.71	0.35	
EF (%)	Non-alcoholic cirrhosis cases	52-86	69.03	8.28	0.287
	Controls	60-71	66.28	3.43	
IVSd	Non-alcoholic cirrhosis cases	0.45-1.12	0.84	0.17	0.0984
	Controls	0.67-1.04	0.89	0.09	
LVPWd	Non-alcoholic cirrhosis cases	0.5-1.9	0.88	0.3	0.5014
	Controls	0.6-1.15	0.85	0.15	

There was no statistically significant difference when the LV systolic function parameters were compared between non-alcoholic cirrhosis patients and controls.

Table 12: PA systolic pressure (in mm Hg)

The PA systolic pressures calculated in non-alcoholic cirrhosis patients and controls are tabulated below.

Type of Cases	Range	Mean	Std. Deviation
Non - Alcoholic Cirrhosis Cases	12.5-56	28.89	9.42
Controls	13-29	20.4	4.21

'p'=0.0001

There was statistically significant difference between the PA systolic pressure values of non-alcoholic cirrhosis cases and controls.

Table 13: LV Mass (in grams)

The LV mass measurements of non-alcoholic cirrhosis patients and controls are given in the table below.

Type of Cases	Range	Mean	Std. Deviation
Non Alcoholic Cirrhosis Cases	76-271	154.1	44.6
Controls	90-210	159.33	41.8

'p'=0.3895

There is no statistically significant difference between LV mass values of non - alcoholic cirrhosis cases and controls.

Table 14 : Left Ventricular Diastolic Dysfunction patterns in cirrhosis patients

The various diastolic dysfunction patterns which were noted are furnished in the following tabular column.

Pattern of diastolic dysfunction	Alcoholic cirrhosis patients (n=38)	Non-alcoholic cirrhosis patients (n=62)	Controls (n=40)
Impaired relaxation pattern	13(34%)	15(24%)	6(15%)
Pseudonormal pattern	4(11%)	7(11%)	2(5%)
Restrictive pattern	2(5%)	7(11%)	2(5%)
Total	19(50%)	29(46%)	10(25%)

Majority of patients in both groups with diastolic dysfunction showed LV relaxation abnormally pattern (>50%) (Stage 1 diastolic dysfunction)

I. 48 cirrhotic patients (48%) had diastolic dysfunction (DD) compared to 10 persons (25%) in the control group which was statistically significant ($p<0.05$)

[The Standard Error of Difference (SED) was 8.47 while the Observed Difference (OD) was 23]

II. 19 patients (50%) of the alcohol cirrhotic had DD compared with 10 (25%) individuals of controls which was significant ($p<0.05$)

[SED was 8.11while the OD was 25]

III. 29 (46%) non-alcoholic cirrhosis patients had DD compared with 10 (25%) individuals in the control group which was statistically significant ($p<0.05$)

[SED was 9.32 while the OD was 21]

IV. 19 patients (50%) of alcoholic cirrhotics had DD compared with 29 (46%) non-alcoholic cirrhotic patients which was not significant ($p>1$)

[SED was 10.28 while OD was only 4]

DISCUSSION

Cirrhosis of liver involves most organs and systems; hence it may be considered as a systemic disease[48]. Knowledge of cardiovascular system involvement in a cirrhotic patient is important in planning treatment and assessing the prognosis. Only a few studies have been done in India assessing the cardiac status of cirrhotic patients.

In this study, simple, non-invasive commonly available test, Colour Doppler Echocardiography was used as the main investigative modality to assess cardiac function. Procedures like cardiac catheterization are invasive, costly and available only in few selected centers. Hence it was not considered.

Only male patients were selected for the study since alcoholism and subsequently alcoholic cirrhosis are very rare in females. Both young and old patients with alcoholic and non – alcoholic cirrhosis were involved in the study. In order to assess the true effect of cirrhosis on cardiac functions, patients with common diseases affecting heart were excluded from the study.

In cirrhosis, circulatory changes in the form of systemic vasodilation and a hyperdynamic state were previously reported[2]. This situation may produce an increase in stroke volume and subsequently cardiac output. This effect on the heart was studied in detail by assessing the M-mode echocardiographic left ventricular dimensions indicating the systolic functions of the heart. But this study showed no significant difference in the ejection fraction among patients and controls. Left ventricular chamber dimensions were comparable.

There was no significant difference in LV mass between cirrhosis and controls and between alcoholics and non alcoholics. This finding is different from an Indian study published by Pazhamalai et al[49]. This variation could be due to rigid criteria adopted in case selection.

A significant increase in the pulmonary artery systolic pressure (PASP) was seen cirrhotics compared to controls in the study. Hypoxemia, intrapulmonary shunting, portal – pulmonary shunting and increased levels of several vasoactive mediators and cytokines may be involved in the development of pulmonary hypertension. Pazhamalai et al[49] also has reported a similar observation recently.

The synthesis of L-carnitine is performed in the liver. So alteration in carnitine metabolism is expected in liver disease, especially in cirrhosis.

However studies estimating the levels of L-carnitine in cirrhosis patients showed conflicting results. Study by Selimoghn MA et al[44] showed that children with cirrhosis have low plasma carnitine concentrations. Another study done in adults by Dr. Krahenbuhl S et al[45] showed that cirrhotics are not carnitine deficient. There was a trend towards higher carnitine levels in alcoholic patients. This may result from increased carnitine biosynthesis because of increased skeletal muscle protein turnover in alcoholic cirrhosis patients. They also found that non – cirrhotic liver disease patients showed no change in plasma carnitine concentration.

Amodio P et al[46] in their study found that there was significantly high levels of carnitine in cirrhotics independently of the aetiology of cirrhosis. They did not found any difference in values in the three Pugh – Child's classes. They concluded that high levels of acetyl carnitine, short chain acyl carnitine, total esterified carnitine and total carnitine found in cirrhosis were linked to liver disease. Alcohol abuse may be only an exacerbating factor.

In a normal heart, during diastole, an initial active phase of relaxation and a later passive phase of filling are present. In the relaxation phase; a series of energy consuming steps occur which are mediated by hydrolysis of ATP[2]. In the latter filling phase, several complex interactions occur like diastolic suction, passive filling, pericardial restraint, ventricular interaction

and viscoelastic forces of the myocardium which determines the 'effective operating left ventricular chamber compliance'[2].

In the present study, left ventricular (LV) diastolic function was studied in depth using parameters like isovolumic relaxation time, mitral inflow velocity pattern and mitral E deceleration time. Cirrhosis patients showed an increased occurrence of diastolic dysfunction compared to controls. This finding was seen in both alcoholic and non - alcoholic patients. Majority of patients showed an impaired LV relaxation pattern indicating that the initial energy consuming step is being affected in cirrhosis. Similar observation was documented earlier by Alexander et al[50] from Mumbai.

A few patients showed advanced diastolic dysfunction in the form of restrictive pattern. This usually occur when the passive stiffness of heart is affected by diffuse fibrosis or when the myocytes are hypertrophied. So , heart may also be influenced by growth factors which mediate fibrosis in liver.

However, there was no significant difference between the occurrence and pattern of diastolic dysfunction among alcoholic and non - alcoholic cirrhosis patients.

Overall, the contributing factors for cardiac involvement in hepatic cirrhosis are summarized below:

Table 15: Contributing factors for cardiac involvement in cirrhosis

1. Circulatory changes
2. Systemic vasodilatation
3. Hyperdynamic circulation
4. Vasoactive mediators
5. Altered cardiac contractility

Suggestions :-

- Since cardiac involvement in cirrhosis is a relatively new area of work, it is suggested that more prospective studies need to be undertaken in a cohort of cirrhosis of various aetiologies to assess the extend of involvement in various stages of cirrhosis.

- *Future area of work*
    - To investigate the therapeutic utility of cardio protective agents in minimizing or altering cardiac involvement in cirrhosis.

- More molecular researches need to be undertaken to delineate the underlying patho physiological mechanisms operating in the development of cirrhotic cardiomyopathy.

Limitations of the study :-

In this part of the country, women alcoholics are a rarity. So to maintain homogeneity among the study population and controls, only men were considered. Hence the observations are limited to men only.

In view of the various interplaying mechanisms for the development of cardiac dysfunction in cirrhosis, and the observation that cardiac involvement worsens the hepatic functional status, there is a need to take up further works in these areas.

CONCLUSIONS

1. Patients with alcoholic and non - alcoholic cirrhosis have higher occurrence of diastolic dysfunction (50% and 46% respectively) than controls which was statistically significant. This observation runs in parallel to other published data.

2. Pulmonary artery systolic pressure was significantly increased in both alcoholic and non - alcoholic cirrhotics when compared with healthy controls. This finding was comparable with already published data.

3. LV systolic function indices (LVIDs, LVIDd, IVSd, LVPWd and EF) were not altered in cirrhosis; be it alcoholic or non - alcoholic and it was not different for healthy controls statistically, in contrast to published observations.

4. Variable observations noted in the present study may likely be related to the rigid criteria adopted in case selection and possibly due to genetic or ethnic difference as well as their susceptibility.

5. In view of the above conclusions, it is suggested to take up a prospective study with long term follow up with and without modern cardio protective agents in order to find out the effective interventions which minimize the progression of cirrhosis and subsequent cardiac dysfunction.

SUMMARY

Cirrhosis is a chronic liver disease with systemic complications. Cardiac involvement in cirrhosis is less studied and rarely reported. Here an attempt was made to design a prospective analytical observational study to find out the functional status of the heart in established alcoholic (n=32) and non - alcoholic (n=68) cirrhosis patients compared with asymptomatic healthy controls. Rigid criteria was adopted in the selection of cases in order to exclude co morbid conditions and other contributing factors. This study was confined among males as women alcoholics could not be identified in this area. The data was analysed statistically.

Left ventricular systolic function parameters (LVIDs, LVIDd, IVSd, LVPWd and ejection fraction) were comparable between alcoholics, non alcoholics and controls ($p>0.05$).

Pulmonary artery systolic pressure (PASP) in cirrhosis patients and controls ranged from 12.5 to 56 mm Hg and 13 to 29 mm Hg respectively. The mean among the two groups were 28.2 ± 9.06 and 20.4 ± 4.21 mm Hg respectively. The difference among cirrhotics and controls with reference to PASP were statistically highly significant ($p=0.0001$).

The LV mass in cirrhotics patients and controls ranged from 74 to 271 gms and 90 to 120 gms respectively. The mean among the two groups were 162.26$\pm$50.65 and 159.33$\pm$41.77 grams respectively. But the difference was not statistically significant (p=0.8917).

48 cirrhotic patients (48%) had diastolic dysfunction compared to 10 persons (25%) in the control group which was significant ($p<0.05$). This significance persisted in both alcoholic and non alcoholic groups. Majority of patients in both subsets of cirrhotic with diastolic dysfunction showed LV relaxation abnormality pattern. (68% in alcoholic and 52% in non alcoholic group respectively)

There was no significant difference in cardiac functions parameters when alcoholic cirrhotics were compared with non alcoholic cirrhotics ($p>0.05$).

The present study has brought out the pattern of cardiac involvement and the comparability of observations with published series. More molecular and clinical studies are required to design effective therapeutic measures to prevent the progression of cirrhosis and its systemic complications.

MASTER CHART

Sl.No	GROUP	LVIDs	LVIDd	EF%	IVSd	LVPWd	E/A RATIO	DT	IVRT	PA sy.pr.	LV mass
1	ALCO. CIRRHO.	2.65	3.59	60	0.67	0.81	0.78	80	140	33.5	74
2	ALCO. CIRRHO.	2.9	4.8	71	0.8	0.9	1.48	178	65	28	150
3	ALCO. CIRRHO.	2.6	4.5	74	1.4	1.2	0.75	192	103	35.3	262
4	ALCO. CIRRHO.	3.72	5.12	61	0.58	0.85	1.51	170	150	13.6	146
5	ALCO. CIRRHO.	3.3	4.3	54	0.8	0.7	0.86	130	140	13.4	187.1
6	ALCO. CIRRHO.	3.32	5.34	76	1.08	0.99	1.41	160	100	33	250
7	ALCO. CIRRHO.	2.6	4.5	70	0.98	0.9	1.18	210	90	46	256
8	ALCO. CIRRHO.	3.5	4.67	50	0.99	1.08	1.21	130	70	26	198
9	ALCO. CIRRHO.	2.56	4.46	81	1.03	0.97	0.92	120	80	25	174.6
10	ALCO. CIRRHO.	4.31	5.2	61	0.87	0.92	1.75	110	80	27.2	246.5
11	ALCO. CIRRHO.	3.46	5.07	68	0.58	0.67	1.71	160	100	18.4	114.2
12	ALCO. CIRRHO.	3.68	5.25	66	0.85	0.67	1.45	100	100	22	159.4
13	ALCO. CIRRHO.	4.35	5.7	55	0.76	0.54	2.09	200	110	37.7	150.6
14	ALCO. CIRRHO.	3.9	5.38	62	1.12	1.21	1.28	160	80	35.5	102.2
15	ALCO. CIRRHO.	2.6	4.2	68	0.9	0.9	0.91	128	68	33.3	137
16	ALCO. CIRRHO.	2.6	4.5	74	1.4	1.2	0.75	192	103	35.9	262
17	ALCO. CIRRHO.	3.32	5.34	76	1.08	0.99	1.41	160	100	33	250
18	ALCO. CIRRHO.	2.65	3.59	60	0.67	0.81	0.78	80	140	33.5	74
19	ALCO. CIRRHO.	3.68	5.25	66	0.85	0.67	1.45	100	100	22	159.4
20	ALCO. CIRRHO.	2.56	4.46	81	1.03	0.97	0.92	120	80	25	174.6
21	ALCO. CIRRHO.	3.3	4.3	54	0.8	0.7	0.86	130	140	13.5	187.1
22	ALCO. CIRRHO.	4.35	5.7	55	0.76	0.54	2.09	200	110	37.8	150.6
23	ALCO. CIRRHO.	3.72	5.12	61	0.58	0.85	1.51	170	150	13.6	146
24	ALCO. CIRRHO.	2.9	4.8	71	0.8	0.9	1.48	178	65	28	150
25	ALCO. CIRRHO.	3.5	4.67	50	0.99	1.08	1.21	130	70	26	198
26	ALCO. CIRRHO.	2.6	4.5	74	1.4	1.2	0.75	192	103	35.4	262

Sl.No	GROUP	LVIDs	LVIDd	EF%	IVSd	LVPWd	E/A RATIO	DT	IVRT	PA sy.pr.	LV mass
27	ALCO. CIRRHO.	2.65	3.59	60	0.67	0.81	0.78	80	140	33.5	74
28	ALCO. CIRRHO.	4.31	5.2	61	0.87	0.92	1.75	110	80	27.3	246.5
29	ALCO. CIRRHO.	2.6	4.2	68	0.9	0.9	0.91	128	68	33.1	137
30	ALCO. CIRRHO.	3.9	5.38	62	1.12	1.21	1.28	160	80	35	102.2
31	ALCO. CIRRHO.	3.32	5.34	76	1.08	0.99	1.41	160	100	33	250
32	ALCO. CIRRHO.	2.9	4.8	71	0.8	0.9	1.48	178	65	28	150
33	ALCO. CIRRHO.	2.56	4.46	81	1.03	0.97	0.92	120	80	25	174.6
34	ALCO. CIRRHO.	2.6	4.5	70	0.98	0.9	1.18	210	90	46	256
35	ALCO. CIRRHO.	3.46	5.07	68	0.58	0.67	1.71	160	100	19	114.2
36	ALCO. CIRRHO.	3.5	4.67	50	0.99	1.08	1.21	130	70	26	198
37	ALCO. CIRRHO.	3.3	4.3	54	0.8	0.7	0.86	130	140	13.6	187.1
38	ALCO. CIRRHO.	3.68	5.25	66	0.85	0.67	1.45	100	100	22	159.4
39	NON ALCO. CIRRHO.	3	4.5	61	0.9	0.9	2.26	267	110	12.5	144
40	NON ALCO. CIRRHO.	2.6	4.5	74	0.6	0.5	1.78	217	68	20.3	76
41	NON ALCO. CIRRHO.	2.7	4.5	70.2	0.9	1.2	0.76	146	70	33.7	181
42	NON ALCO. CIRRHO.	4.1	5.6	52	0.6	1.9	0.56	121	107	37	181
43	NON ALCO. CIRRHO.	3.59	5.56	73	0.58	0.54	1.69	160	100	30	118.1
44	NON ALCO. CIRRHO.	3.42	5.04	69	0.88	0.73	1.44	200	90	19.1	211
45	NON ALCO. CIRRHO.	3.05	5.03	78	1.12	0.85	1.03	150	70	32	164.6
46	NON ALCO. CIRRHO.	3.86	5.34	62	0.72	0.81	1.38	160	62	35	212.9
47	NON ALCO. CIRRHO.	3.68	5.34	67	0.9	0.94	1.42	120	110	26	139
48	NON ALCO. CIRRHO.	3.1	4.04	55	1.03	0.9	1	100	80	28	163.1
49	NON ALCO. CIRRHO.	2.92	5.43	84	0.76	0.72	2.31	130	110	33	91
50	NON ALCO. CIRRHO.	3.14	4.31	61	0.67	0.67	2.22	130	100	19.8	160.5
51	NON ALCO. CIRRHO.	2.51	4.85	86	0.94	0.76	1.6	90	110	43.6	151.6
52	NON ALCO. CIRRHO.	3.16	4.85	62	0.45	0.58	1.83	100	100	29.7	80
53	NON ALCO. CIRRHO.	3.5	4.85	67	0.9	0.76	1.59	120	101.5	29.1	149.3
54	NON ALCO. CIRRHO.	3.28	4.76	75	1.03	0.99	1.14	110	80	30.4	207
55	NON ALCO. CIRRHO.	3.1	4.89	77	1.08	1.12	0.9	147	90	41	186

Sl.No	GROUP	LVIDs	LVIDd	EF%	IVSd	LVPWd	E/A RATIO	DT	IVRT	PA sy.pr.	LV mass
56	NON ALCO. CIRRHO.	3.2	4.26	61	0.91	0.76	2.05	180	110	25.4	94
57	NON ALCO. CIRRHO.	3.05	4.17	71	0.67	0.9	1.29	170	90	25	215
58	NON ALCO. CIRRHO.	3.63	5.47	68	0.9	1.2	2	140	120	14.9	162
59	NON ALCO. CIRRHO.	2.96	4.35	71	0.94	0.8	0.57	80	90	19	160
60	NON ALCO. CIRRHO.	3.18	4.82	70	0.77	1.08	0.88	130	180	35	146
61	NON ALCO. CIRRHO.	2.74	4.08	58	0.9	0.7	1.46	220	190	36	127
62	NON ALCO. CIRRHO.	3	4.3	66	1	0.8	1.86	146	107	56	118
63	NON ALCO. CIRRHO.	2.6	4.1	68	0.9	0.8	1.5	140	75	19	271
64	NON ALCO. CIRRHO.	4.1	5.6	52	0.6	1.9	0.56	121	107	37	181
65	NON ALCO. CIRRHO.	3.5	4.85	67	0.9	0.76	1.59	120	101.5	29.1	149.3
66	NON ALCO. CIRRHO.	3.59	5.56	73	0.58	0.54	1.69	160	100	30	118.1
67	NON ALCO. CIRRHO.	3.42	5.04	69	0.88	0.73	1.44	200	90	19.1	211
68	NON ALCO. CIRRHO.	2.96	4.35	71	0.94	0.8	0.57	80	90	19	160
69	NON ALCO. CIRRHO.	2.51	4.85	86	0.94	0.76	1.6	90	110	43.6	151.6
70	NON ALCO. CIRRHO.	2.7	4.5	70.2	0.9	1.2	0.76	146	70	33.7	181
71	NON ALCO. CIRRHO.	3.18	4.82	70	0.77	1.08	0.88	130	180	35	146
72	NON ALCO. CIRRHO.	3	4.5	61	0.9	0.9	2.26	267	110	12.5	144
73	NON ALCO. CIRRHO.	3.68	5.34	67	0.9	0.94	1.42	120	110	26	139
74	NON ALCO. CIRRHO.	2.7	4.5	70.2	0.9	1.2	0.76	146	70	33.7	181
75	NON ALCO. CIRRHO.	2.92	5.43	84	0.76	0.72	2.31	130	110	33	91
76	NON ALCO. CIRRHO.	3.1	4.89	77	1.08	1.12	0.9	147	90	41	186
77	NON ALCO. CIRRHO.	3.2	4.26	61	0.91	0.76	2.05	180	110	25.4	94
78	NON ALCO. CIRRHO.	3.14	4.31	61	0.67	0.67	2.22	130	100	19.8	160.5
79	NON ALCO. CIRRHO.	3.16	4.85	62	0.45	0.58	1.83	100	100	29.7	80
80	NON ALCO. CIRRHO.	3.05	5.03	78	1.12	0.85	1.03	150	70	32	164.6
81	NON ALCO. CIRRHO.	3.68	5.34	67	0.9	0.94	1.42	120	110	26	139
82	NON ALCO. CIRRHO.	2.51	4.85	86	0.94	0.76	1.6	90	110	43.6	151.6
83	NON ALCO. CIRRHO.	2.6	4.5	74	0.6	0.5	1.78	217	68	20.3	76
84	NON ALCO. CIRRHO.	3.5	4.85	67	0.9	0.76	1.59	120	101.5	29.1	149.3

Sl.No	GROUP	LVIDs	LVIDd	EF%	IVSd	LVPWd	E/A RATIO	DT	IVRT	PA sy.pr.	LV mass
85	NON ALCO. CIRRHO.	3.59	5.56	73	0.58	0.54	1.69	160	100	30	118.1
86	NON ALCO. CIRRHO.	3	4.5	61	0.9	0.9	2.26	267	110	12.5	144
87	NON ALCO. CIRRHO.	3.28	4.76	75	1.03	0.99	1.14	110	80	30.4	207
88	NON ALCO. CIRRHO.	3.05	4.17	71	0.67	0.9	1.29	170	90	25	215
89	NON ALCO. CIRRHO.	4.1	5.6	52	0.6	1.9	0.56	121	107	37	181
90	NON ALCO. CIRRHO.	2.92	5.43	84	0.76	0.72	2.31	130	110	33	91
91	NON ALCO. CIRRHO.	3.68	5.34	67	0.9	0.94	1.42	120	110	26	139
92	NON ALCO. CIRRHO.	3	4.3	66	1	0.8	1.86	146	107	56	118
93	NON ALCO. CIRRHO.	2.6	4.1	68	0.9	0.8	1.5	140	75	19	271
94	NON ALCO. CIRRHO.	2.6	4.5	74	0.6	0.5	1.78	217	68	20.3	76
95	NON ALCO. CIRRHO.	2.74	4.08	58	0.9	0.7	1.46	220	190	36	127
96	NON ALCO. CIRRHO.	3.42	5.04	69	0.88	0.73	1.44	200	90	19.1	211
97	NON ALCO. CIRRHO.	3.63	5.47	68	0.9	1.2	2	140	120	14.9	162
98	NON ALCO. CIRRHO.	3.14	4.31	61	0.67	0.67	2.22	130	100	19.8	160.5
99	NON ALCO. CIRRHO.	3.28	4.76	75	1.03	0.99	1.14	110	80	30.4	207
100	NON ALCO. CIRRHO.	3.05	5.13	78	1.12	0.85	1.03	150	70	32	164.6
101	CONTROL	3.26	5.17	69	0.91	0.96	1.3	208	99	29	208
102	CONTROL	3.05	5.22	71	0.97	0.99	1.33	210	100	27	210
103	CONTROL	3.13	4.34	63	0.85	0.72	0.97	202	63	17	99
104	CONTROL	3.41	4.76	67	0.81	0.88	1.15	204	67	22	164
105	CONTROL	3.29	4.79	69	0.89	0.91	1.21	203	66	24	170
106	CONTROL	3.18	5.12	71	0.94	1.04	1.29	211	98	23	204
107	CONTROL	2.92	4.13	60	0.8	0.62	0.91	198	60	14	98
108	CONTROL	3.37	4.87	65	0.95	0.82	1.21	203	81	22	176
109	CONTROL	3.04	5.09	69	0.99	0.93	1.29	199	95	21	199
110	CONTROL	2.99	4.34	66	0.86	0.77	1.04	200	84	18	164
111	CONTROL	2.94	4.27	63	0.81	0.61	0.97	201	64	15	109
112	CONTROL	3.33	4.98	71	1.01	0.91	1.13	207	91	26	188
113	CONTROL	3.09	4.63	66	0.95	0.84	1.05	205	88	22	177

Sl.No	GROUP	LVIDs	LVIDd	EF%	IVSd	LVPWd	E/A RATIO	DT	IVRT	PA sy.pr.	LV mass
114	CONTROL	2.99	4.39	64	0.91	0.73	0.96	199	65	19	134
115	CONTROL	2.91	4.17	60	0.72	0.6	0.89	197	60	14	94
116	CONTROL	3.14	4.75	67	0.84	0.87	0.9	201	77	19	175
117	CONTROL	3.39	5.04	70	0.97	0.99	0.97	205	92	17	182
118	CONTROL	3.11	4.57	66	0.89	0.86	0.91	203	87	23	134
119	CONTROL	3.24	4.79	69	0.94	0.92	0.94	205	91	28	141
120	CONTROL	3.07	4.19	62	0.87	0.63	0.9	198	59	15	91
121	CONTROL	3.16	4.43	65	0.92	0.69	0.99	200	71	19	98
122	CONTROL	3.33	4.72	68	0.98	0.86	1.17	204	69	13	145
123	CONTROL	2.95	4.21	65	0.8	0.65	1.01	199	62	15	96
124	CONTROL	2.91	4.18	61	0.67	0.6	0.91	198	60	14	90
125	CONTROL	2.99	4.33	65	0.71	0.62	1.05	201	67	17	101
126	CONTROL	3.1	4.65	67	0.82	0.83	1.22	204	74	21	153
127	CONTROL	3.32	4.99	71	0.96	0.96	1.3	206	86	17	179
128	CONTROL	3.15	4.86	67	0.91	0.92	1.27	204	87	25	182
129	CONTROL	2.96	4.41	60	0.85	0.84	1.16	202	67	19	131
130	CONTROL	3.03	4.49	62	0.77	0.87	1.14	202	65	19	135
131	CONTROL	3.14	4.88	68	0.79	0.93	1.22	205	79	23	1877
132	CONTROL	3.37	5.07	67	0.94	1.02	1.31	206	99	19	194
133	CONTROL	3.09	5.17	71	1.01	1.12	1.34	209	100	20	208
134	CONTROL	3.12	4.76	65	0.91	0.86	1.09	201	73	27	201
135	CONTROL	3.22	4.93	66	0.89	0.94	1.22	202	88	24	197
136	CONTROL	2.99	4.34	60	0.71	0.69	1.19	199	62	21	126
137	CONTROL	3.38	5.18	71	0.99	1.03	1.31	210	98	22	208
138	CONTROL	3.28	5.22	70	1.02	1.15	1.34	211	99	21	210
139	CONTROL	3.07	5.01	68	1.04	0.97	1.29	210	97	19	209
140	CONTROL	3.19	5.04	66	0.94	0.94	1.27	209	94	26	206

Figure 13: Pattern of Diastolic dysfunction (DD) in Alcoholic cirrhosis patients

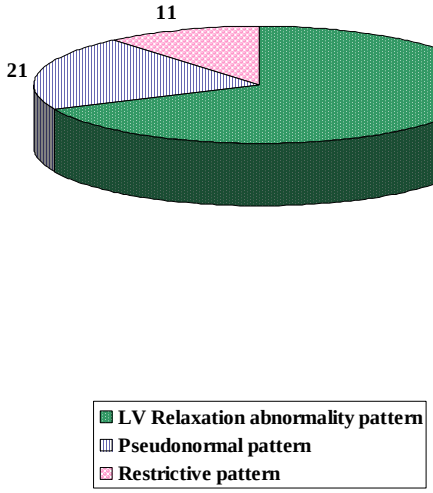


Figure 14: Pattern of Diastolic dysfunction (DD) in Non - alcoholic cirrhosis patients

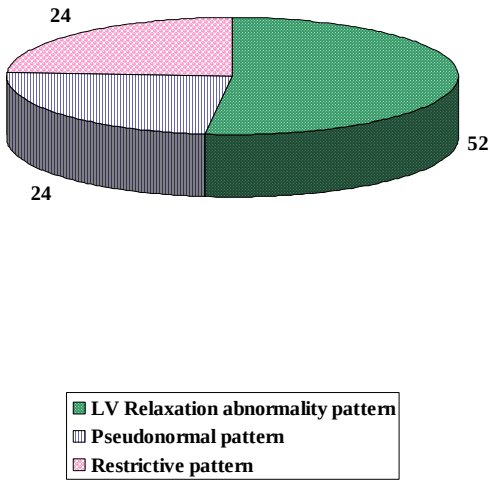


Figure 4: Age distribution of patients in the study

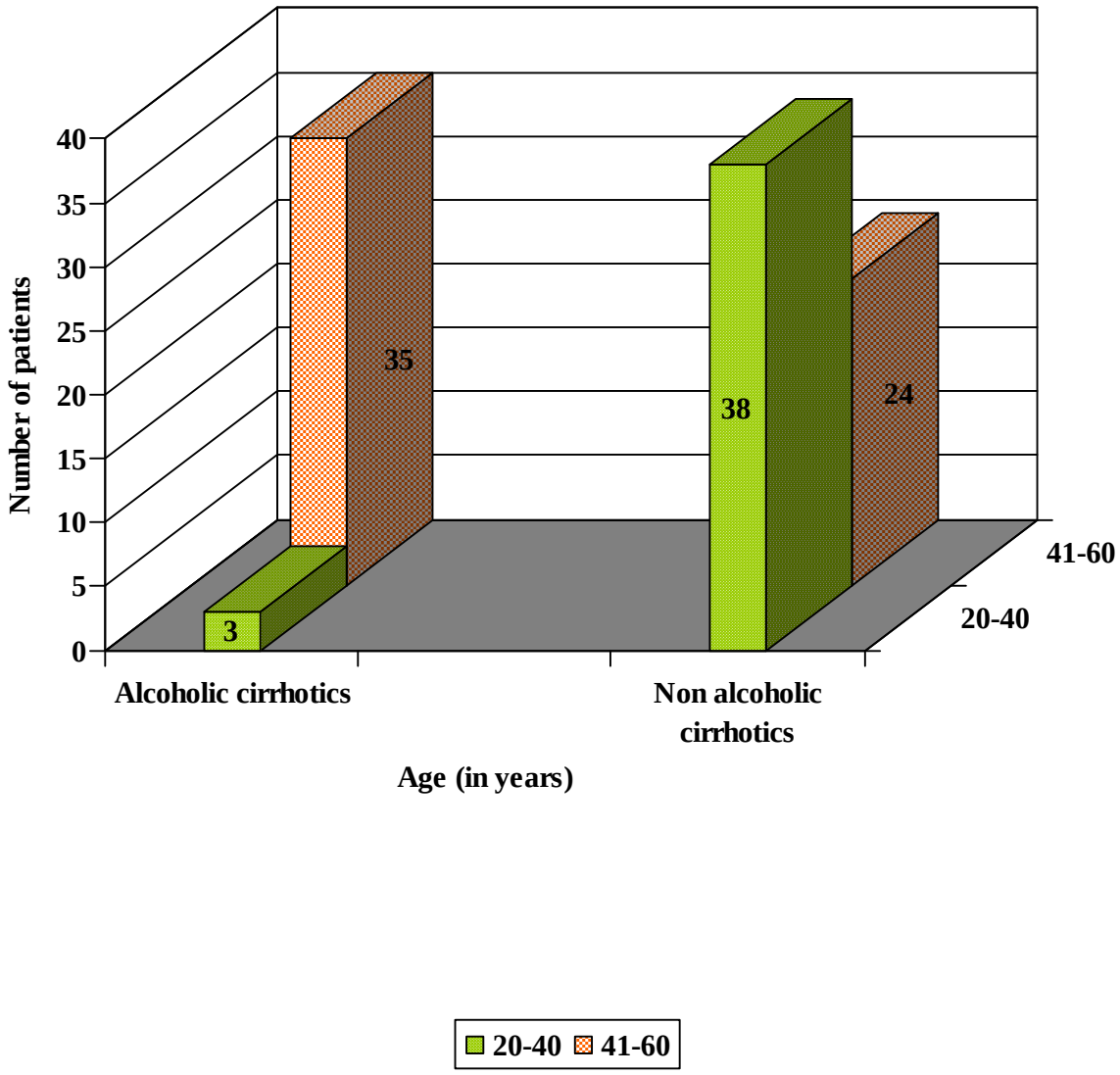


Figure 5: Comparison of PASP between cirrhotics and controls

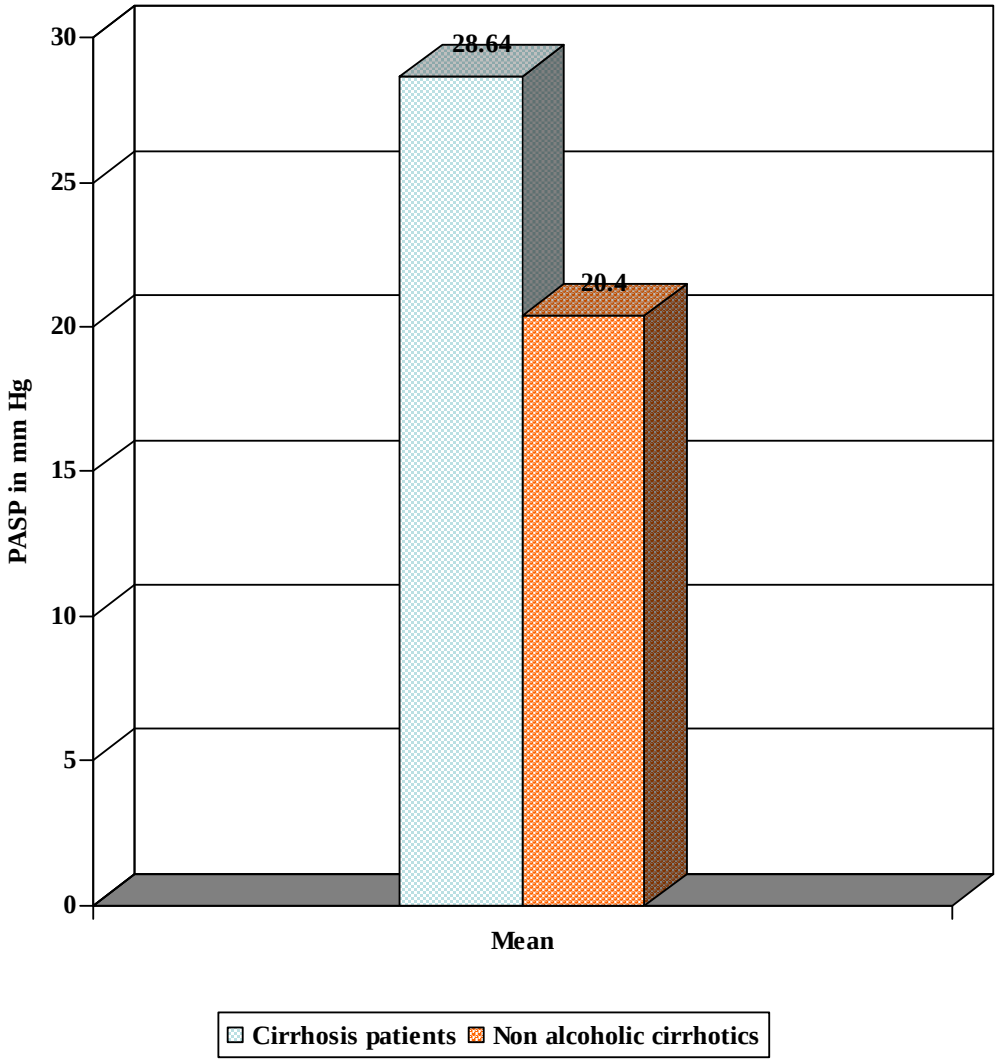


Figure 6: Comparison of LV mass between cirrhotics and controls

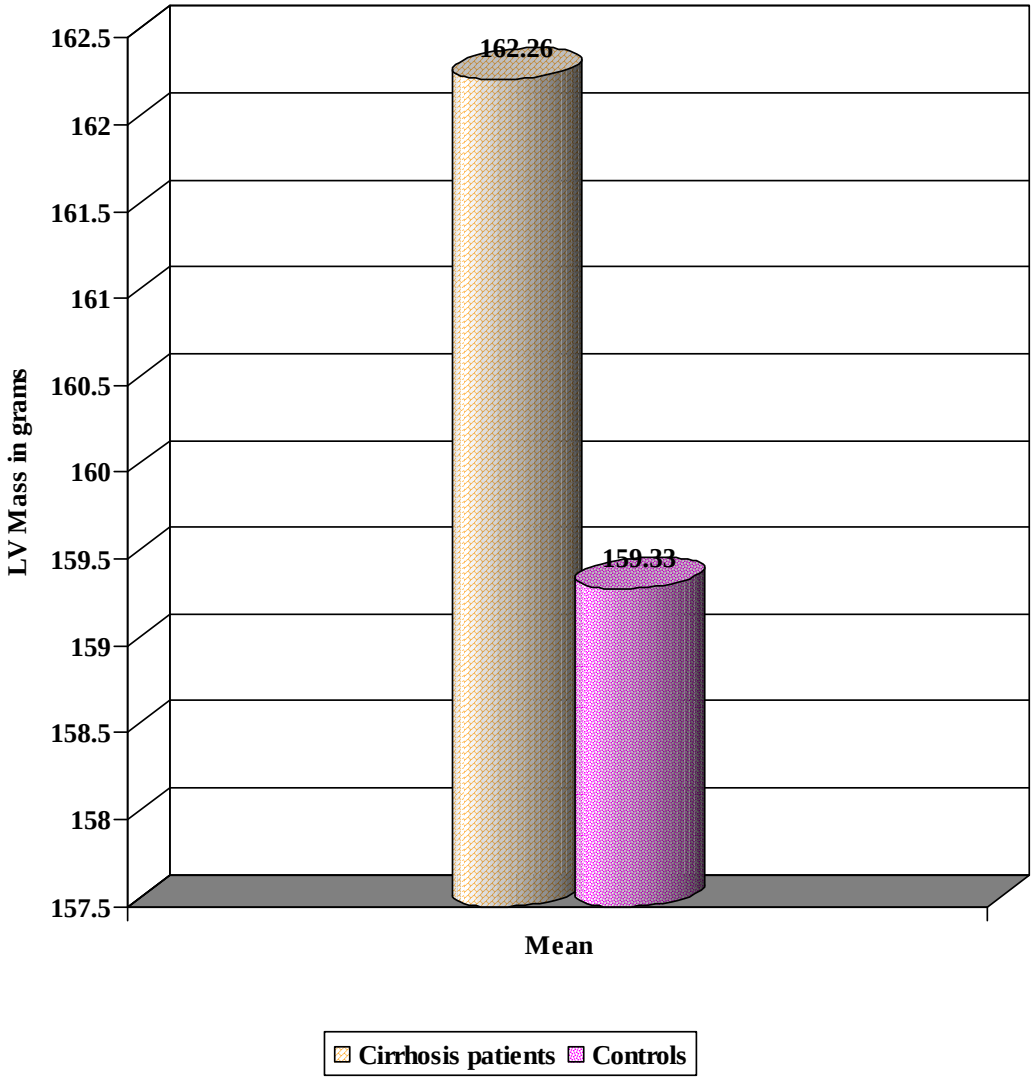


Figure 7: Comparison of PASP between alcoholic and non alcoholic cirrhosis patients

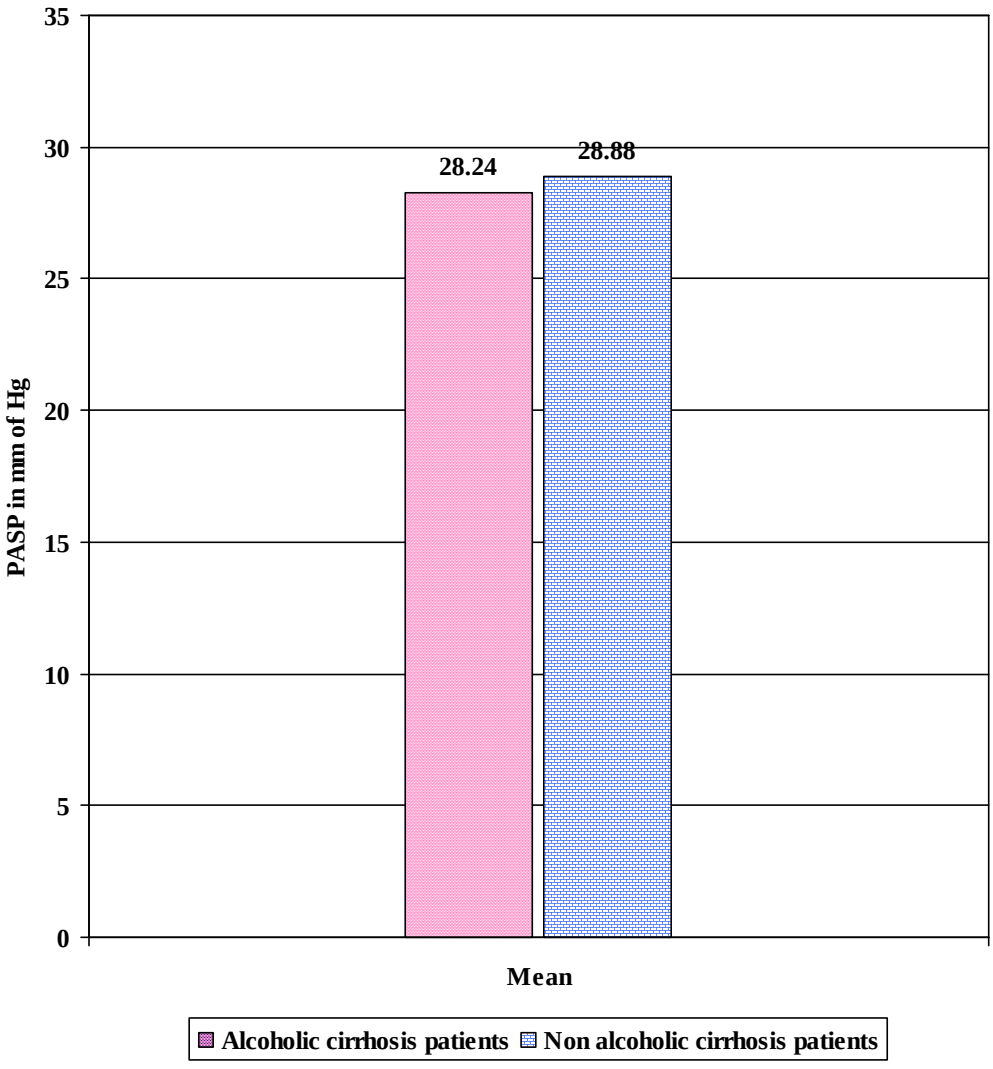


Figure 8: Comparison of LV Mass between alcoholic and non alcoholic cirrhosis patients

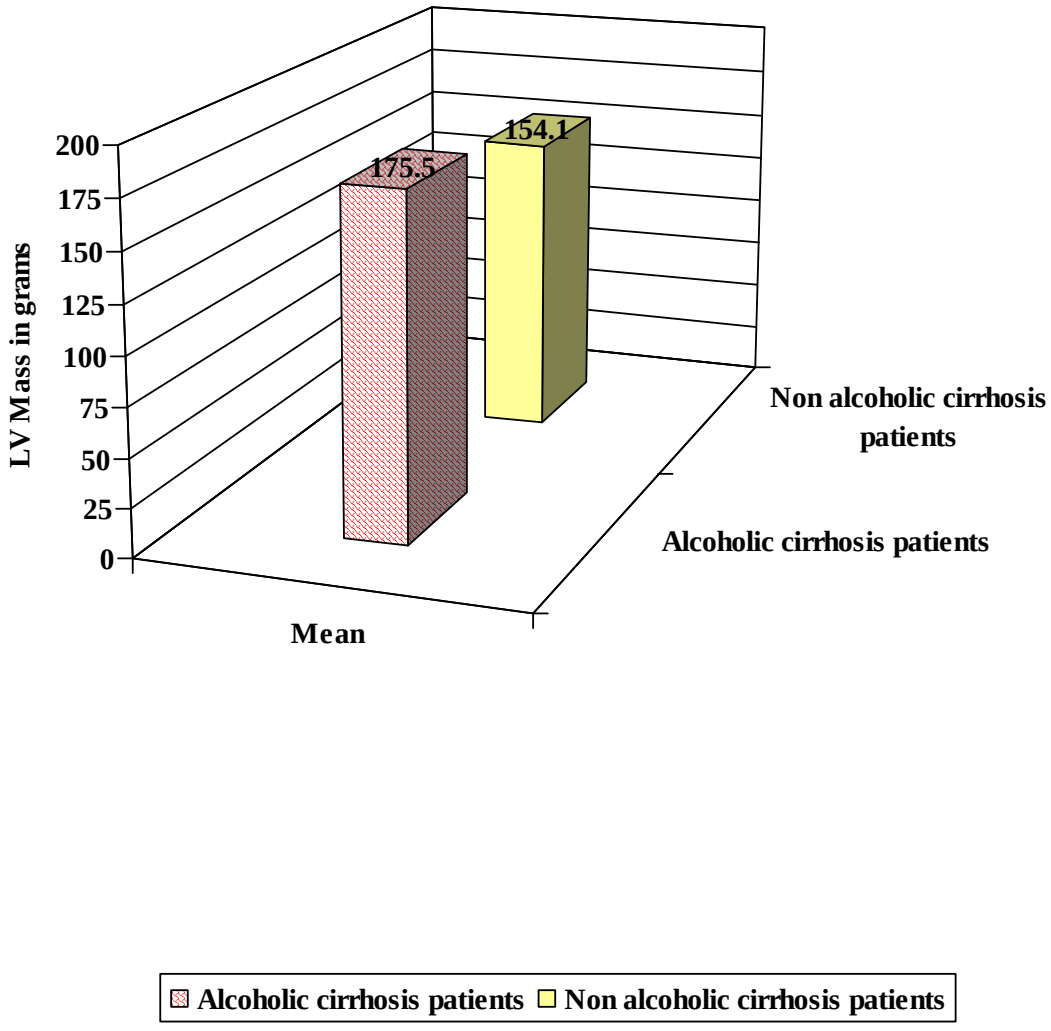


Figure 9: Comparison of PASP between alcoholic cirrhosis cases and controls

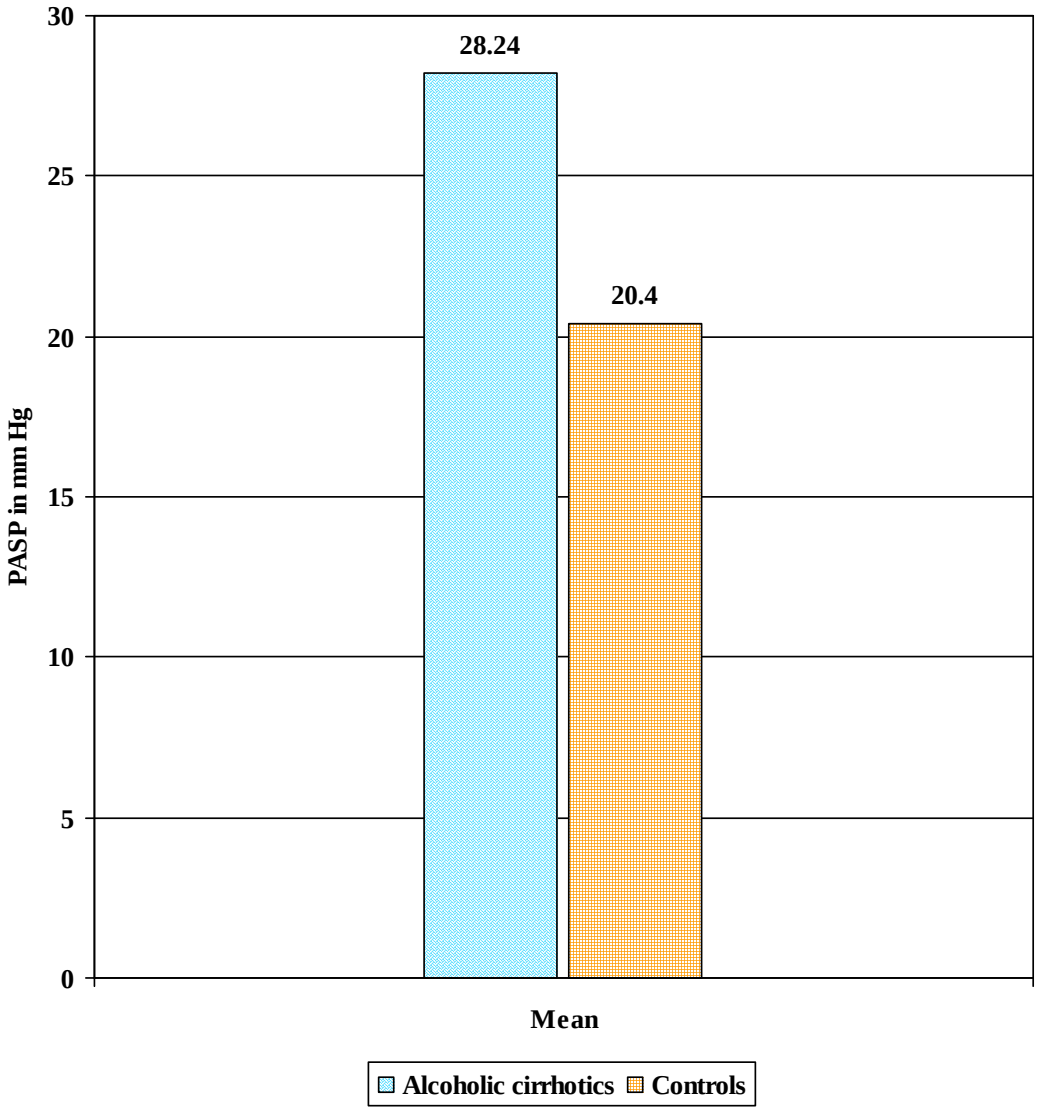


Figure 10: Comparison of LV Mass between alcoholic cirrhosis cases and controls

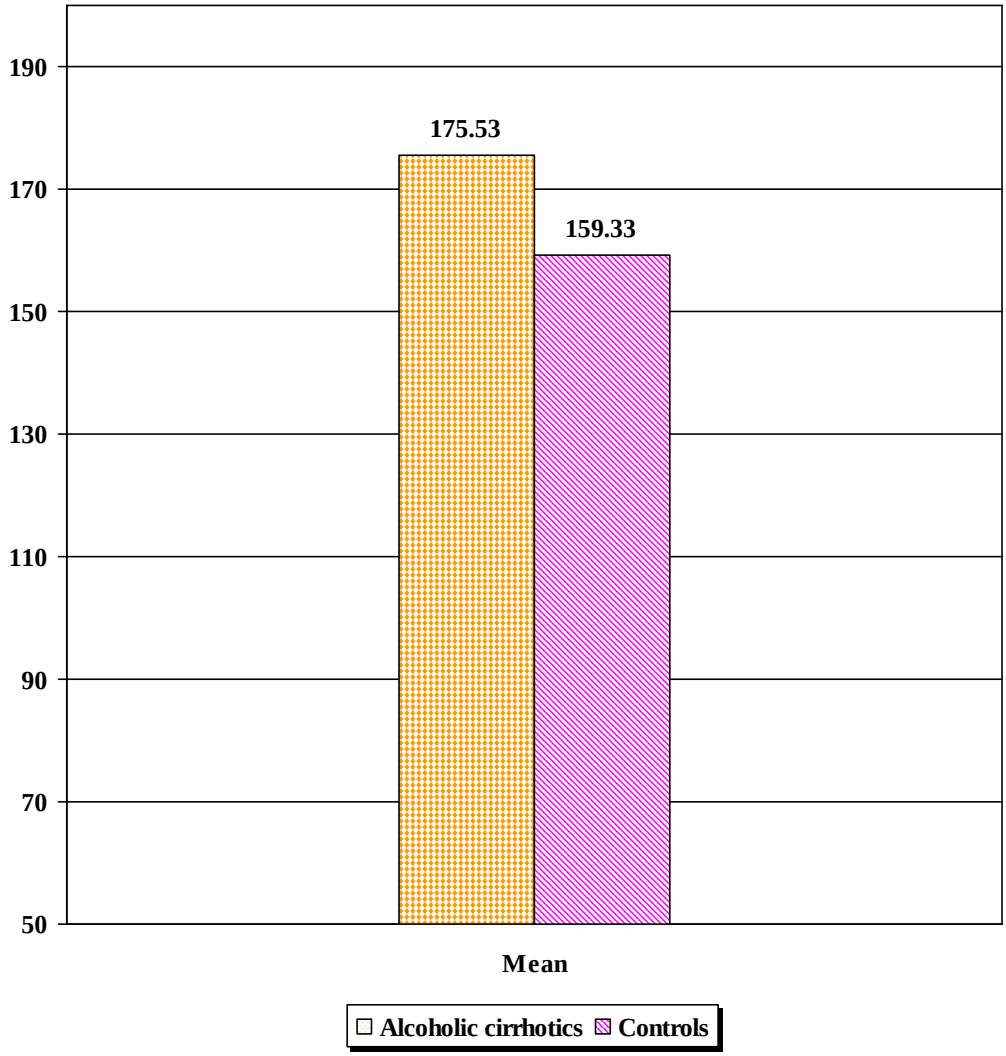


Figure 11: Comparison of PASP between non – alcoholic cirrhotics and controls

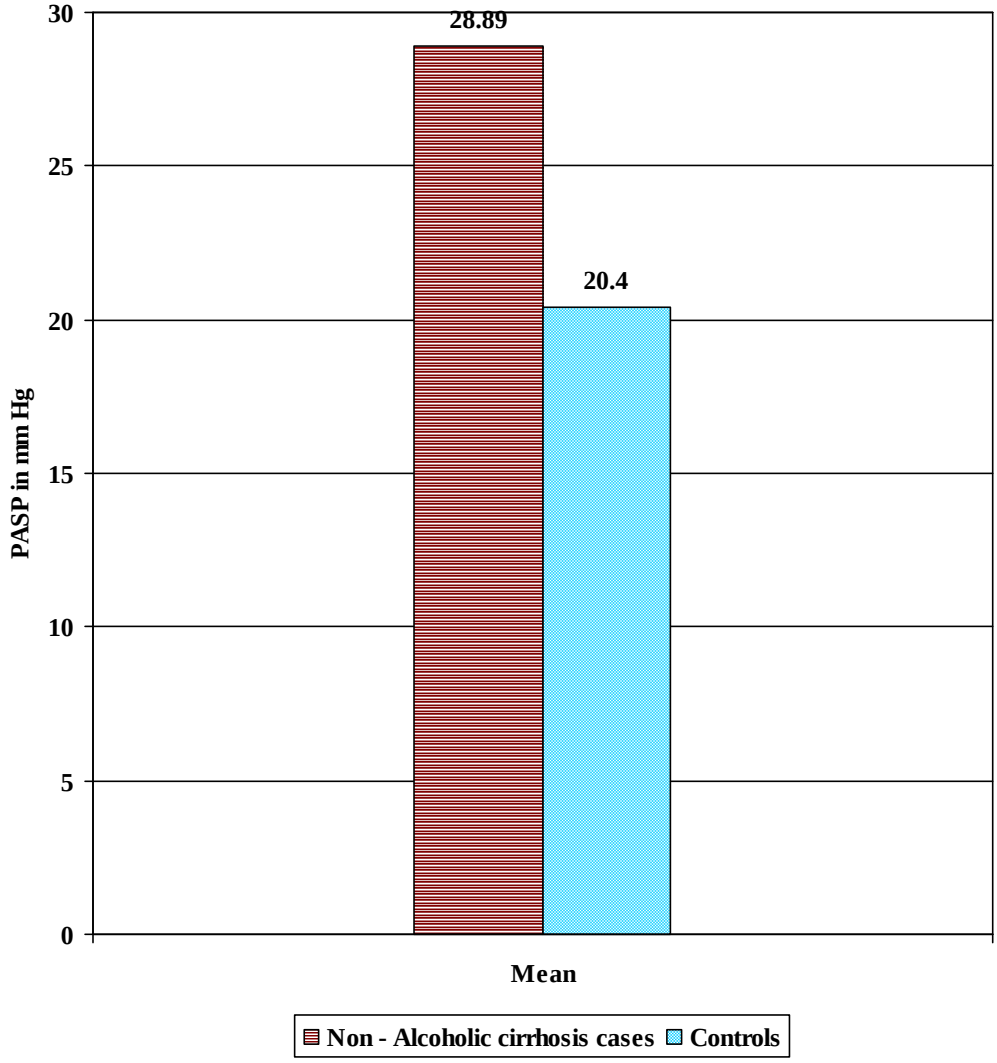
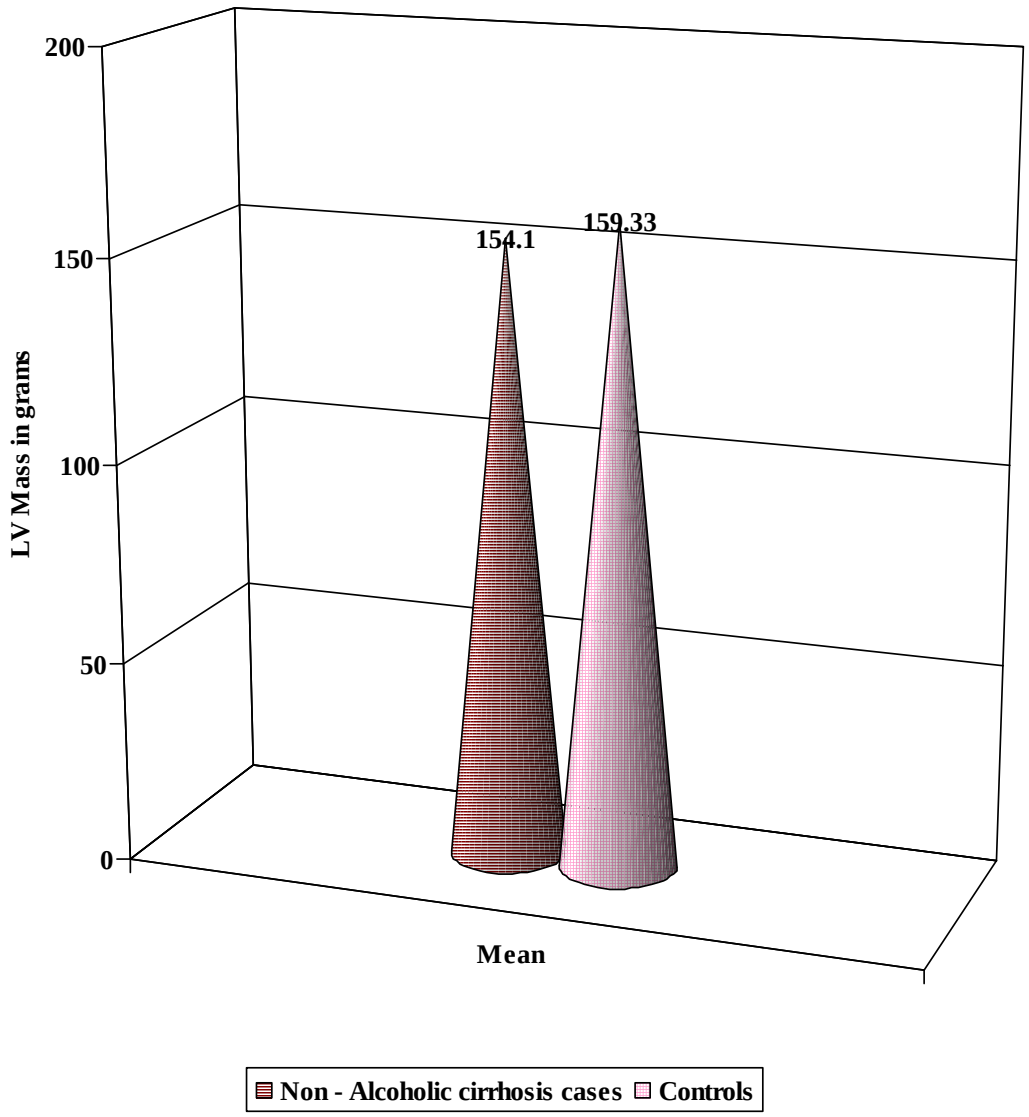
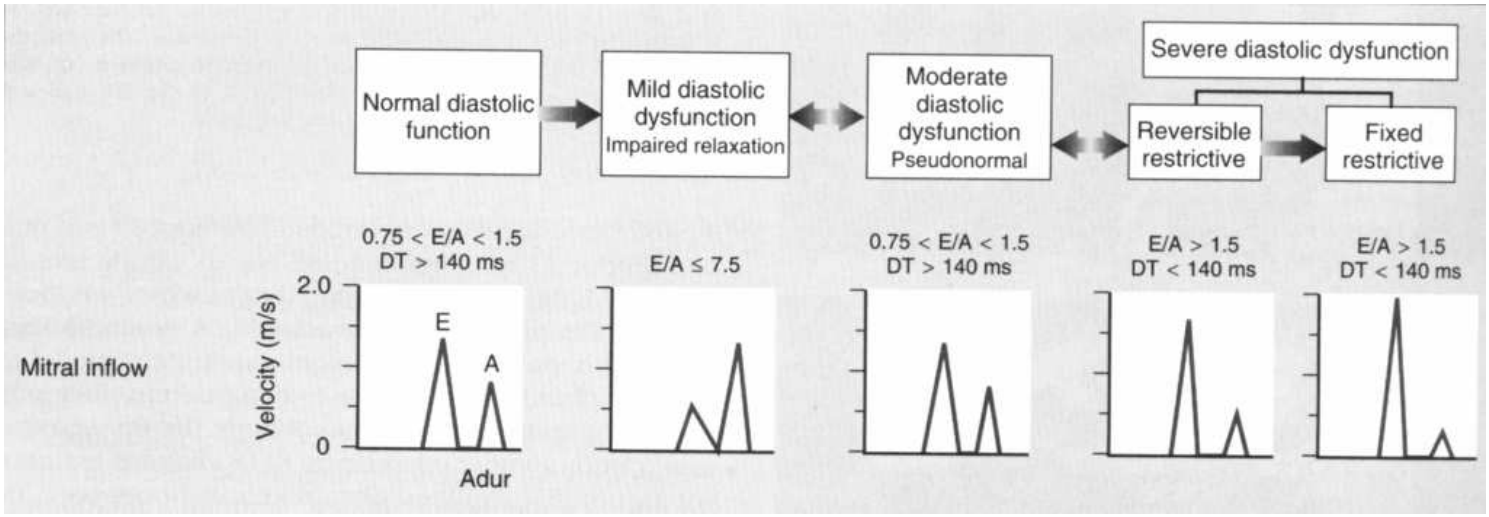
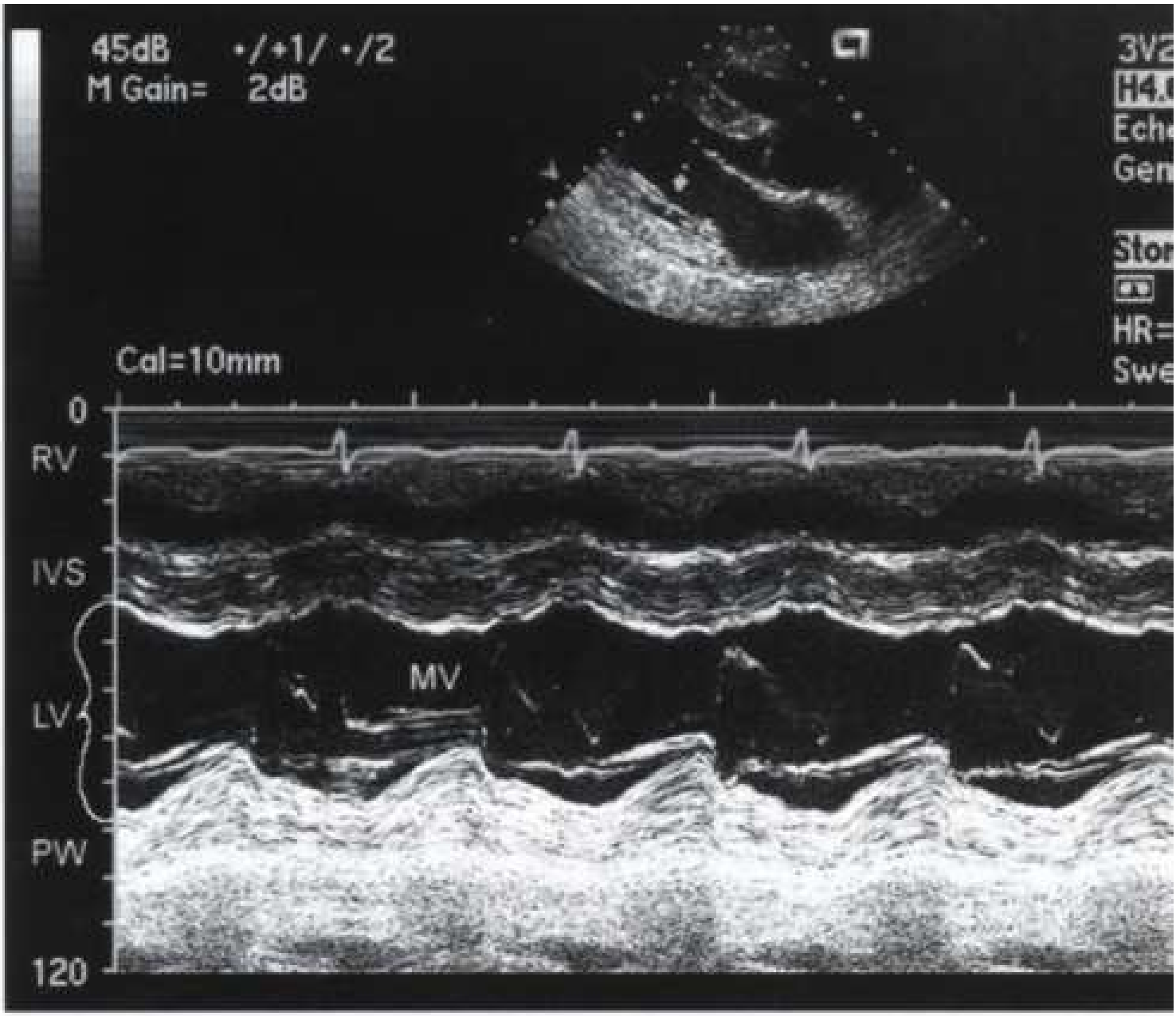
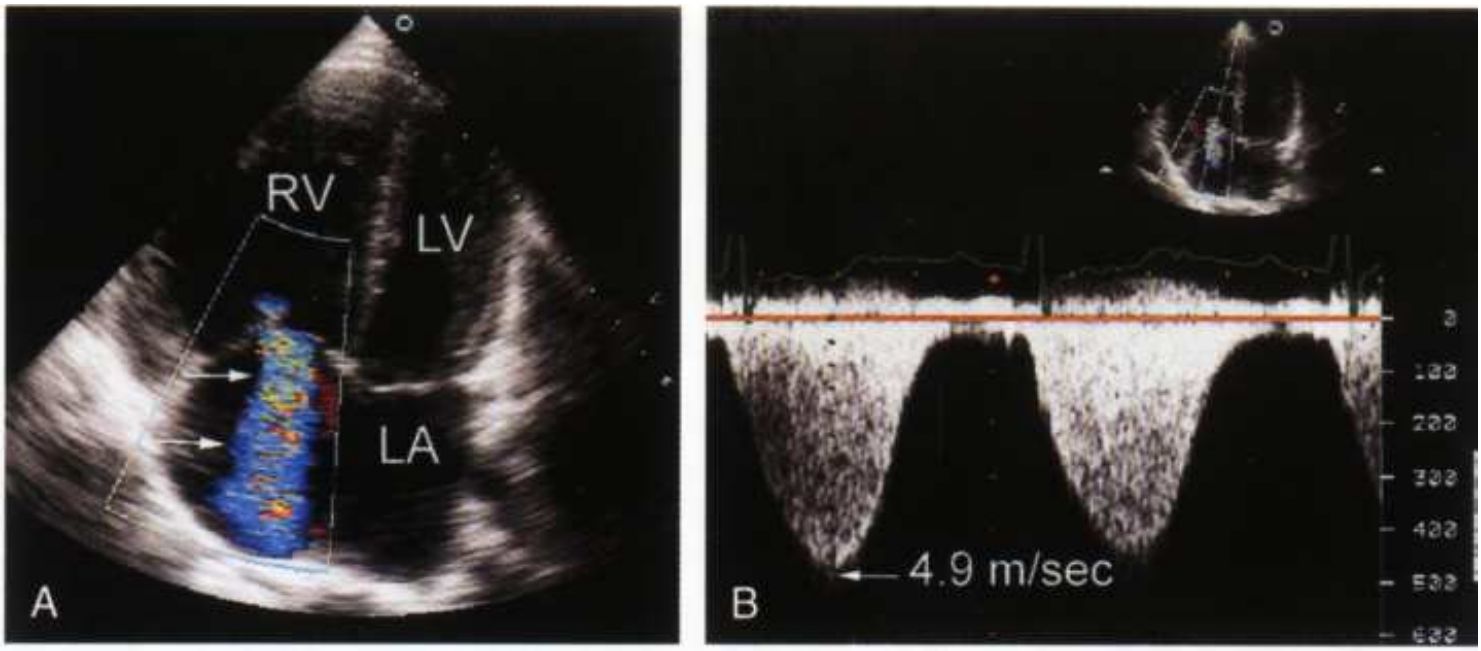


Figure 12: Comparison of LV Mass between non – alcoholic cirrhotics and controls




Normal diastolic function
Mild diastolic dysfunction
Impaired relaxation
Moderate diastolic dysfunction
Pseudonormal
Severe diastolic dysfunction
Reversible restrictive
Fixed restrictive
0.75 < E/A < 1.5
DT > 140 ms
E/A ≤ 7.5
0.75 < E/A < 1.5
DT > 140 ms
E/A > 1.5
DT < 140 ms
E/A > 1.5
DT < 140 ms
Mitral inflow
Velocity (m/s)
2.0
0
E
A
Adur


45dB
M Gain= 2dB
Cal=10mm
0
RV
IVS
MV
LV
PW
120


RV
LV
LA
A
4.9 m/sec
B