A STUDY ON CARDIAC DYSFUNCTION IN NON DIABETIC,NON HYPERTENSIVE PATIENTS WITH LIVER CIRRHOSIS

DISSERTATION SUBMITTED TO THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfilment of the requirements for the degree of

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(GENERAL MEDICINE)

Registration No.: 201711361

DEPARTMENT OF GENERAL MEDICINE

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

TIRUNELVELI – 627011

MAY-2020

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON CARDIAC DYSFUNCTION IN NON DIABETIC NON HYPERTENSIVE PATIENTS WITH LIVER CIRRHOSIS"** submitted by **Dr. M.PACKIASELVAM**, to 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 direct supervision & guidance.

Professor & Head of the Department,
Department of General Medicine
Tirunelveli Medical College,
Tirunelveli.

Unit Chief,
Department of General Medicine
Tirunelveli Medical College,
Tirunelveli.

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I hereby certify that this dissertation entitled "**A STUDY ON A STUDY ON CARDIAC DYSFUNCTION IN NON DIABETIC,NON HYPERTENSIVE PATIENTS WITH LIVER CIRRHOSIS"** is a record of work done by **Dr. M.PACKIASELVAM**, in the Department of General Medicine, Tirunelveli Medical College, Tirunelveli, during her postgraduate degree course period from 2017- 2020. This work has not formed the basis for previous award of any degree.

Date :

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The DEAN

Tirunelveli Medical College,

Tirunelveli - 627011.

DECLARATION

I solemnly declare that the dissertation entitled **"A STUDY ON CARDIAC DYSFUNCTION IN NON DIABETIC NON HYPERTENSIVE PATIENTS WITH LIVER CIRRHOSIS"** is done by me at Tirunelveli Medical College Hospital, Tirunelveli Under the guidance and supervision of **Prof.Dr.M.Ravichandran M.D,** the dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

Place: Tirunelveli
Date:

DR.M.PACKIASELVAM
Reg no:201711361
Postgraduate Student,
M.D General Medicine,
Department of General Medicine,
Tirunelveli Medical College
Tirunelveli.

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC

REF NO:1215/GM/2017

PROTOCOL TITLE: STUDY OF CARDIAC DYSFUNCTION IN NON-DIABETIC NON-HYPERTENSIVEN PATIENTS WITH LIVER CIRRHOSIS

PRINCIPAL INVESTIGATOR: Dr.PACKIASELVAM.M, MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: PG STUDENT
DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI

Dear Dr.PACKIASELVAM, MBBS, The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during The IEC meeting held on 15.12.2017.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of The Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of The validity
4. An annual status report should be submitted.
5. The TIREC will monitor The study
6. At The time of PI's retirement/leaving the institute, The study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in The original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and The revised budget form should be submitted.
   c. if the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, The same should be documented.
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   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
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STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman, MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.J.SureshDurai, MD
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

CERTIFICATE – II

This is to certify that this dissertation work entitled **"A STUDY ON CARDIAC DYSFUNCTION IN NON DIABETIC NON HYPERTENSIVE PATIENTS WITH LIVER CIRRHOSIS"** of the candidate **Dr.M.PACKIASELVAM** with registration Number **201711361** for the award of **M.D.** Degree in the branch of **GENERAL MEDICINE (I).** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **3 percentage** of plagiarism in the dissertation.

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https://www.researchgate.net/publication/12303124_Hyperdynamic_circulation_in_portal_hypertension_A_comparative_model_of_arterio-venous_fistula
https://gut.bmj.com/content/52/2/293
https://quizlet.com/12900601/abdominal-ultrasound-liverbiliary-tract-flash-cards/
https://musculoskeletalkey.com/portal-hypertension/
https://www.researchgate.net/publication/7257325_Cardiac_and_vascular_changes_in_cirrhosis_Pathogenic_mechanisms

Instances where selected sources appear:

6

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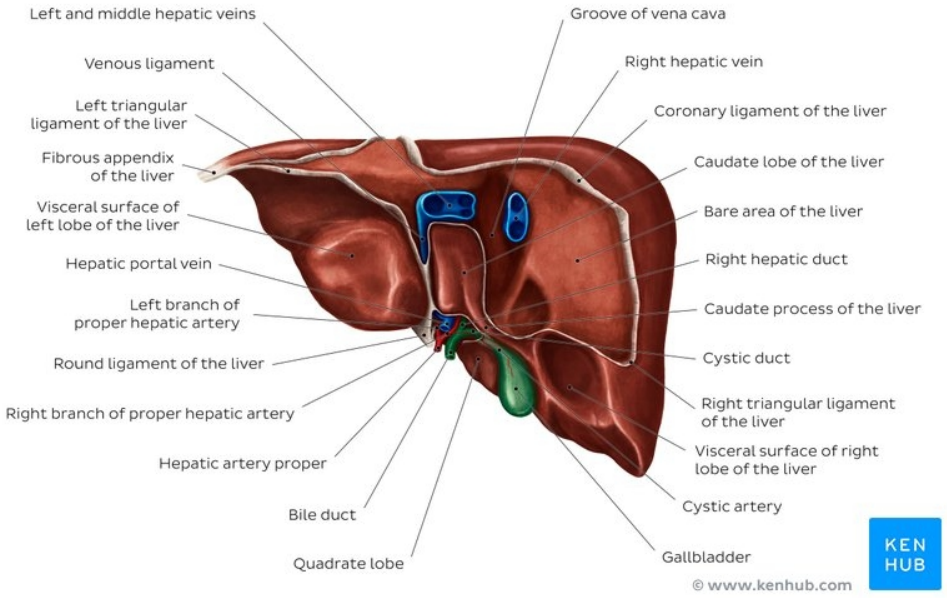
CONTENT

INTRODUCTION:

Cirrhosis and portal hypertension is associated with “hyperdynamic syndrome “which is characterised by increased cardiac output and heart rate and splanchnic vasodilatation and reduced systemic vascular resistance(1). Although there is a hyperdynamic circulation the ventricular response to sympathetic stimuli was found to be reduced in cirrhotic patients. Initially it was thought these changes were seen only in alcoholic patients with cirrhosis but later it was found that patients with non alcoholic cirrhosis also had similar cardiac functional abnormalities thus the term “cirrhotic cardiomyopathy” was introduced to describe these changes in cirrhotic patients.(3-7).



Cirrhotic cardiomyopathy is characterised by impaired cardiac systolic response to stressful stimuli, impaired diastolic relaxation and electrophysiological abnormalities in cirrhotic patients with previously no known cardiac disease(7-9).There are many factors which can contribute to the decreased cardiac contractile response like impaired beta adrenergic receptor functioning, release of endogenous cannabinoids like anadamine which have cardiodepressant activity(26),presence of cardiodepresant substances like nitric oxide and carbon monoxide. Recent studies have shown that abnormalities of Na-Cachannel in cardiac cells also play a role in the pathogenesis of contractile dysfunction in cirrhotic patients. The abnormalities of

the Na^{+}/Ca^{2+} exchanger in cirrhotic patients result in the excess Ca^{2+} influx leading to cardiomyocyte apoptosis [10, 33].

Diastolic dysfunction can be seen in echocardiography as increased E/A ratio and prolonged deceleration time. Increase in stiffer collagen type 1 with decrease in more compliant type 3 collagen has also been found to play a role in diastolic dysfuction(42)

Overt heart failure usually does not manifest in cirrhotic cardiomyopathy but stressful conditions like liver transplantation, TIPS and infections can convert latent cardiac dysfuction to overt heart failure.

The management of this condition is largely supportive and it has not been extensively studied. if overt heart failure develops it is managed conservatively with salt and fluid restriction, diuretics and other supportive measures. Orthoptic liver transplantation can improve the functions but it takes several months to develop.

AIM OF THE STUDY

1. To study the cardiac dysfunction in cases diagnosed with cirrhosis of liver in nonalcoholic patients with other causes of cirrhosis

2. To study the relationship between the severity of cirrhosis and the presence of cirrhotic cardiomyopathy

REVIEW OF LITERATURE

Cirrhosis is defined histologically as a diffuse hepatic process characterised by progressive scarring and fibrosis and change from normal liver architecture to structurally abnormal nodules. The word cirrhosis is coined from the greek word “kirrhos” which means orange referring to the colour of the damaged liver.

Cirrhosis affected approximately 2.8million people worldwide out of which 1.3 million deaths occurred in 2015. Deaths from cirrhosis are estimated to become the 12 leading cause of mortality by 2020(9).

CLASSIICATION OF CIRRHOSIS:

According to World Health Organisation cirrhosis is classified as:

- **MORPHOLOGIC**:

  Micronodular, macronodular, mixed

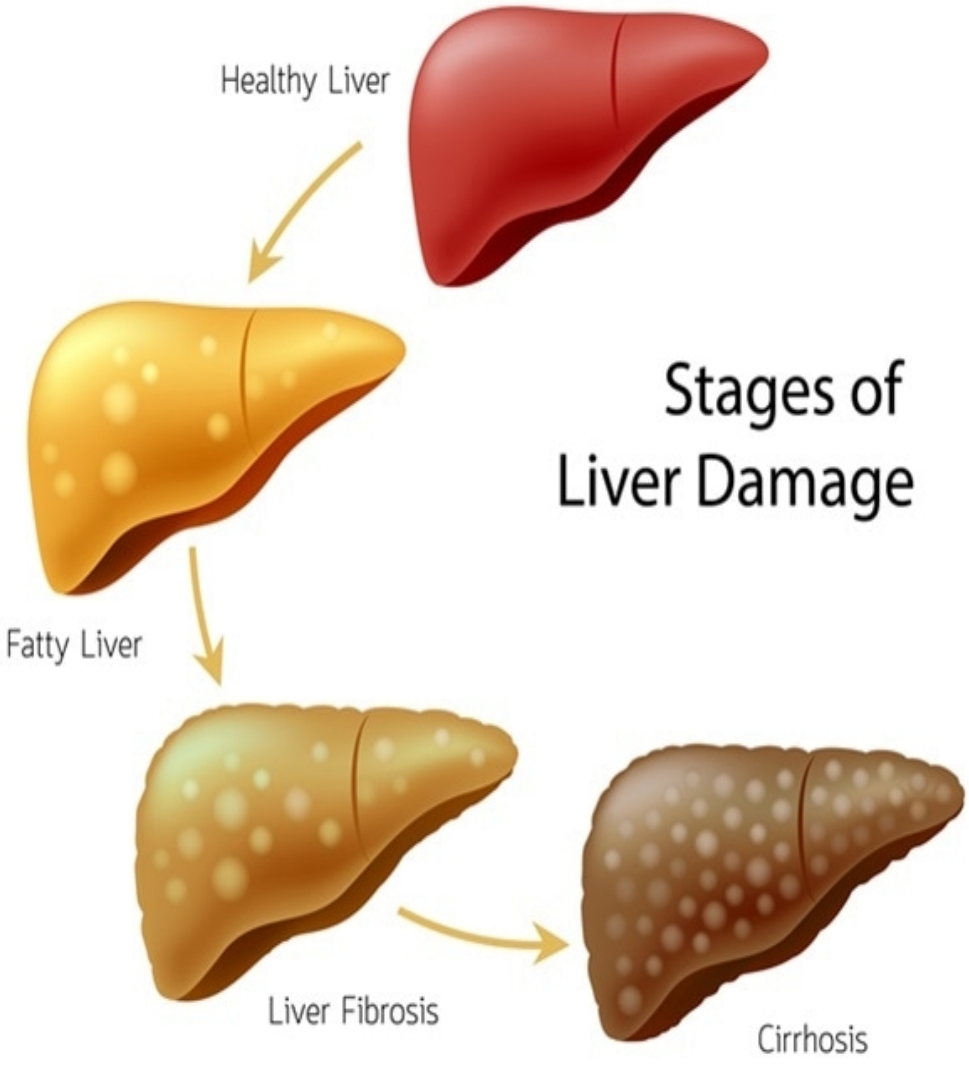
- **HISTOLOGIC:**

  Portal, post necrotic, post hepatitis, biliary, congestive

- **ETIOLOGIC:**

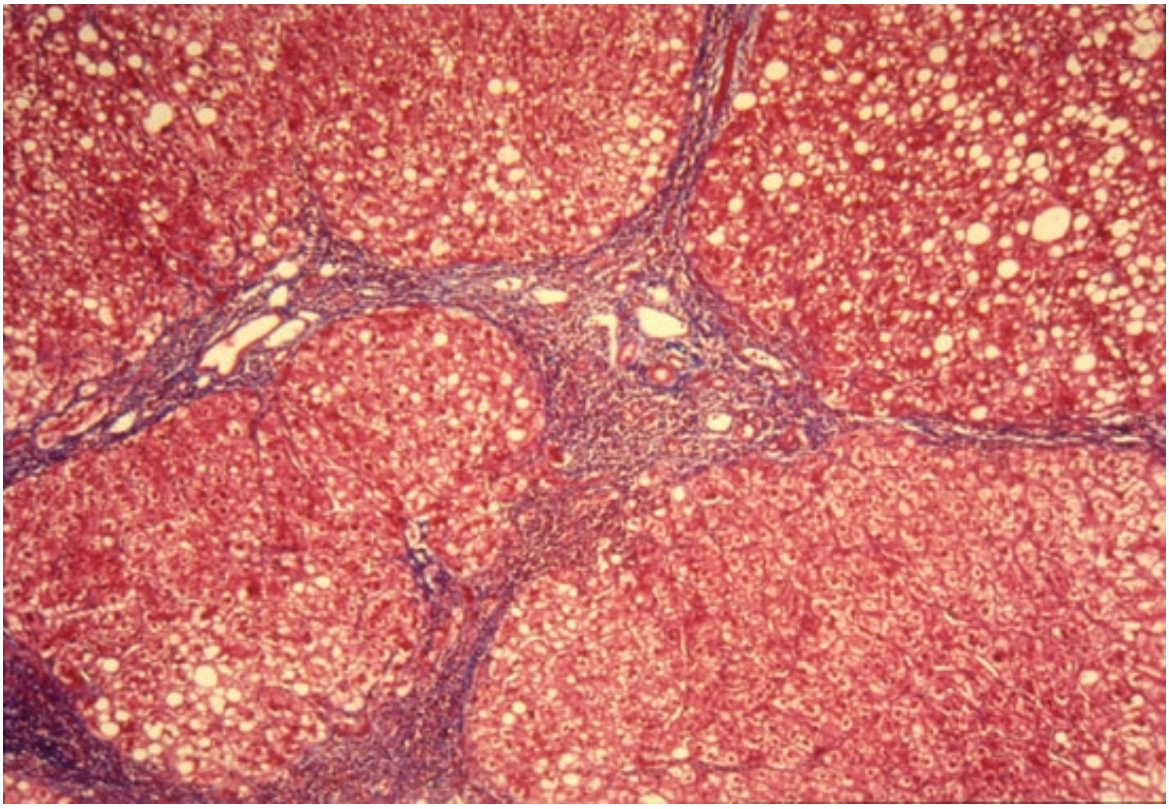
  Genetic, Toxic, Infectious, Biliary, Cryptogenic, Vascular

PATHOPHYSIOLOGY OF CIRRHOSIS:



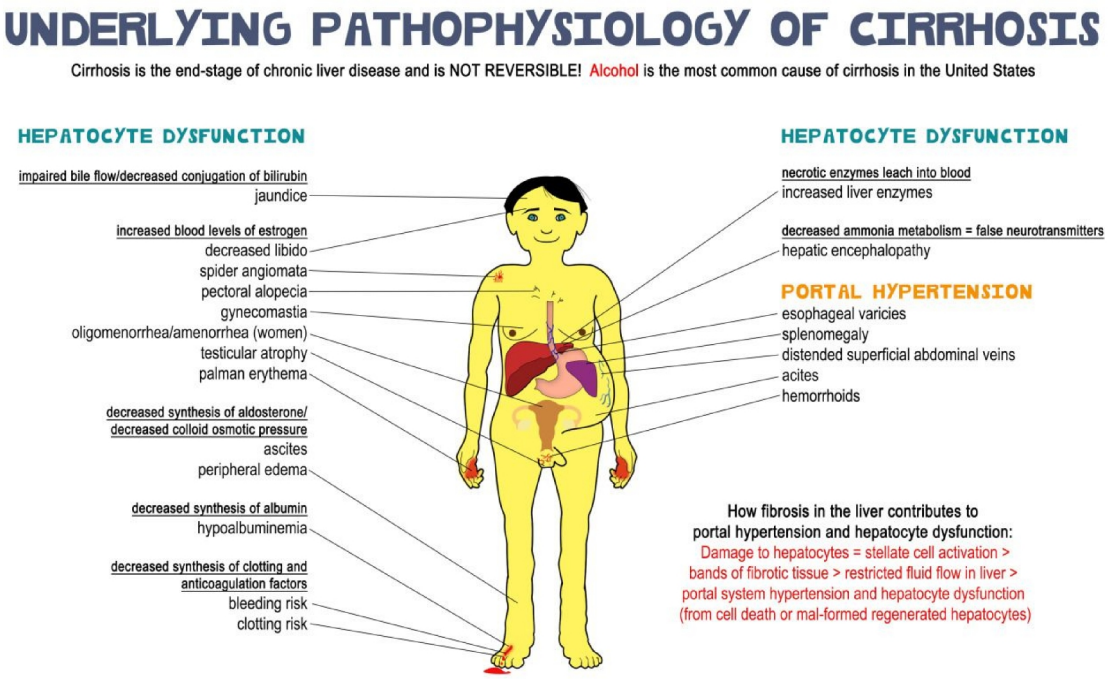
The pathology of cirrhosis can be described in the following sequence of events:

1. Injury
2. Degeneration
3. Fibrosis
4. Formation of fibrovascular membranes
5. Parenchymal dissection into nodules
6. Rearrangement of blood circulation
7. Cirrhosis



Histology of Cirrhotic Liver showing

1. **Fibrotic nodules**
2. **Disruption of liver archtitecture and**
3. **Fibrous trans connecting the portal triads**



Patients with end stage liver disease manifest a hyperdynamic circulation due tosplanchnic vasodilatation and decreased vascular resistance , increase in heart rate and cardiac output. Clinically these changes due to hyperdynamic circulation manifest with warm skin, spider angiomas, palmar erythema and bounding pulse. These changes were first described in patients with alcoholic cirrhosis and the term “latent alcoholic cardiomyopathy” was used however future studies showed that the same hemodynamic dysregulation was found in cirrhotic patients with other etiologies too.

PATHOGENESIS OF HYPERDYNAMIC CIRCULATION:

Splancnic and peripheral vasodilatation

Decreased effective circulating volume

Decreased renal perfusion leading to activation of RAAS, ADH and sympathetic nervous system

Renal artery vasoconstriction ,sodium Retention and volume expansion

These circulatory changes lead to the development of multiple life-threatening complications including hepatorenal syndrome (HRS), ascites, spontaneous bacterial peritonitis (SBP), gastroesophageal varices, and hepatopulmonary syndrome.

One of the most important features of cirrhosis is portal hypertension. About 90% of cases of portal hypertension is caused by cirrhosis of liver. The portal vein provides 80%of blood supply to liver and 20 % of its oxygen requirements. It also carries anti atrophic factors which prevents atrophy of the liver cells. Since it is a valve less system pressure anywhere in the system is the same. Portal hypertension indicates increased pressure in the portal venous system. Normal portal venous pressure is 10 mmhg . As a consequence, the gradient between portal pressure (PP) and inferior vena cava pressure (IVC) (portal pressure gradient, PPG) is increased above the upper normal value of 5 mm Hg. The significance of portal hypertensive syndrome is characterised by its complications which include

- Upper gastrointestinal bleeding from ruptured gastroesophageal varices,
- Ascites
- Hepatorenal Syndrome,

Child-Turcotte-Pugh Classification

	1 point	2 points	3 points
Encephalopathy	0	1-2	3-4
Ascites	none	slight	moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT prolonged (s)	1-4	5-6	>6
(INR)	<1.7	1.8-2.3	>2.3

Child's A = 5-6 points Child's B = 7-9 points Child's C = 10-15 points

- Portosystemic encephalopathy

  which represent the leading causes of death and of liver transplantation in patients with cirrhosis.

Clinically significant portal hypertension(CSPH) is characterised by hepatic venous pressure gradient more than 10 mmhg, the stage of disease where clinical manifestations appear. CSPH develops in majority of patients with cirrhosis during the course of disease and studies have proven that CSPH is already present at the time of diagnosis in approximately 60% of histologically proven, well compensated cirrhosis case.it is an independent predictor of survival in cirrhosis patient .international normalized ratio, alanine aminotransferase (ALT) level, and albumin are also independent predictors of clinically significant portal hypertension(11)

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION:

Anatomically the portal vein is formed by the union of the superior mesenteric vein and the splenic vein. The mesenteric vein collects blood from the splanchnic circulation. Thus, portal venous inflow is determined by the state of constriction or dilatation of splanchnic arterioles .Portal hypertension is characterised by an increased vascular resistance in the portal venous system at any level both to vascular resistance and to portal blood flow. Therefore it is classified as prehepatic(portal and splenic vein thrombosis),intrahepatic(cirrhosis) or post hepatic(budd chiarri syndrome),cirrhosis being the most common cause. In cirrhosis ,increased resistence is mostly caused by distorted hepatic architecture but in one third of the cases it is due to hepatic vasoconstriction amenable to vasodilators.

(12) The mechanism behind intrahepatic vasoconstition is :

Release of endogenous vasoconstrictors substances endothelin and reduced bioavailability of nitric oxide

Contraction of stellate cells and myofibroblasts and vascular smooth muscle cells in portal venules

Other intra-hepatic factors such as collagenosis of the space of Disse,

hepatocyte swelling and the resistance offered by portal-systemic collaterals

contribute. These may change intra-hepatic resistance and blood flow especially at a sinusoidal level. Porto systemic collaterals develop as a result of the increased pressure and reduce the increased resistance. However although portal blood flow is diverted through collaterals portal hypertension persists because of increased portal venous inflow caused by splanchnic vasodilatation which in turn is caused by increased release of nitric oxide. The most important collaterals are the gastro esophageal varices. Although varices have been assumed

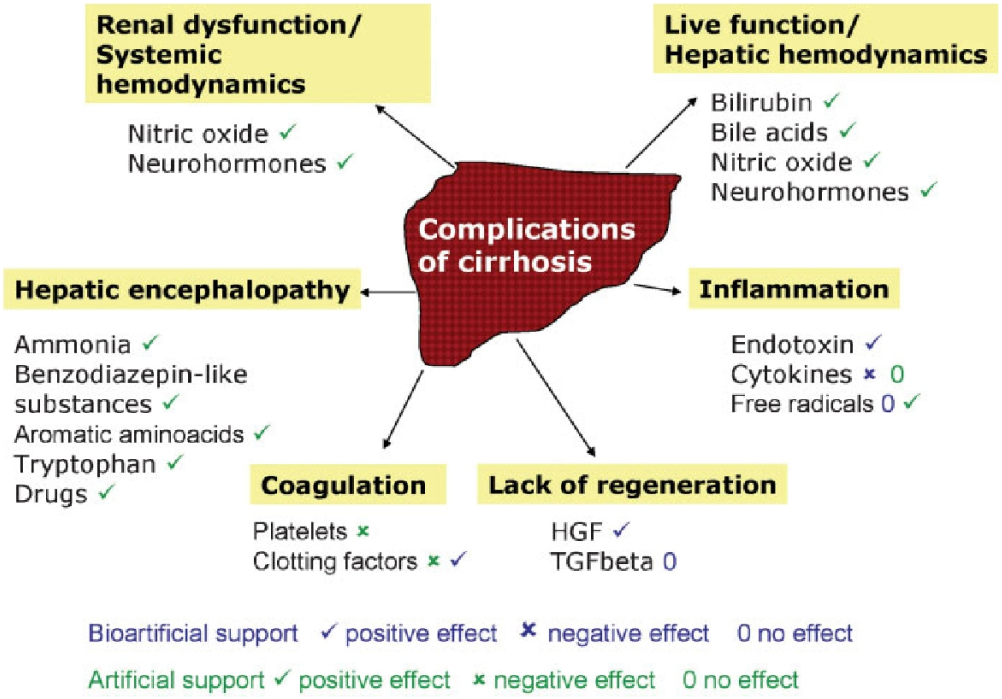
due to the dilatation of pre-existing blood vesssels , new theories suggest a process of neoangiogenesis is also implicated in the formation of varices(13).

The most important factor contributing to hyperdynamic circulation is Splanchnic vasodilatation Azygous blood flow is increased. Gastric mucosal blood flow rises. The increased portal flow raises the oesophageal variceal transmural pressure. The total portal flow is increased (hepatic and collaterals) but the actual portal flow reaching the liver is reduced(7). There are multiple factors responsible for maintain the factors hyperdynamic splanchnic circulation. There is an interaction between vasodilators and vasoconstrictors. These substances can be formed by the hepatocyte, fail to be inactivated by it or be of gut origin and pass through intra-hepatic or extrahepatic venous shunts.

Endotoxins and cytokines, largely formed in the gut, are important triggers. The endotoxins activate the vascular endothelium to produce NO and endothelin. Vasodilators include Prostacyclin which is produced by portal vein endothelium. It may play a major role in the

circulatory changes of portal hypertension due to chronic liver disease.

Cardiac and vascular changes in cirrhosis



The cardiovascular system in patients with cirrhosis or portal hypertension is abnormal. There is a hyperdynamic circulation with increased cardiac output and decreased vascular resistance. Although the cardiac output increases the ventricular response in stressful situations like infection, haemorrhage , TIPSS, other surgeries is reduced or drugs is paradoxically reduced a condition known as

cirrhotic cardiomyopathy. These cardiovascular changes have been assumed to be a responsible factor for many of the complications of cirrhosis like

- Salt and water retention
- Variceal bleeding
- Hepatopulmonary syndrome(18,19,20,21,22)

HYPERDYNAMIC CIRCULATION

Peripheral vasodilatation is the main factor responsible for hyperdynamic circulation and portal hypertension in cirrhosis. But a lot remains unknown regarding the factors leading to peripheral vasodilatation. However, the factors directly initiating vasodilatation remain obscure. An important hypothesis in the past few decades ids the “humoral factor “hypothesis. In cirrhosis, the increased intrahepatic resistance leads to portosystemic collateral formation. These portosystemic collaterals allow the gut derived humoral substances to bypass the liver and directly enter the systemic circulation without detoxification by the liver. The humoral factors which have been described as mediators of vasodilatation are:

1.Endocannabinoids

2.Nitric oxide.

Endocannabinoids :

Endocannabinoids are lipid mediators of the same cannabinoid (CB) receptors that mediate the effects of marijuana. The endocannabinoid system (ECS) consists of

- CB receptors,
- Endocannabinoids, and
- the enzymes involved in their biosynthesis and degradation, and it is present in both brain and peripheral tissues, including the liver.

The hepatic endocannabinoid system is activated in cirrhosis and the activation of vascular and cardiac CB(1) receptors by macrophage-derived and platelet-derived endocannabinoids is responsible for the vasodilatation and he vasodilated state and cardiomyopathy, which can be reversed by CB(1) blockade. It has been found In mouse models of liver fibrosis, the activation of CB(1) receptors on hepatic stellate cells is fibrogenic, and CB(1) blockade slows the progression

of fibrosis.CB1 receptor activation also plays an important role in the pathophysiology of Fatty liver induced by a high-fat diet or chronic alcohol intake, which Hepatic CB1 receptor activation also can lead to insulin resistance and dyslipidemias. Although the documented therapeutic potential of CB(1) blockade is limited by neuropsychiatric side effects, these may be mitigated by using novel, peripherally restricted CB(1) antagonists.(14)

The vasodilatory effect of endogenous cannabinoids in cirrhosis was first reported in 2001(23) Anandamide is an endogenous cannabinoid which acts on CB1 receptors. Increased levels of anandaides was found in monocytes of cirrhotic rats(23,24), and there is increased expression of its receptorCB1 in vascular endothelium of patients with cirrhosis.(23). Monocytes recovered from cirrhotic rats were infused into normal rats and it was shown to decrease the mean arterial pressure in the recipients. SR141716A a CB1 receptor antagonist was administered to cirrhotic rats and it was found to raise the peripheral vascular resistance.(23,24). SR141716A has been shown to significantly increase the decreased arterial pressure in cirrhosis, and blocks the hypotension induced by the infusion of

isolated cirrhotic monocytes into normal rats(23,24). In addition, mesenteric blood flow and portal venous pressure in cirrhotic rats was also found to be reduced by administration of SR141716A(23). All of these data show that the CB1 receptors regulate the vascular tone in both the splanchnic and systemic circulations in cirrhosis., In mouse models of liver fibrosis, the activation of CB(1) receptors on hepatic stellate cells is fibrogenic, and CB(1) blockade slows the progression of fibrosis . Anandamide rapidly produces apoptosis of hepatic stellate cells in a dose dependent manner . This effect could(10) change the hepatic sinusoids and microcirculation in hepatic sinusoids and support the development of portal hypertension which in turn leads to hyperdynamic circulation.

The mechanism behind cirrhosis leading to increased endocannabinoids was found to be stimulation of endocannabinoid production by bacterial endotoxins in cirrhosis (26). The up regulation of CB1 receptors in cirrhotic vascular endothelium and thus increased end-organ sensitivity may also enhance endo cannabinoid vasodilator tone 23.

Nitric oxide

Nitric oxide (NO) is an important mediator of liver physiology and pathophysiology. NO is generated by three isoforms of nitric oxide synthases (NOSs)

neuronal NOS(nNOS;NOS1)

inducible NOS (iNOS; NOS2), and

endothelial NOS (eNOS; NOS3)

e NOS and i NOS important in liver diseases

NOS catalyzes the oxidation of L-arginine to NO and citrulline [2]. In the cell, nNOS and iNOS are predominantly found in the cytosol, while eNOS binds to the membrane via palmitoylation and myristoylation [3].

E NOS and I NOS have opposite roles in the development of liver disease.

NO produced by e NOS

Inhibits the inflammatory activation of Kuppfer cells and enhances beta oxidation of fatty acids thus protecting the liver fat deposition

NO and its derivatives produced by i NOS has been found to promote the formation of NAFLD. Simvastatin [3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor], which is known to increase eNOS activity and thus NO production, was also shown to mitigate NASH-related liver fibrosis by inhibiting HSC activation [74) An NO donor 29 or NOS3 genetransfection27, which compensates for the decreased hepatic NOS3 expression, significantly lowers the increased portal pressure in cirrhosis. Overall, Enos-derived NO or NO donors can be protective, while iNOS-derived NO is generally pathological). This may be related to the microenvironments at the sites of iNOS induction where generated NO can facilitate the formation of ROS and RNS with other available radicals.

While the pathogenesis of NASH remains to be elucidated, a “double-hit theory” has been proposed in which the “first hit” involves hepatic fat accumulation and the “second hit” could be any additional insult to the liver. iNOS-derived NO could be an important second hit.

In portal hypertension, regulation of NO is opposite inside and outside of the liver. There is decreased NO availability in the intrahepatic circulation but paradoxically NO production in splanchnic and systemic arteries increases and causes excessive vasodilation, resulting in increased blood flow to the portal vein and thereby worsening portal . Moreover, it was experimented and found normalization of NO production in cirrhotic rats, by achieving normal concentrations of aortic cGMP with small doses of the NOS inhibitor L-NAME, normalizes the decreased peripheral vascular resistance and the increased cardiac output 33. In vitro, an NO inhibitor reverses the hyporeactivity of blood vessels from cirrhotic rats to vasoconstrictors 34.

All these results strongly support the hypothesis that increased NO production is a major factor in the peripheral arterial vasodilation of cirrhosis. The agents promoting nitric oxide production include

inflammatory cytokines and endotoxin. The role of norfloxacin in cirrhosis is selective intestinal decontamination and getting rid of the bacterial endotoxins in the gut and partially reverses the hyperdynamic circulation in cirrhosis. The endotoxins promoting nitric oxide production are derived from:

1. Alcohol which damages gastrointestinal mucous membrane can facilitate transfer of bacteria into the circulation.

2. Portosystemic shunting allows gut-derived bacterial endotoxins to bypass into the systemic circulation.

3.There is increased intestinal permeability cirrhotic patients with portal Hypertension due to structural abnormalities leading to vascular congestion and edema 37.

4. Intestinal bacterial overgrowth and bacterial translocation are increased in cirrhosis 38.

Other possible factors stimulating NO production include cytokines such as TNF-α, IL-1, IL-6, and IFN-γ39-41 Among these, TNF-αappears to have a very important role in liver fibrosis . TNF alpha is

a pleotropic cytokine produced by a variety of immune cells and promotes inflammation, proliferation and apoptosis. TNF alpha stimulates hepatic stellate cells(HSC)which are the primary cells that contribute to liver fibrosis among the various cellular sources that differentiate into myofibroblasts [4]. It was also found that anti-TNF-α antibody increases mean arterial pressure and systemic vascular resistance, and decreases cardiac index and portal pressure thereby proving the pathogenic role of TNF alpha in fibrosis of liver. 42. There has been recent evaluation of the activity of the Larginine-NO pathway at different levels 43. Although NOS2 mRNA was detectable in the cirrhotic aorta, no NOS2 protein was observed in Western blots. It is not clear why the mRNA was not expressed as a protein. It might have been degraded or not been transcribed. It is also possible that 13 the method of Western blotting did not allow for identification of small amounts of NOS2 protein.

A consistent augmentation in the expression of NOS3 mRNA and protein levels is observed in cirrhotic rats. Because NOS3 can be upregulated by stimuli such as shear stress and mechanical deformation, some have suggested that hyperdynamic circulation is the cause rather than the consequence of the activation of the NO

pathway (31, 46, 47). In addition, there may be other reasons for the increased NOS3. Estrogens have shown to increase NOS 3 and cirrhosis is associated with increased levels of estrogens (48,49,50). Other factors which may stimulate NOS3 expression need further investigation.

There is another isoform of NOS, neuronal NOS (nNOS or NOS1) whose expression is significantly increased in rat cirrhotic aortae 51. Furthermore, an NOS specific inhibitor, 7-nitroindazole (7-NI), significantly decreased the sodium and water retention and normalized the hyperdynamic indices such as cardiac index, mean arterial pressure, and systemic vascular resistance in these rats 51. Biecker et al also showed that nNOS partially compensates for the absence of eNOS in producing hyperdynamic circulation in eNOS-gene knockout mice (52). These data indicate that the nNOS isoform plays a major pathogenic role in hyperdynamic circulation, and perhaps even in renal salt and water retention in cirrhosis.

It seems that endocannabinoids and nitric oxide may both play an important role in hyperdynamic circulation, but what is the

relationship between them? The literature remains inconclusive. In a kidney study,

Deutsch et al found that the vasodilatation of anandamide is NO dependent, because the NOS inhibitor L-NAME completely blocked the vasodilatory effect of anandamide, similar to a CB1 antagonist 53. However, another study showed no effect of L-NAME infusion on the hypotensive effects of anandamide 24.

Some studies suggest the possible involvement of other humoral vasodilators, but a definitive pathogenic role for any of these substances remains elusive. This list includes: glucagons , prostaglandins , GABA, VIP , bile acids , endotoxin, histamine and adenosine .

CENTRAL NEURAL MECHANISMS

Although many researches have focused on the humoral mediators, in recent years the role of CNS activation in pathogenesis of hyperdynamic circulation has been studied. it was demonstrated that primary afferent denervation by capsaicin reversed the hyperdynamic circulation in rats with cirrhosis or portal hypertension due to portal vein stenosis (PVS)61. What is the relationship between the CNS and hyperdynamic circulation in portal hypertension? Using c-fos, an immediate early gene (whose protein product can be detected by immuno histochemistry, as a marker of central neuronal activation, it was showed that the brainstem and hypothalamic cardiovascular-regulatory nuclei are activated at the first day after PVS, whereas the hyperdynamic circulation does not start up until 3-5 days after PVS. This time sequence suggests that central neural activation is the initiating signal in the pathogenesis of hyperdynamic circulation.

Subsequently, in portal hypertensive rats, when c-fos antisense oligonucleotide was microinjected into one of the major cardiovascular regulatory brainstem nuclei, the nucleus tractus solitarius (NTS), to block local Fos expression. This treatment

completely blocked the development of the hyperdynamic circulation, i.e., abnormalities in cardiac output, mean arterial pressure and systemic vascular resistance were completely eliminated 62. In normal control rats, c-fos antisense oligonucleotides had no effect62. These results indicate that central neural activation is a sine qua non for the development of the hyperdynamic circulation in portal hypertension.

The CNS, as the controller of the circulation, presumably would not arbitrarily activate the cardiovascular system without reason. This raises the question of what the initiating signal is. Likely, it is somehow related to the portal hypertension per se. Moreover, the exact route of signaling from the periphery to the CNS remains unclear. The aforementioned capsaicin study suggests that primary afferent nerves may be the signaling pathway from the periphery to the CNS . A subsequent study showed that capsaicin-treated BDL rats improve the renal function and do not develop ascites. Moreover, both BDL-cirrhotic and portal hypertensive rats show diminished Fos expression in NTS after capsaicin-induced denervation of the afferent nerves as neonates. These observations indicate that intact primary afferent innervation is necessary for the central neuronal activation

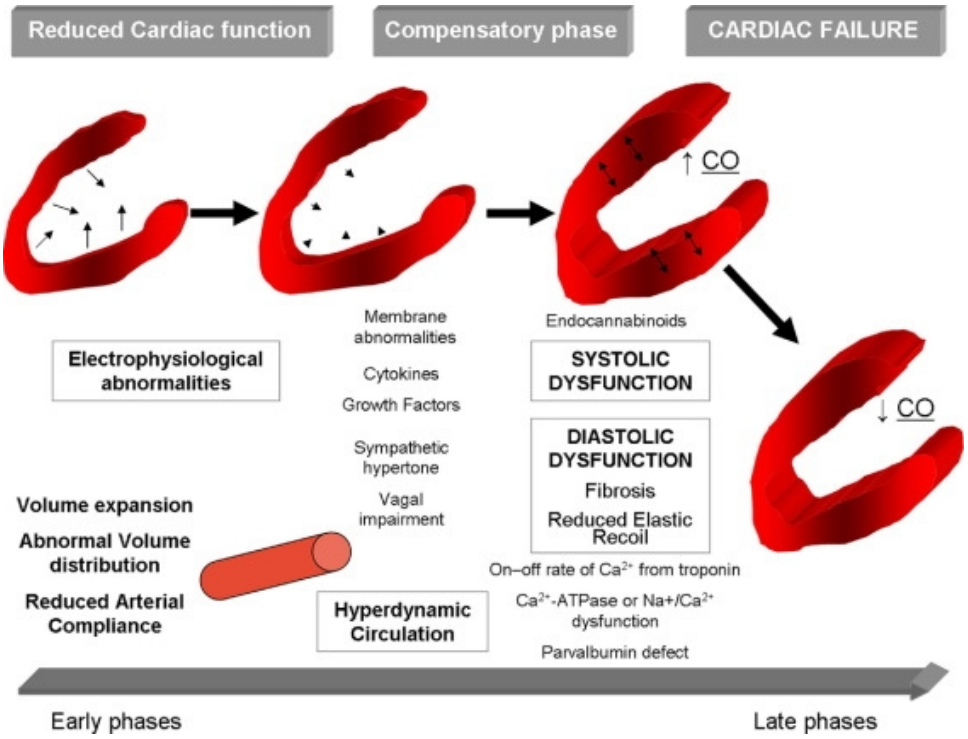
and development or maintenance of hyperdynamic circulation. Additionally, sodium retention and ascites formation is also dependent on either the presence of hyperdynamic circulation or intact afferent innervation, or both. The complex relationship between CNS activation, local or neurohormonal humoral factor stimulation, and cardiovascular disturbances in cirrhosis/portal hypertension continues to be studied in several labs.

CIRRHOTIC CARDIOMYOPATHY

There has been proven association between cirrhosis and cardiac dysfunction over the years. The cardiac changes in cirrhotic patients can manifest as systolic, diastolic and electrophysiological abnormalities (1). Due to its latent nature there is limited evidence regarding actual prevalence of cirrhotic cardiomyopathy as patients usually have near normal cardiac function unless exposed to stress (physiological or pharmacological (2).

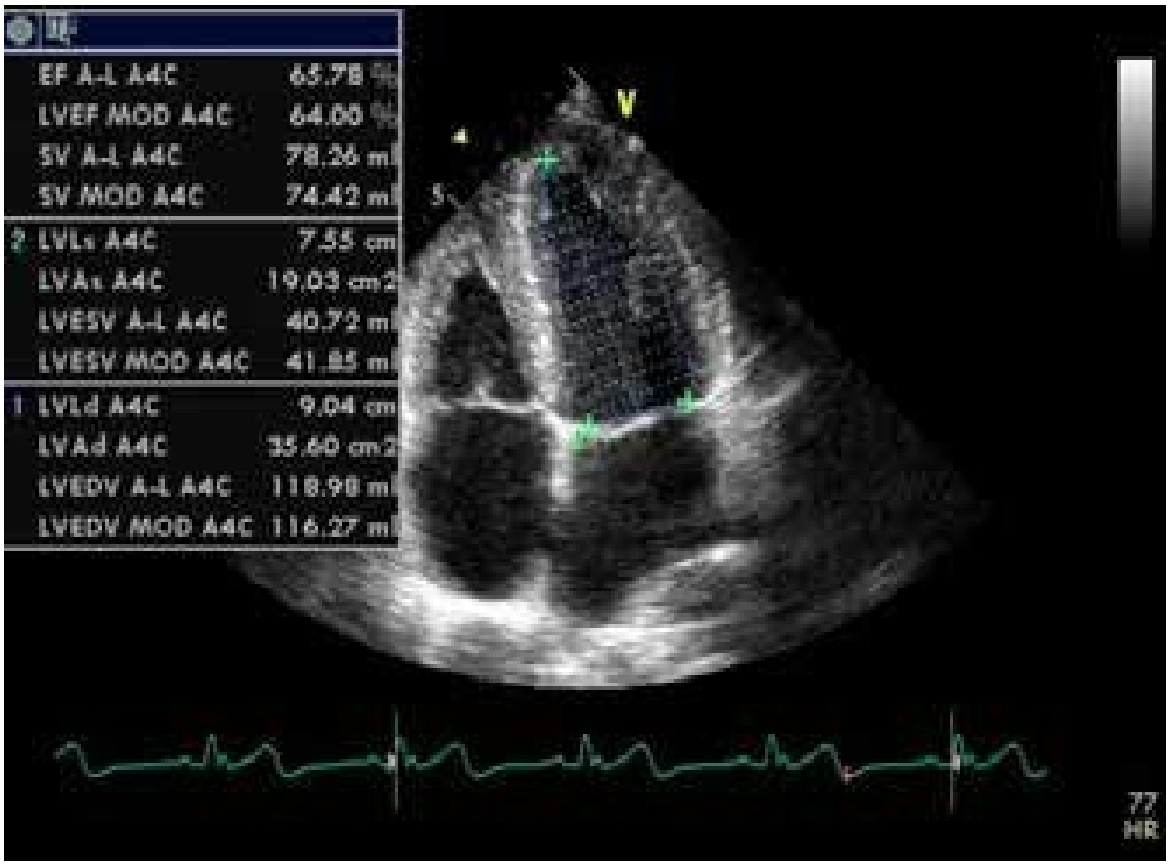
Definition:

Cirrhotic cardiomyopathy is a phenomenon of blunted cardiac response to physiological or pharmacological stimuli inspite of an increased basal cardiac output in patients with cirrhosis in the absence of any known cardiac disease.



Initially cardiac dysfunction war though to be due to direct alcoholic cardiotoxcity but similar depressed cardiac response war also found in patients with non alcoholic cirrhosis.

Criteria for cirrhotic cardiomyopathy



1. **Systolic dysfunction**

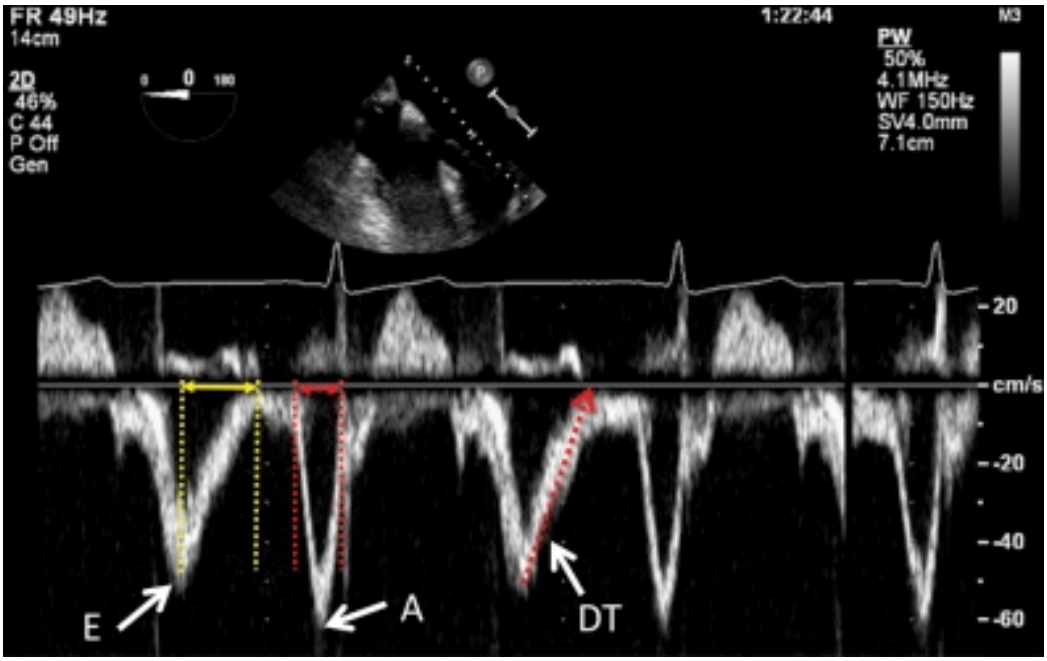
   Blunted increase in CO on exercise or pharmacological stimuli EF < 55%

2. **Diastolic dysfunction**

   Ratio of early and late phase of ventricular filling E/A <1

   Lengthening of Decelaration time > 200msec

Isolvolumetric relaxation time > 80msecs



3. Supportive criteria

Electro physiological abnormalities

Electro mechanical dissociation

QT prolongation

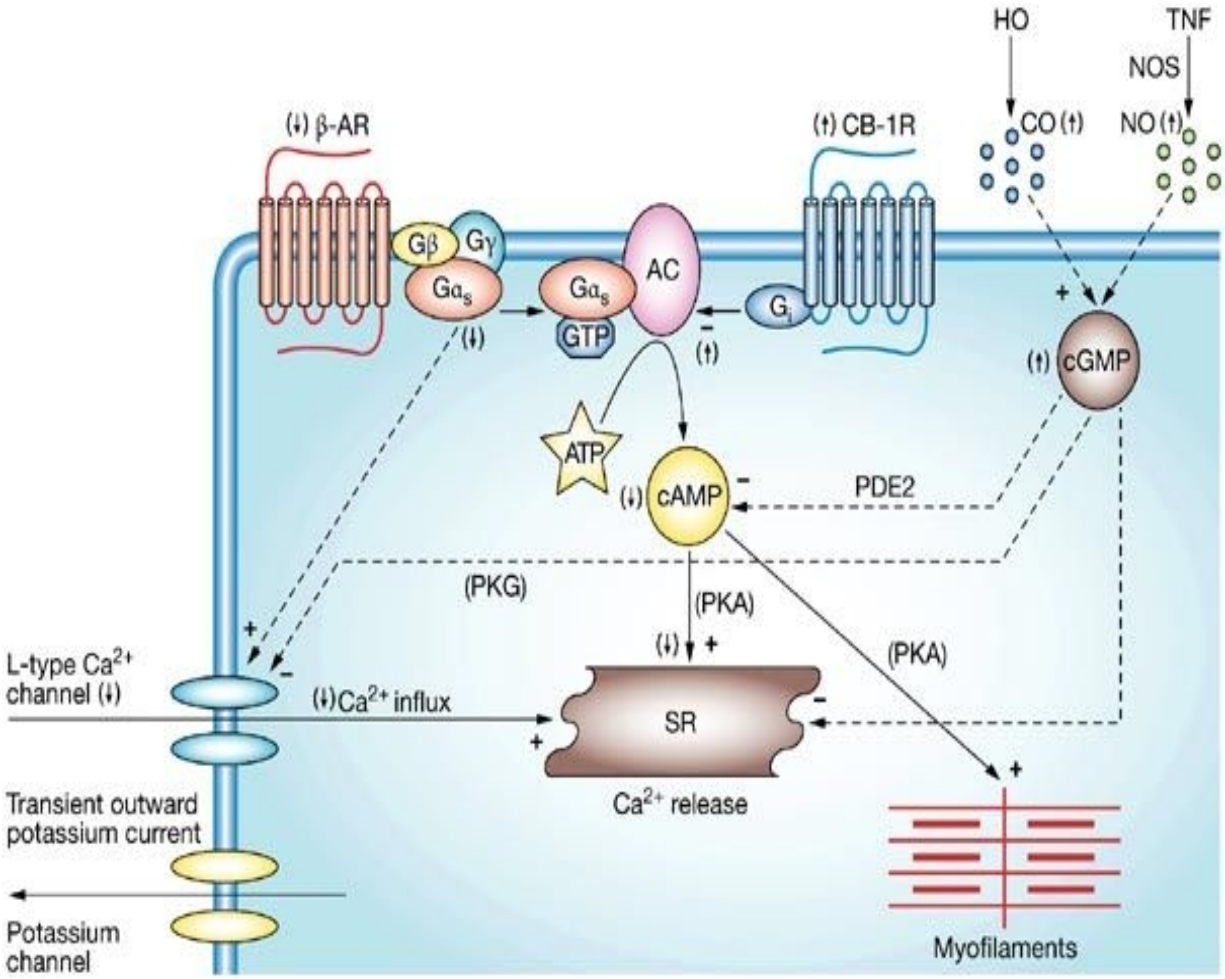
Left Atrial Hypertrophy

Increased Myocordial mass

Increased Pro BNP & BNP

Increased Troponin I

Pathophysiology

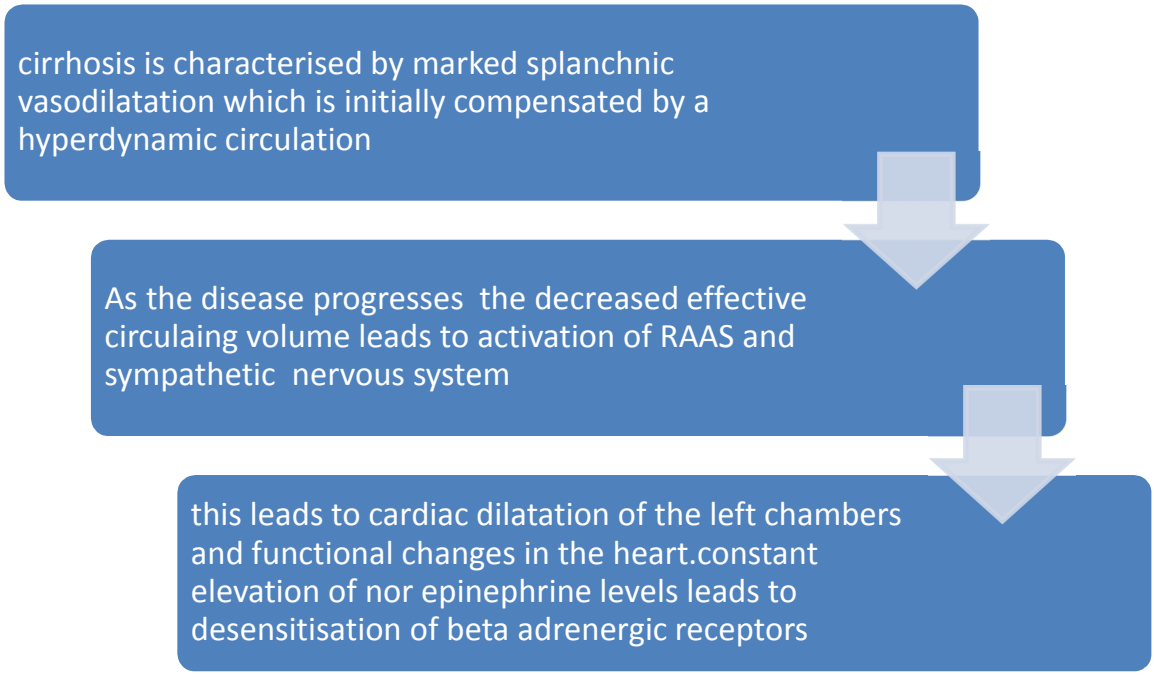


Cellular Pathophysiology of cirrhotic cardiomyopathy pictorial representation

It is a multifactorial process involving neurohumoral and cellular mechanisms which include

- Cardiac autonomic dysfunction
- Defective beta adrenoreceptors
- Membrane changes
- Humoral cardiodpressant factors

Cardiac autonomic dysfunction and defective beta receptors plays a important rule in systolic dysfunction seen in cirrhotic cardiomyopathy



Alterations in membrane permeability:

- The fluidity of cell membranes decrease and plasma membrane becomes more rigid in patients with cirrhosis due to excessive lipid accumulation

- These interfere with the activation of calcium channels and beta receptors in the membrane of cardiac myocytes there by interfering with the cardiac contractility.

Humoral cardio depressant factors:

Endocannabinoids like arachidonyl ethanolamine (AEA) and 2 arachidonyl glycerol are increased in cirrhosis. They can interact with CB1 receptors in the cardiac cells and reduce the response to beta adrenergic stimulation and decrease cardiac contractility.

Diastolic dysfunction:

The pathology of diastolic dysfunction is poorly understood I cirrhosis but diastolic function is more common and can be demonstrated in echocardiogram even at rest unlike systolic dysfunction.

Electrophysiological changes:

Functional changes in ion channels particularly potassium channels in cell membrane of cardiac myocytes play a role in electrophysiological changes which can manifest as:

- Prolonged repolarisation
- Defective cardiac excitation contraction coupling

Clinical features:

Phenomenon of "autotreating":

Overt heart failure may not be apparent because of the peripheral vasodilatation in response to splanchnic vasodilatation thereby decreasing the preload. Patients may present with :

Exertional dyspnoea

Pedal edema

Ascitis , all of which can be due to cirrhosis as well .The only difference is that in cirrhosis there will be hydrothorax and no fank pulmonary congestion.

Stressful conditions like **infections, TIPSS , liver transplantation** can change the picture rapidly from latent to overt heart failure.

In TIPPS there is a rapid shift of blood from mesenteric veins into systemic circulation leading to increased preload and heart failure.

STAGES OF DIASTOLIC DYSFUNCTION

Grade	Stage	Dominant Pathophysiology
1	Impaired relaxation	Delayed LV early diastolic active relaxation Normal LA pressure Low opening LA-LV pressure gradient Reduced LV suction force
2	Pseudonormalization	Delayed LV early diastolic active relaxation Mildly elevated LA pressure Low opening LA-LV pressure gradient Reduced LV suction force
3	Restrictive filling (Reversible)	Noncompliant LV chamber (increased stiffness) Diminished LV suction force High opening LA-LV pressure gradient Elevated LA pressure (inflow by "pushing" blood) Failing LA contractility Responds positively to preload reduction
4	Restrictive filling (Irreversible)	Same as Stage 3 No improvement with preload reduction.

- **M**ost cases show grade 1 and grade 2 diastolic dysfunction . The grade of diastolic dysfunction correlates with the severity of liver disease.
- E/A(early to late diastolic flow)ratio has been used to measure the diastolic dysfunction and it has been shown that E/A ratio increases significantly with the Child Pugh Grade of cirrhosis

SYSTOLIC DYSFUNCTION:

- **S**ystolic dysfunction is manifested as 'increase in cardiac output and ejection fraction in response to exercise or vasoactive drug stimulation was less that of normal subjects'
- The pre-ejection period(which replresents the ventricular depolarisation)/left ventricular ejection time(mechanical systole) ratio has been seen to increase from baseline after exercise in cirrhotic patients which is called **electromechanical uncoupling.**

ECG CHANGES:

- Prolonged QT interval(>440msecs)

Supportive criteria:

Left atrial volume >34ml/m2

Increased myocardial mass

Increased cardiac enzymes

These changes tend to correlate with the severity of liver disease and appears to be reversible after liver transplant.

MATERIALS AND METHODS

Patients included in the study were recruited from the Department of General Medicine at Tirunelveli Medical College Government Hospital during the period of 2017-2019.

Inclusion criteria

Non alcoholic patients diagnosed with cirrhosis of formed the study group.

Exclusion criteria

Cases with the following features were excluded from the study –

- Cases who are hypertensive
- Diabetic cases
- Alcoholic cases
- Cases with severe ascites
- Coronary artery disease and heart failure patients
- Cases with risk factors for cardiomyopathy other than cirrhosis
- Recent UGI bleed history bleed
- Cases with severe anemia

Investigations done include

- Complete blood count,
- Liver function test
- Ultrasound scan of the abdomen along with
- Doppler scan,
- Viral markers,
- Ascitic fluid analysis,
- Electrocardiography, and echocardiography.
- Coagulation profile

  The parameters assessed were in echocardiography are E/A ratio and ejection fraction.

The diagnostic criteria included E/A ratio less than 1 in this study. and ejection fraction of 60% were considered mean of the normal values while doing statistical analysis.

The statistical analysis was done using SSPS software version 15. Univariate and multivariate analysis were done with Chi Square test. P value of < 0.05 was observed to be significant. Percentage calculation was done whenever appropriate.

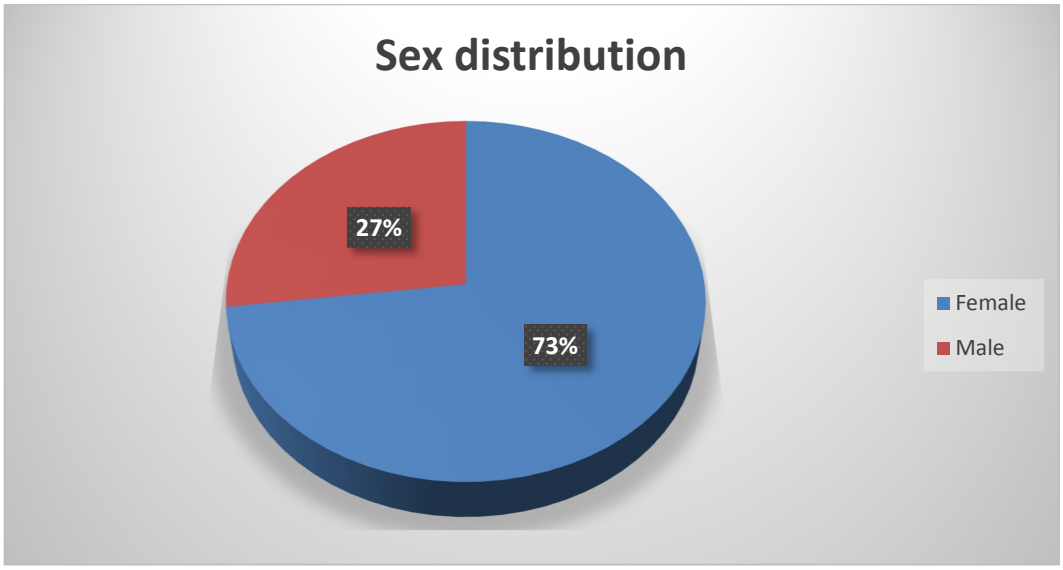
Of the 100 cases included in this study 33 patients were below 40 years of age, 36 cases were between 40 and 50 years of age and 31 cases were above 50 years of age.

RESULTS

The total number of cases included in this study was 100. Of these, there were 73 females and 27 males.

Sex distribution

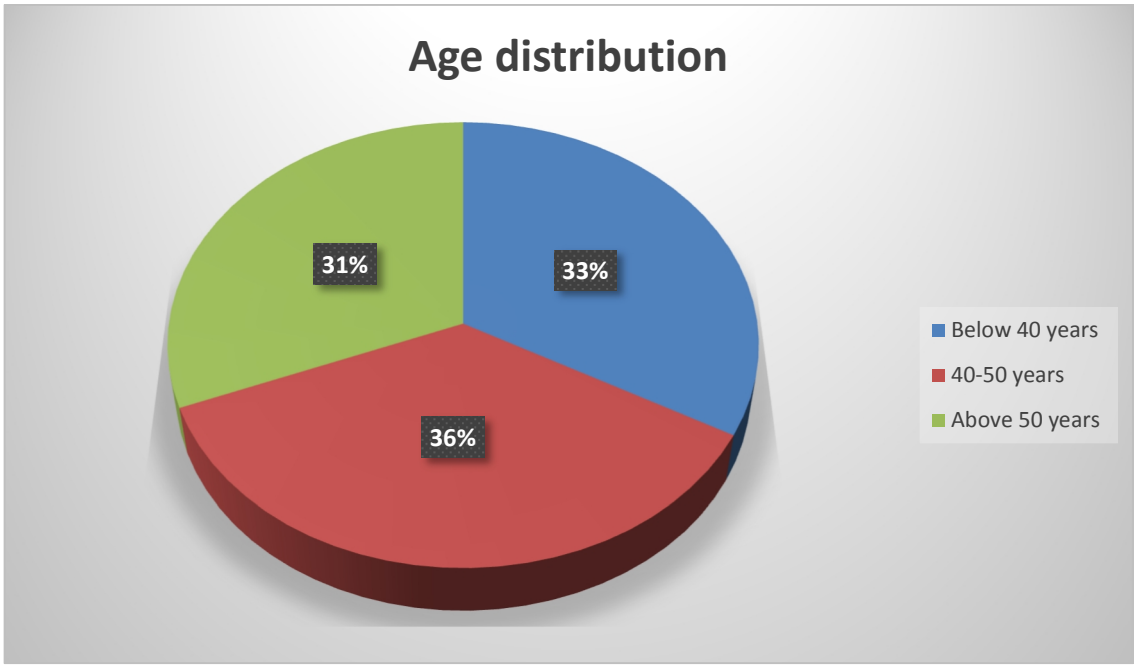
Sex	Frequency	Percentage
Female	73	73
Male	27	27
Total	100	100



Of the 100 cases included in this study 33 patients were below 40 years of age, 36 cases were between 40 and 50 years of age and 31 cases were above 50 years of age.

Age distribution

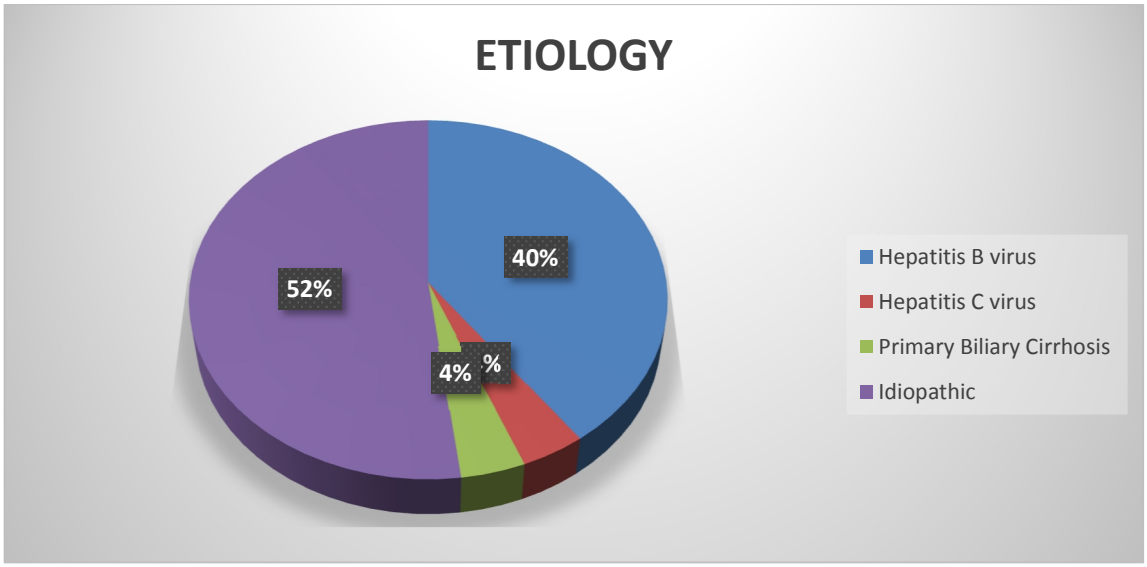
Age group in years	Frequency	Percentage
Below 40 years	33	33.00
40-50 years	36	36.00
Above 50 years	31	31.00
Total	100	100.00



In 40 cases, cirrhosis was due to hepatic B viral infection, 4 due to hepatitis C, 4 due to primary biliary cirrhosis and in 52 patients it is idiopathic.

ETIOLOGY

Etiology	Frequency	Percentage
Hepatitis B virus	40	40.00
Hepatitis C virus	4	4.00
Primary Biliary Cirrhosis	4	4.00
Idiopathic	52	52.00
Total	100	100

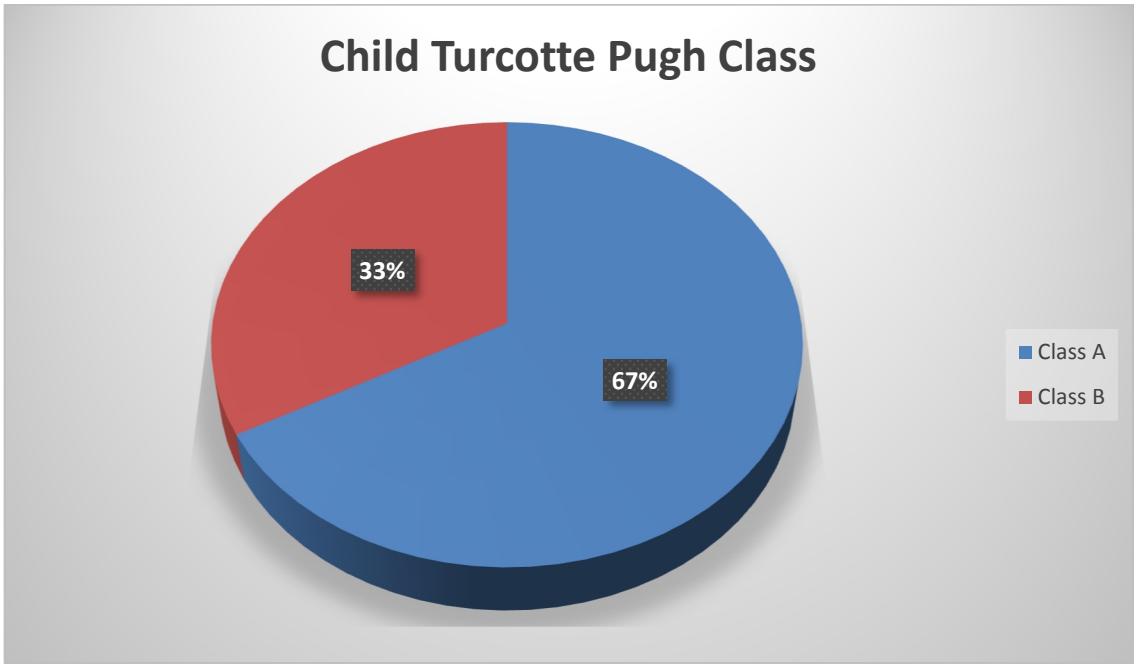


Clinical findings

Of the 100 cases included in the study, 80 cases had ascites (80%). 83 cases had varices (83). 67 cases (67%) had Class A Child Turcotte Pugh Score. 33 cases (33%) had Class B Child Turcotte Pugh Score. There were no cases which belonged to Class C of CTP scoring who had cirrhosis.

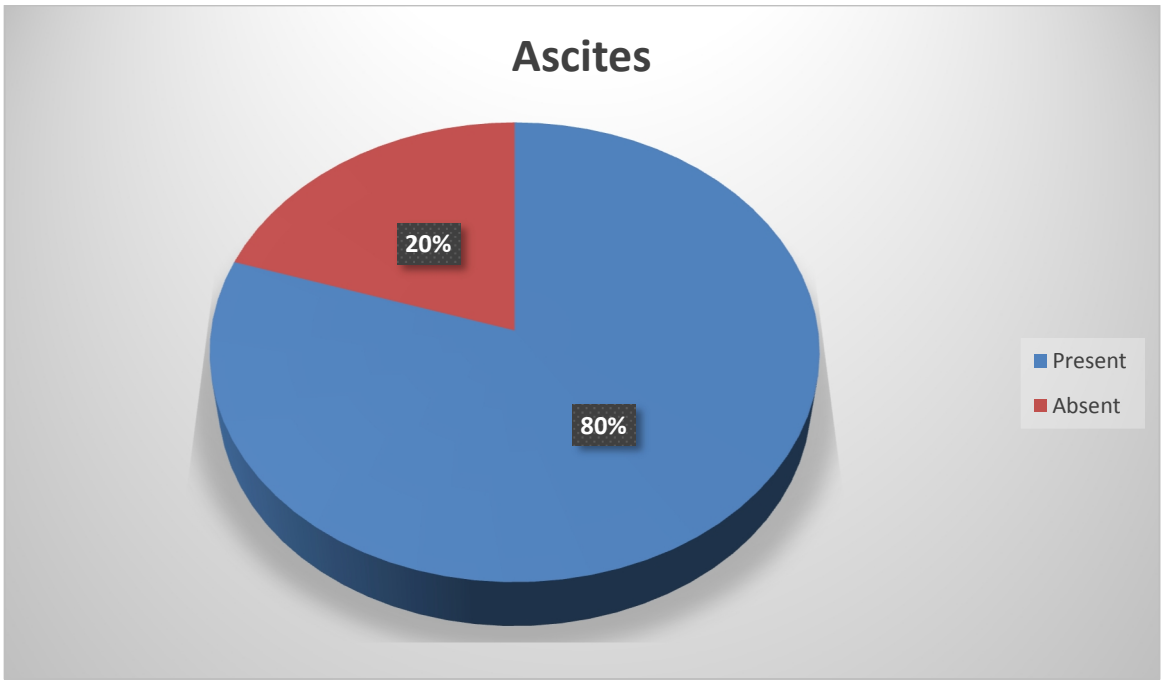
Child Turcotte Pugh Class

CTP Class	Frequency	Percentage
Class A	67	67.00
Class B	33	33.00
Total	100	100.00


Child Turcotte Pugh Class
33%
67%
Class A
Class B

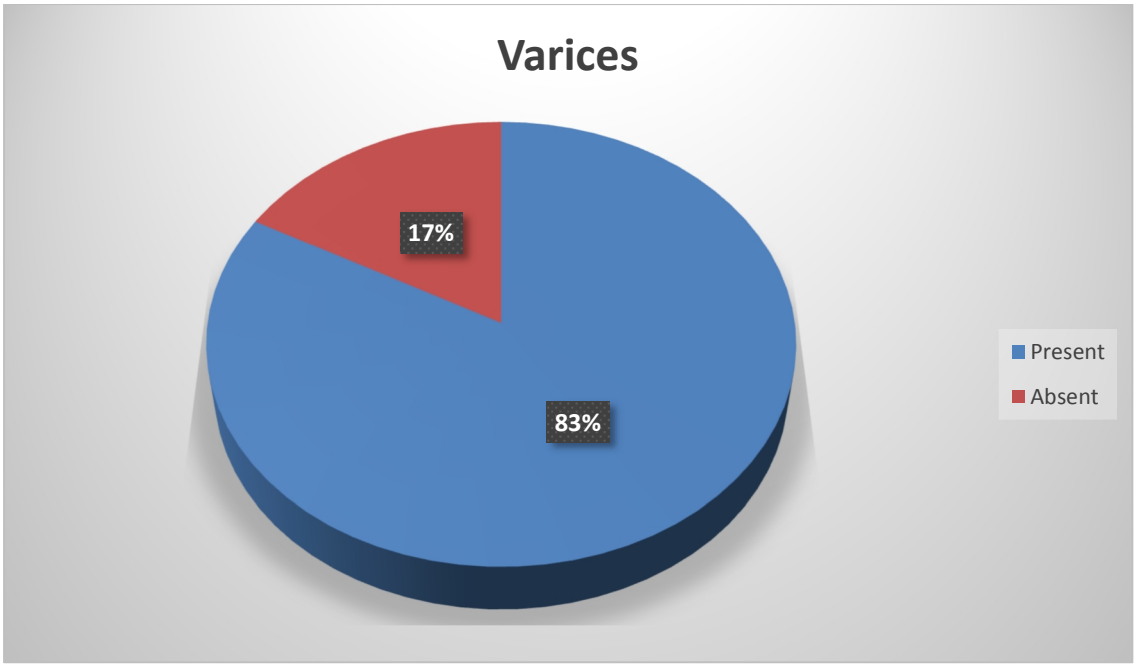
Ascites

Ascites	Frequency	Percentage
Present	80	80.00
Absent	20	20.00
Total	100	100.00



Varices

Varices	Frequency	Percentage
Present	83	83.00
Absent	17	17.00
Total	100	100.00

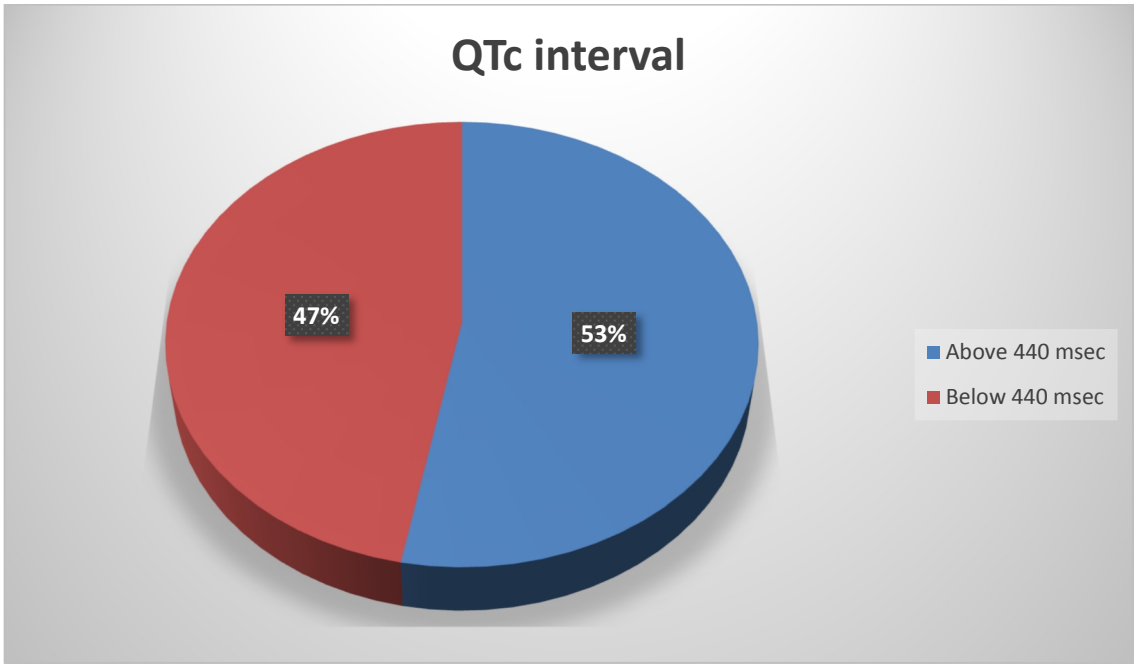


Conduction disturbances

Out of the 100 cases who were included in the study, 53 patients had QTc interval of more than 440 msec. Of these 53 patients were 36 males and 17 were female patients.

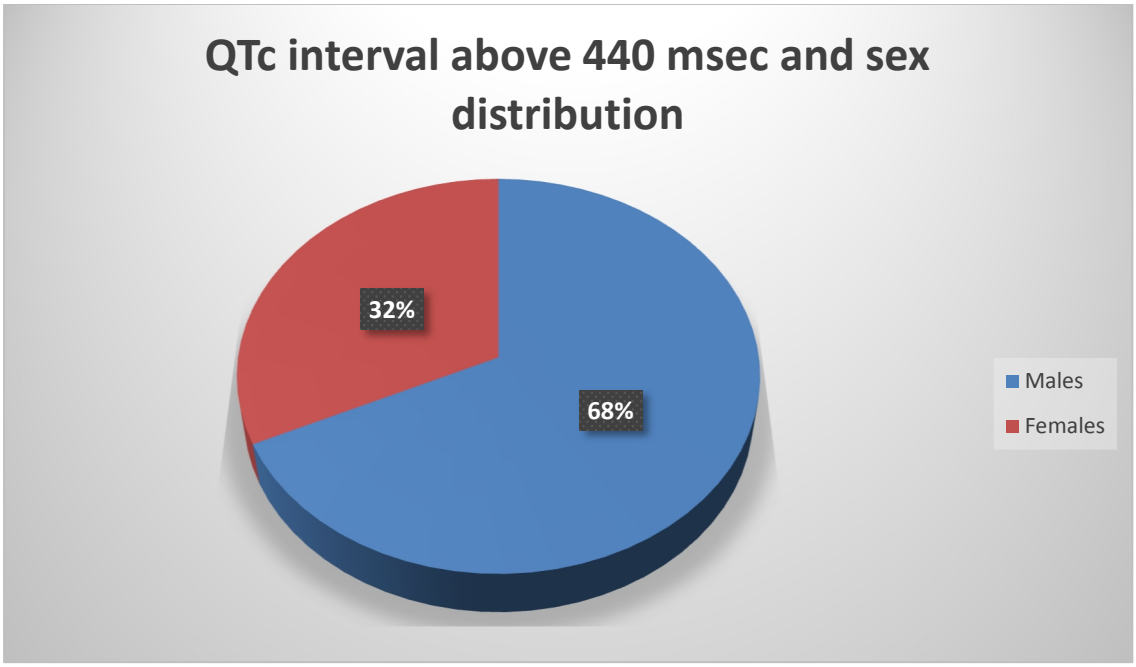
QTc interval

QTC value	Frequency	Percentage
Above 440 msec	53	53.00
Below 440 msec	47	47.00
Total	100	100.00



QTc interval above 440 msec and sex distribution

Sex	Frequency	Percentage
Males	36	68.00
Females	17	32.00
Total	53	100.00

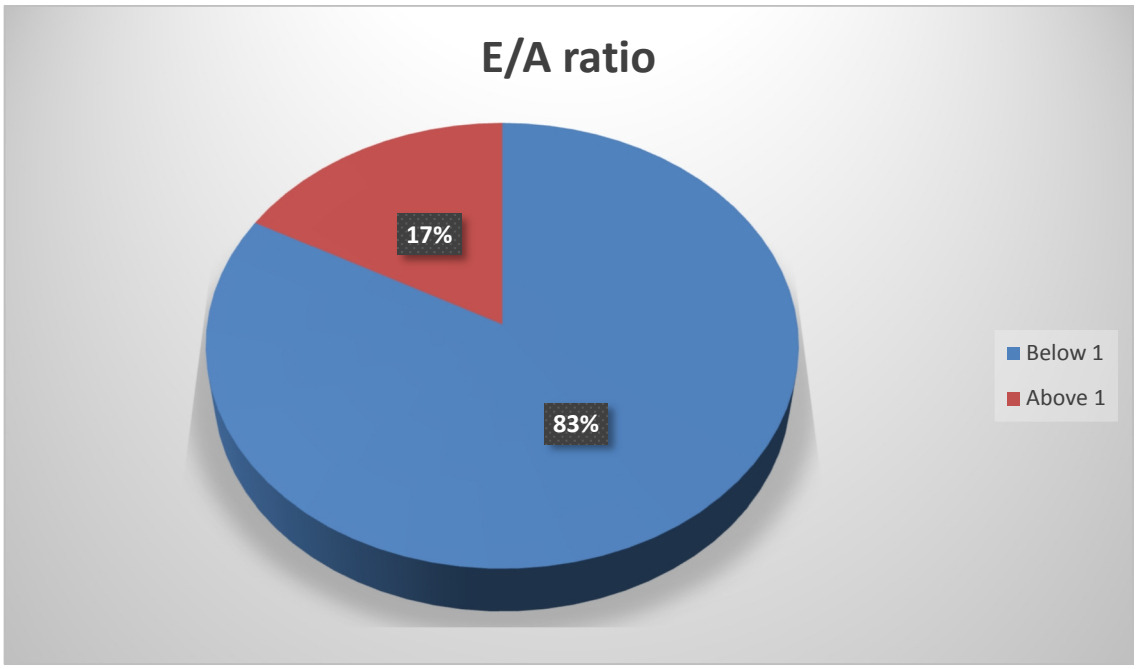


Left ventricular dysfunction

Out of the 100 cases, the ratio of early diastolic and late diastolic filling velocity (E/A ratio) was less than 1 in 83 cases. Of these 83 cases 69 were females and 14 were males.

E/A ratio

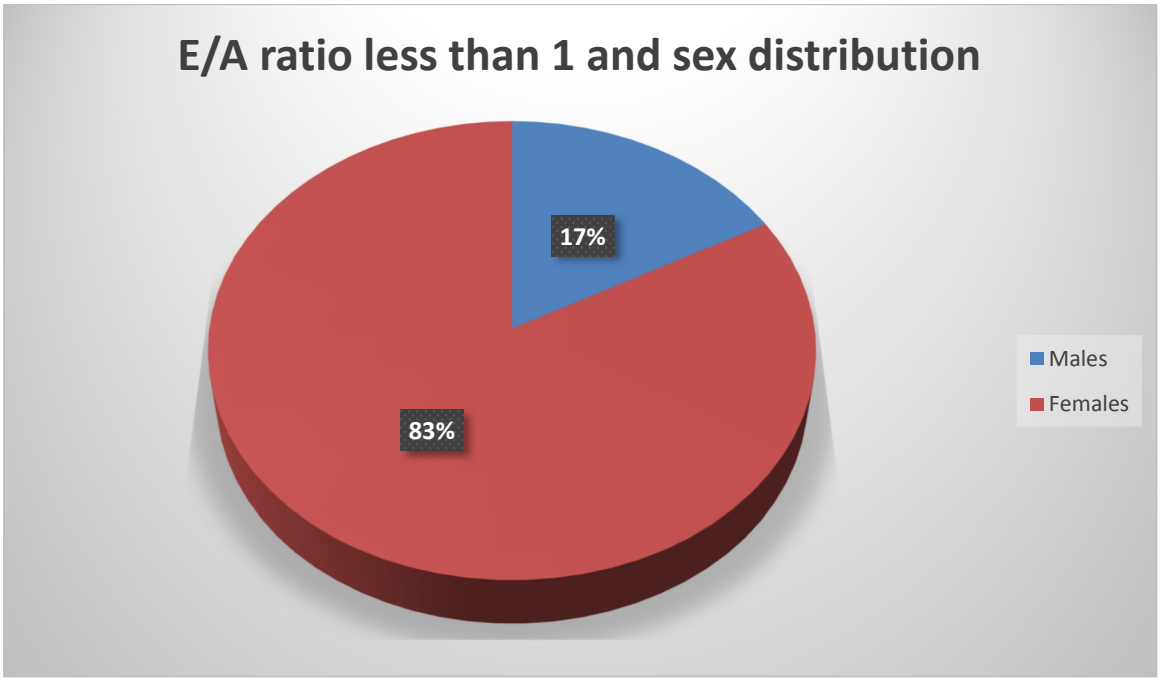
Value	Frequency	Percentage
Below 1	83	83.00
Above 1	17	17.00
Total	100	100.00



E/A ratio less than 1 and sex distribution

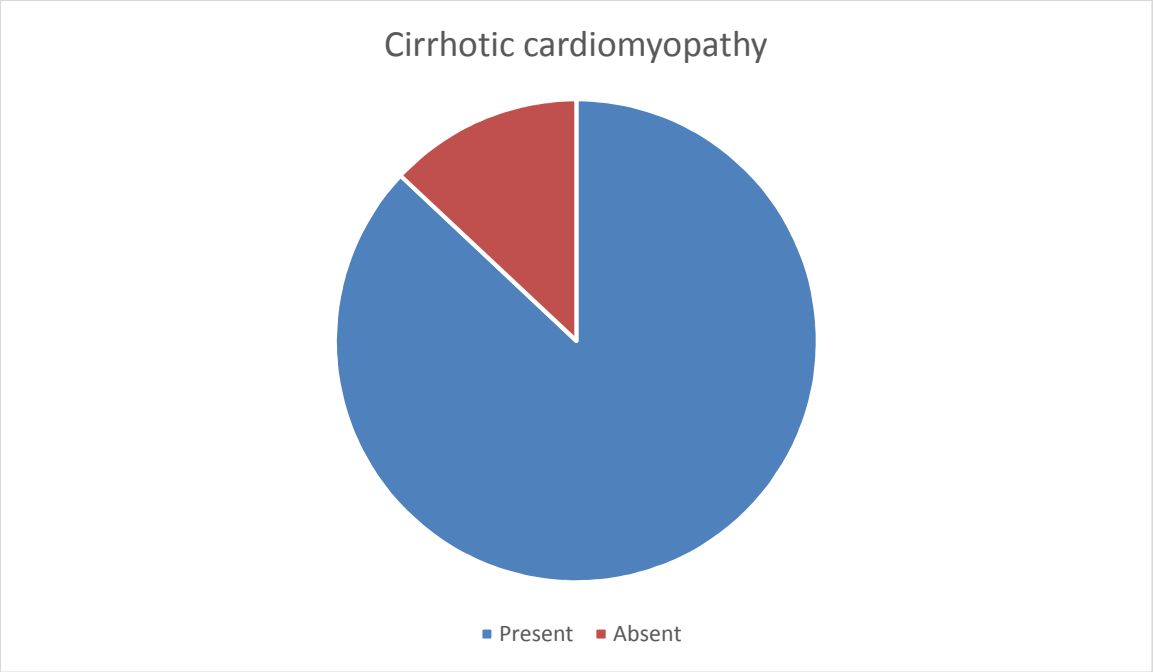
Sex	Frequency	Percentage
Males	14	17.00
Females	69	83.00
Total	83	100.00

Out of the 100 cases included in this study 87 patients had features cirrhotic cardiomyopathy. These cases had a prolonged QTc interval of more than 440 msec or an E/A ratio of less than 1. Of these 87 cases,27 were males and 60 were females.



Cirrhotic cardiomyopathy

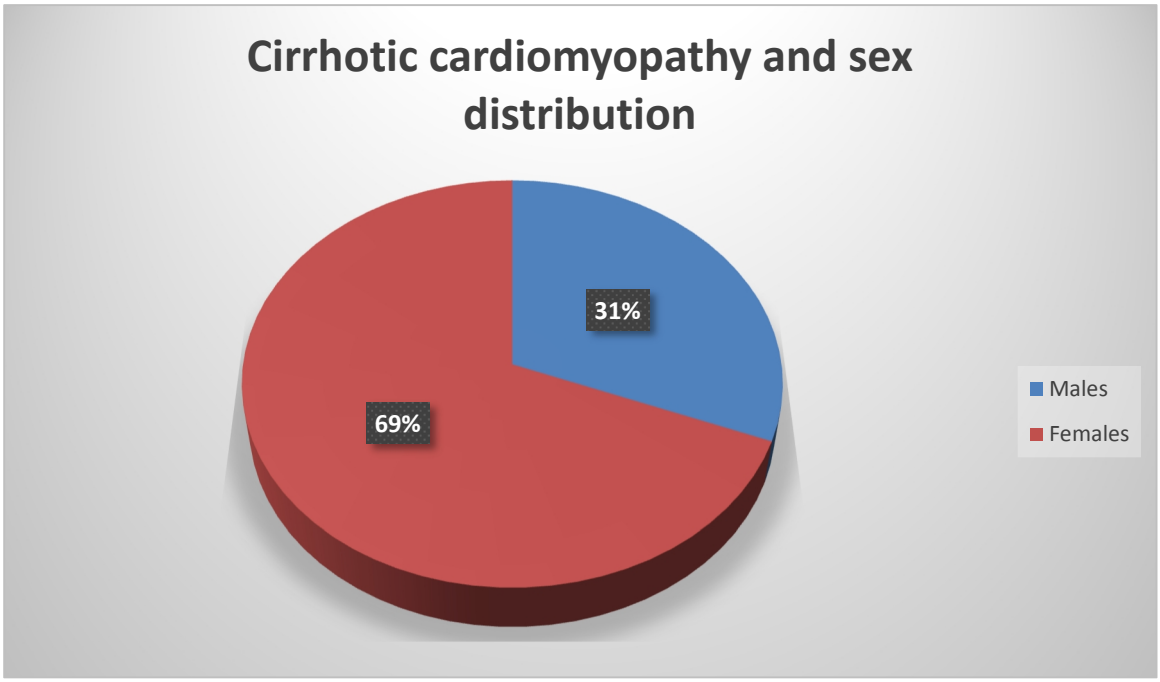
	Frequency	Percentage
Present	87	87.00
Absent	13	13.00
Total	100	100.00



Cirrhotic cardiomyopathy and sex distribution

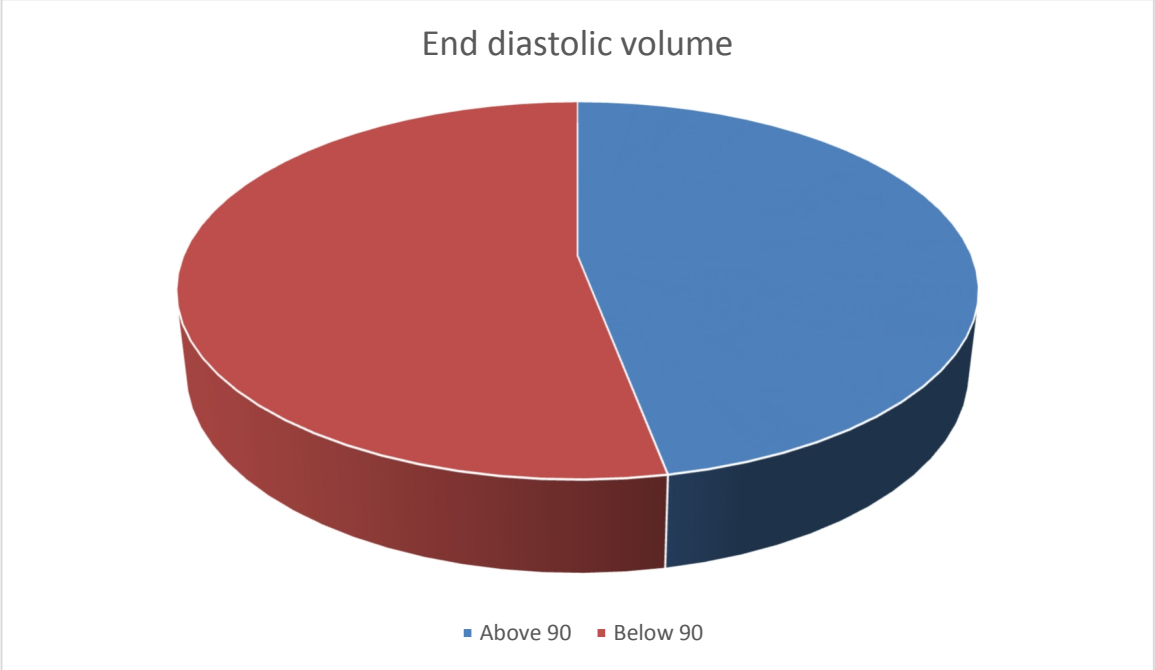
Sex	Frequency	Percentage
Males	27	31.00
Females	60	69.00
Total	87	100.00

Of the 100 patients included in this study, 47 patients had end diastolic volume above 90. 10 patients had end systolic volume above 38. 97 patients had ejection fraction above 60%.



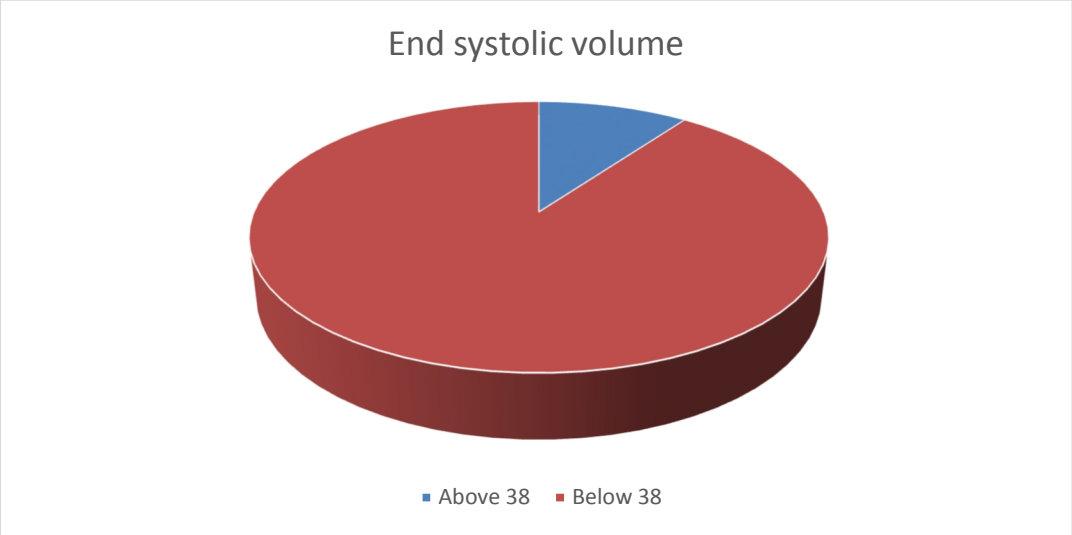
End diastolic volume

End diastolic volume	Frequency	Percentage
Above 90	47	47.00
Below 90	53	53.00
Total	100	100.00



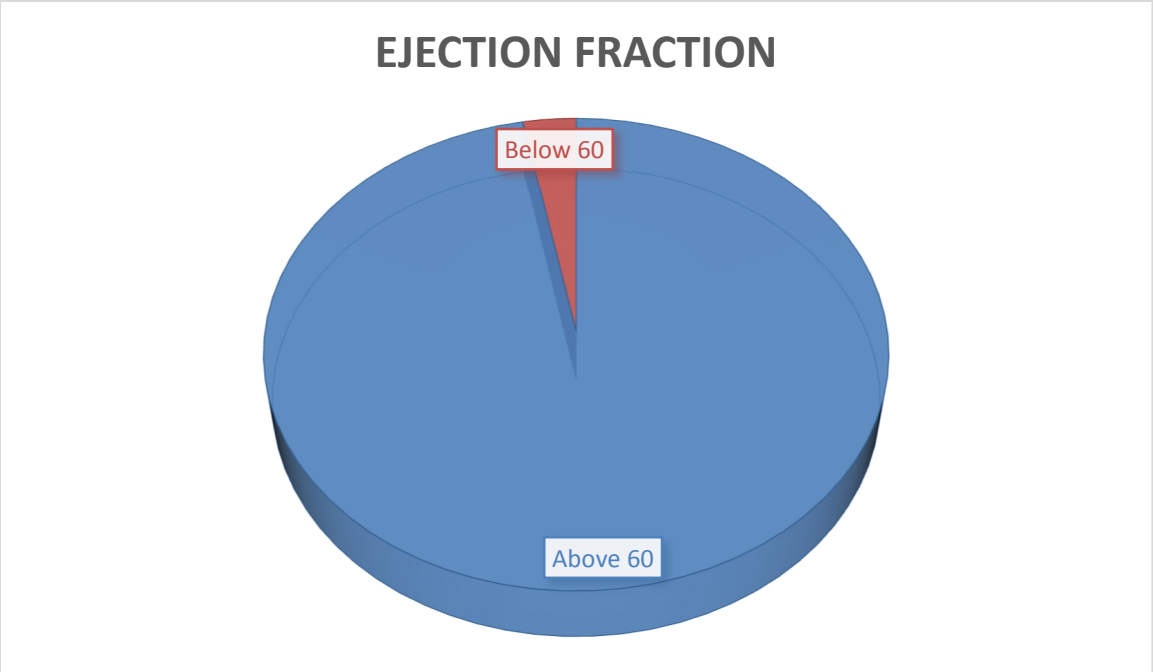
End systolic volume

End systolic volume	Frequency	Percentage
Above 38	10	10.00
Below 38	90	90.00
Total	100	100.00



Ejection fraction

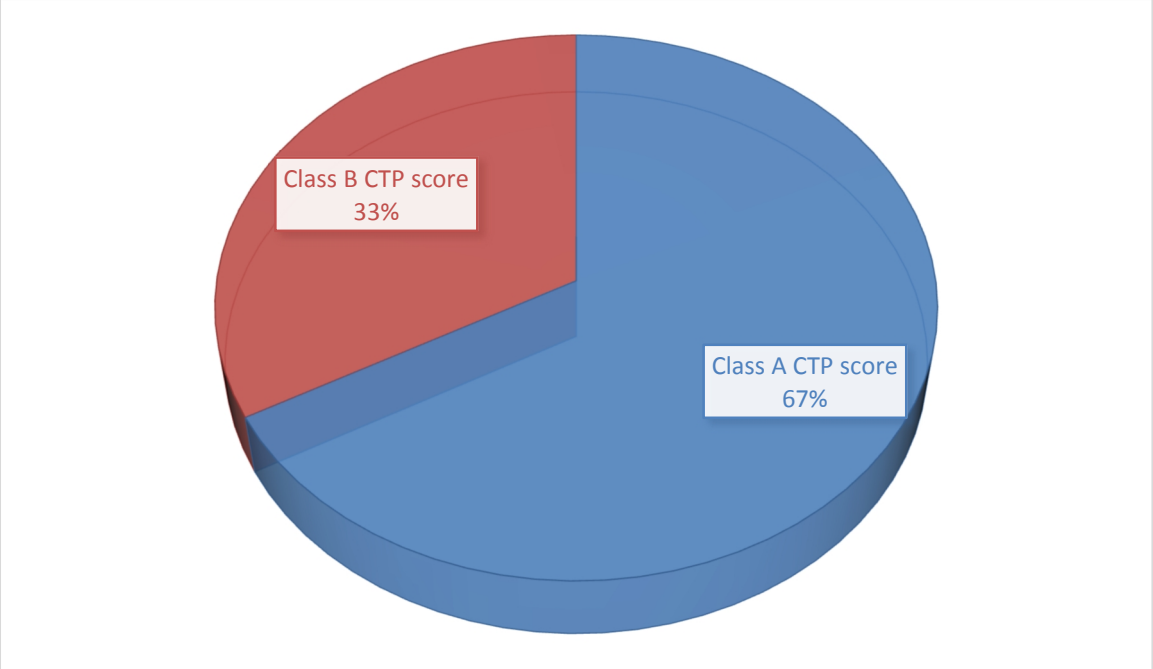
Ejection fraction	Frequency	Percentage
Above 60	97	97.00
Below 60	3	3.00
Total	100	100.00



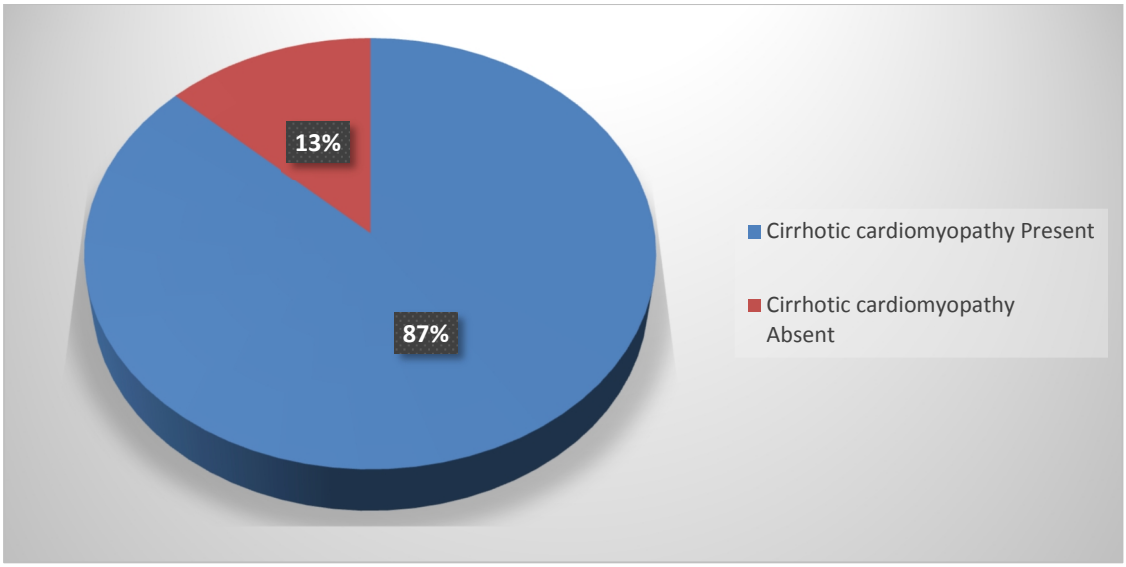
Statistical analysis

Out of the 100 cases, 87 showed features of cirrhotic cardiomyopathy. 67 patients had Class A Child Turcotte Pugh score. 33 patients had Class B Child Turcotte Pugh score. 54 patients with cirrhotic cardiomyopathy had Class A Child Turcotte Pugh score. 33 patients with cirrhotic cardiomyopathy had Class B Child Turcotte Pugh score. 13 patients with Class A Child Turcotte Pugh score did not have cirrhotic cardiomyopathy. The 'p' value of this association between Child Turcotte Pugh score and cirrhotic cardiomyopathy is 0.128 and it is not significant. This implies that cirrhotic cardiomyopathy is not influenced by the class of Child Turcotte Pugh score.

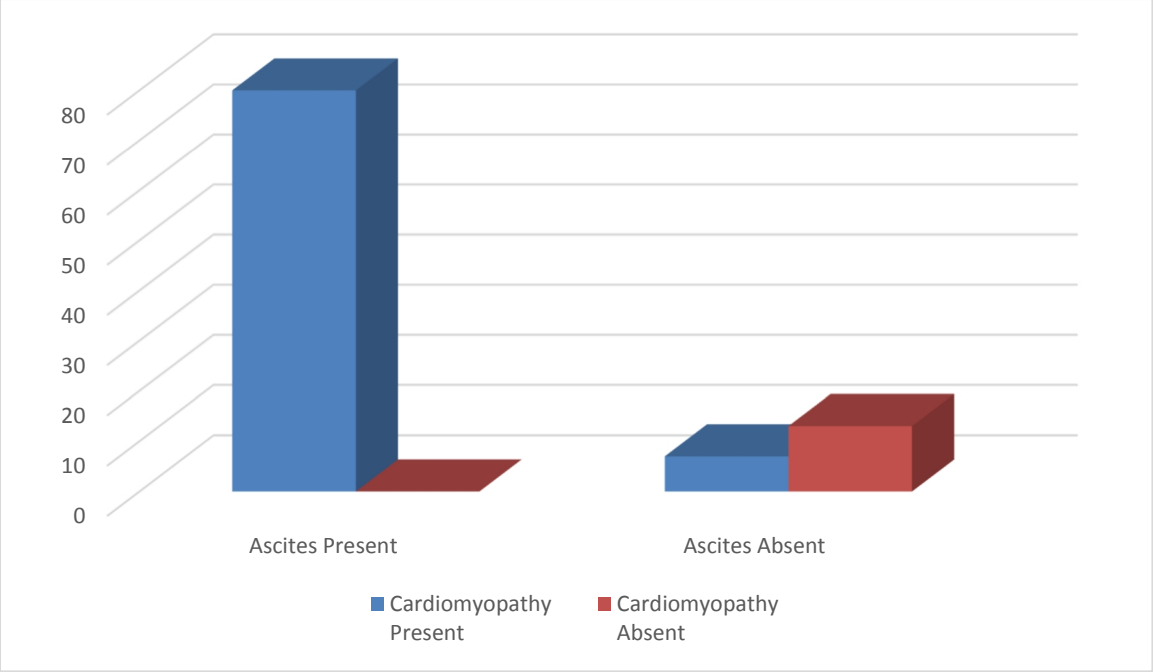
	Cardiomyopathy Present	**Cardiomyopathy absent**	**Total**
Class A CTP score	54	13 (20%)	67 (67%)
Class B CTP score	33	0	33 (33%)
Total	87	13	100 (100%)
			P value = 0.336



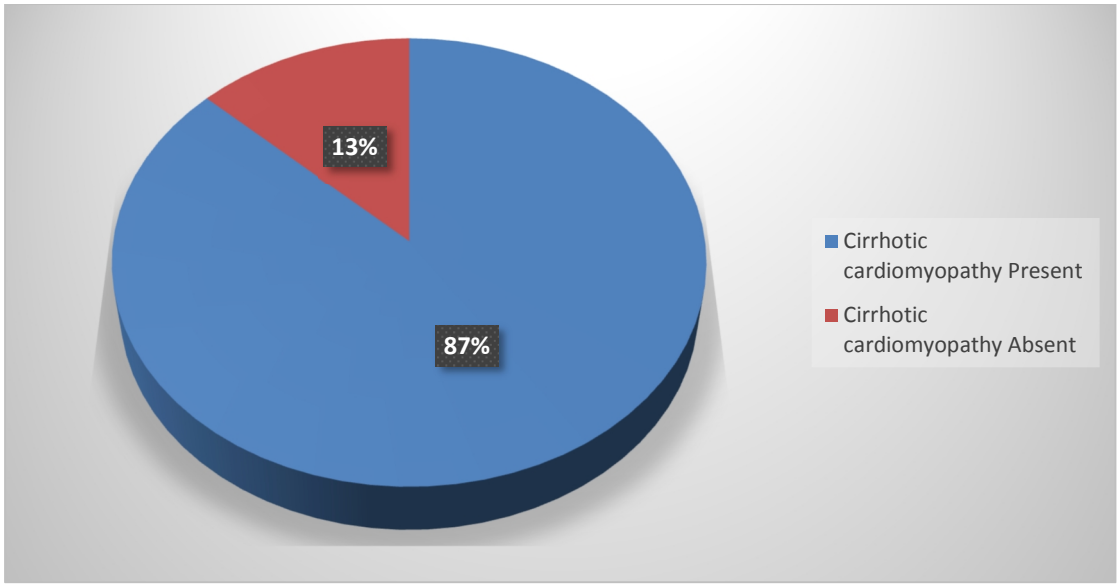
80 of the 100 cases had ascites. Of the 87 cases that had cirrhotic cardiomyopathy 80 cases had ascites. All the cases that had ascites showed features of cirrhotic cardiomyopathy. 7 cases without ascites also showed features of cirrhotic cardiomyopathy. 13 of the 100 cases did not show features of cirrhotic cardiomyopathy. All these 13 cases did not have ascites. The 'p' value of the association of ascites and cirrhotic cardiomyopathy is 0.0002 and it is significant. This implies presence of ascites is a significant finding in cases who have cirrhotic cardiomyopathy.



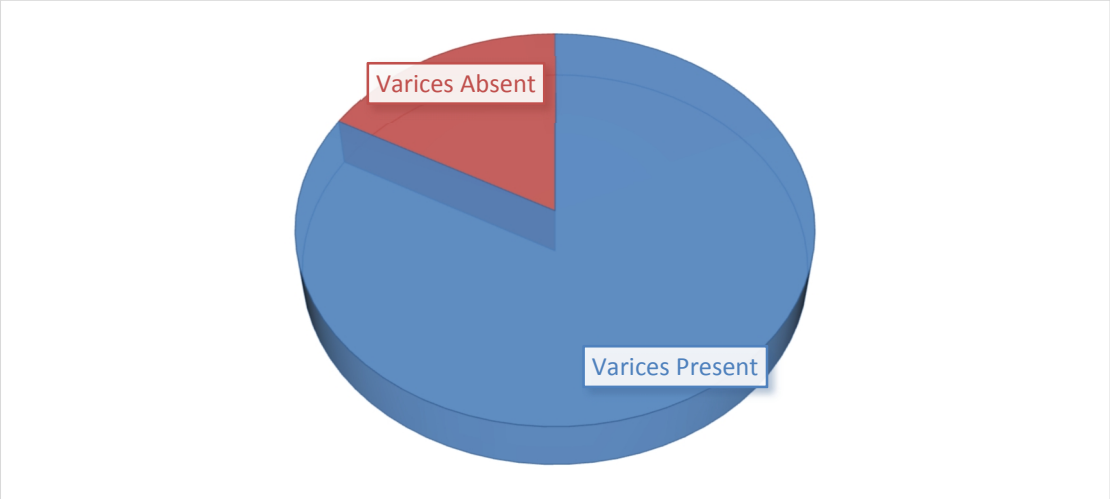
	Cardiomyopathy Present	**Cardiomyopathy Absent**	**Total**
Ascites Present	80 (100%)	- -	80
Ascites Absent	7 (33.3%)	13	20
Total	87(87%)	4 (13.%)	100 (100%)
			P value = 0.0002



83 of the 100 cases had varices. Of the 87 cases that had cirrhotic cardiomyopathy, 70 had varices. 13 cases with varices did not have cirrhotic cardiomyopathy. 17 cases with cirrhotic cardiomyopathy did not have varices. The 'p' value of the association between cirrhotic cardiomyopathy and varices is 0.336 and it is not significant. This implies presence of varices is not a significant finding in cases that have cirrhotic cardiomyopathy.

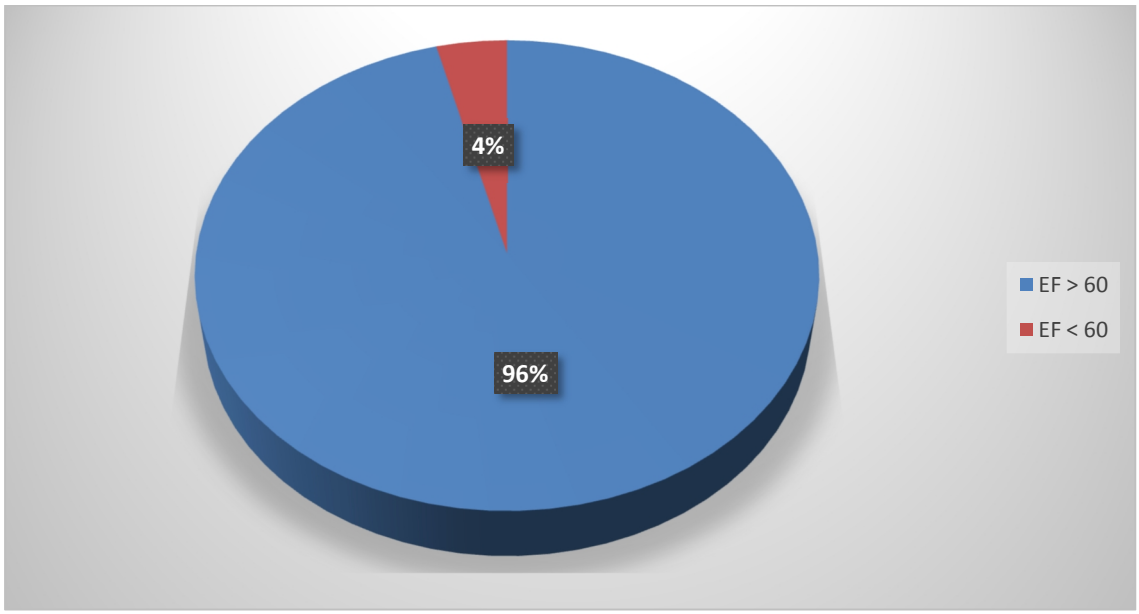


	Cardiomyopathy Present	**Cardiomyopathy absent**	**Total**
Varices Present	70	13	83 (83.00%)
Varices Absent	17		17 (17.00%)
Total	87	13	100 (100%)
			P value = 0.336



96 cases had ejection above 60.3 patients had EF below 60. 83 patients with cirrhotic cardiomyopathy had EF above 60. 4 case with diastolic dysfunction had EF below 60. 13 patients with EF above 60 did not have diastolic dysfunction. The ‘p’ value of this association between EF and diastolic dysfunction is 0.689 and it is not significant. This implies that abnormality of EF is not a significant feature of cirrhotic cardiomyopathy.

	Diastolic dysfunction Present	Diastolic dysfunction Absent	Total
EF > 60	83	13 (14.00%)	96
EF < 60	4		4
Total	87	13 (14.00%)	100(100%)
			P value = 0.689



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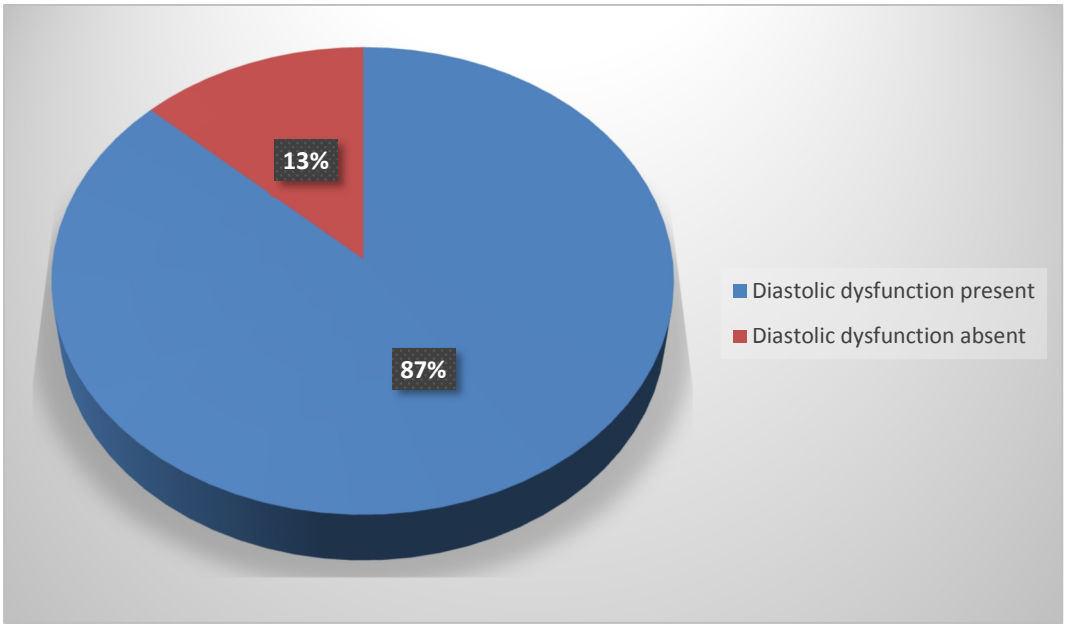
	Diastolic dysfunction Present	Diastolic dysfunction Absent	Total
EF > 60	83	13 (14.00%)	96
EF < 60	4		4
Total	87	13 (14.00%)	100(100%)
			P value = 0.689



	EF > 60	EF < 60	Total
Diastolic dysfunction present	83	4 (3.8%)	87(87.00%)
Diastolic dysfunction absent	13		13 (13.00%)
			P value = 0.689

DISCUSSION

The study we conducted shows 40 cases had cirrhosis because of HBV infection, 4 caused by HCV infection, 4 caused by primary biliary cirrhosis and in 52 cases the reason was idiopathic. Out of the 100 cases studies the characteristic featrues of cirrhotic cardiomyopathy were observed in 87 cases. The evidence of cirrhotic cardiomyopathy was seen in all etiologies and not just alcoholic cirrhosis. It has been shown in other studies that various etiologies of cirrhosis can lead to cirrhotic cardiomyopathy. It was also found in many studies that cardiac dysfunction in cirrhotics was independent of the cause of the cirrhosis. Our study has also prove that the incidence of cirrhotic cardiomyopathy was not dependent on the cause of cirrhosis.

We took 100 cases for our study out of which 73 were females and 27 males. Among the 73 females 60 of them showed evidence of cirrhotic cardiomyopathy. It has been observed that out of the 27 males all of them had evidence of cirrhotic cardiomyopathy. Our study is confirming that there is negligible significance in sex distribution and that evidence of cirrhotic cardiomyopathy is observed in majority of the cirrhotics. Liu et al[13] in their study found that some amount of diastolic dysfunction is seen in almost all cirrhotics.

In the study we conducted 33% (30 subjects)of the cases were below 40 years and 67% more than 40 years. The 13 patients who did not show features of cirrhotic cardiomyopathy were less than 40 years. This is statistically significant and signifies that the incidence of cirrhotic cardiomyopathy increase with age and is more commonly seen in older people.this correlates with the results of a study conducted by Rabie et al that diastolic dysfunction in cirrhotic patients is strongly associated with or age which is similar to the finding of our study.

Ascites was present in 80% of the cases as one of the complaints during their first admission and it was also observed that all the cases who had ascites also showed the features of cirrhotic cardiomyopathy. 33% of the cases who did not have ascites had features of cirrhotic cardiomyopathy. It was observed that 92% of the patients with cirrhotic cardiomyopathy also had ascites ascites and in 8.00% there was no evidence of ascites. This in turn confirms that evidence of ascites and the incidence of cirrhotic cardiomyopathy has a very important correlation significantly ('p'=0.0002).It was found in a study conducted by Wong et al[17] that diastolic dysfunction may be the initial factor contributing to the development of heart failure which can be followed by systolic dysfunction in patients with cirrhosis, The development of features of cirrhotic ccardiomyopathy can be an important contributor to the development of

Ascites.

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cirrhotic ccardiomyopathy can be an important contributor to the development of sodium and fluid retention leading to ascites since the figures also suggest thet 92 % of cases with cirrhotic cardiomyopathy also have ascites. . But in certain other studies such as the one conducted by Pozzi et al[110] in their study have shown that later stages of cirrhosis is invariably associated with left ventricular diastolic dysfunction whether or not ascites is present. But in this study we found that ascites was present in majority of cases with diastolic dysfunction. Lee et al[13] found that once cirrhosis has advanced to a moderate stage with the development of ascites some degree of diastolic dysfunction is always present.

67% of the cases were found to have CTP Class A cirrhosis. 33% of the cases presented with Class B cirrhosis. 80% of Class A had charactistic features of cirrhotic cardiomyopathy while all the cases with Class B showed features of cirrhotic cardiomyopathy. 61.5% of the cases with cirrhotic cardiomyopathy had Class A cirrhosis. 38.5% had Class B cirrhosis. 20% of Class A and 13.3% of Class B cirrhosis did not have features of cirrhotic cardiomyopathy. The severity of cirrhosis as based on CTP does not correlate with the

presence of cirrhotic cardiomyopathy ('p'= 0.336). In previous studies such as the ones conducted by Bernardi et al[116] and Rabie et al in their found that the frequency of cardiac dysfunction was associated with the severity of cirrhosis as assessed by Child Turcotte Pugh score. Similar observation was done by Rabie et al[116] in their study on diastolic dysfunction in cirrhotics. But in our study no such correlation was found.

0.543). Bader Faiyaz Zuberi et al[120] in their study conducted in cirrhotics from Pakistan have found that QTc were significantly higher in cirrhotic patients as compared with non-cirrhotic controls. Similarly Bernardi et al[119] found that QTc interval was significantly prolonged in cirrhotic patients when compared with healthy individuals. Lehman[121] found that prolonged QTc interval was seen more in female cirrhotics. But this study did not show any such correlation.

46.7% of the cases had end diastolic volume above 90. 85.7% of the cases with EDV above 90 had E/A ratio below 1. 87.5% of cases with EDV below 90 also had E/A ratio below 1. 46.2% of the cases with E/A ratio below 1 had EDV above 90. 53.8% of the cases with

E/A ratio below 1 had EDV below 90. These findings indicate that end diastolic volume is not significant indicator of diastolic dysfunction ('p' = 0.885). Alexander Jacob et al[122] in their study done in Asian population with cirrhosis have found that end diastolic volume is not statistically significant in them. Kelbaek et al[123] in their study have found that the left ventricular end diastolic volume is normal in cirrhotics. Rectar et al[124] found that the size of the left ventricle was normal in cirrhotics. Laffi et al[125] in their study have found that left ventricular end diastolic volume is increased in cirrhotic patients.

10% of the cases had end systolic volume above 38. 66.7% of the cases with ESV above 38 had E/A ratio below 1. 88.9% of the cases with ESV below 38 also had E/A ratio below 1. 7.7% of the cases with E/A ratio below 1 had ESV above 38. 25% of the cases with E/A ratio above 1 also had ESV above 38. These findings indicate that end systolic volume is not significant indicator of cardiac dysfunction ('p' = 0.282). Alexander Jacob et al in their study done in Asian population with cirrhosis have found that end systolic volume is not statistically significant in them. Kelbek et al in their study have found

that the left ventricular end systolic volume is normal in cirrhotics. Rectar et al found that the size of the left ventricle was normal in cirrhotics. Laffi et al in their study have found that left ventricular end systolic volume is increased in cirrhotic patients.

96.7% of the cases had ejection fraction above 60%. 86.2% of the cases with EF above 60 had E/A ratio below 1. 96.2% of the cases with E/A below 1 had EF above 60. All the cases that had E/A ratio above 1 also had EF above 60. These findings indicate that ejection fraction is not significant indicator of cardiac dysfunction ('p' = 0.689). Alexander Jacob et al in their study done in Asian population with cirrhosis have found that ejection fraction is not statistically significant in them.

CONCLUSION

- Contrary to older perceptions patients with cirrhosis due to causes other than alcohol do present with features of cirrhotic cardiomyopathy.
- The most common manifestation is in the form of diastolic dysfunction which is shown to occur as E/A ratio less than 1.
- Cirrhotic cardiomyopathy occurs independent of the cause of cirrhosis.
- Mild to moderate degree of diastolic dysfunction is seen in majority of cirrhotic.
- The incidence of Diastolic dysfunction increases with age in cirrhosis and occurs more commonly in older population.
- Ascites has been observed in is all cases with diastolic dysfunction.
- The severity of cirrhosis is independent of the presence of diastolic dysfunction

BIBLIOGRAPHY

1. Cardiovascular dysfunction in patients with liver cirrhosis Giuseppe Fede, Graziella Privitera, Tania Tomaselli, Luisa Spadaro, and Francesco Purrello

2. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57:268–278. [PubMed] [Google Scholar]

3. Moller S, Henriksen JH. Cirrhotic cardiomyopathy. J Hepatol. 2010;53:179–190. [PubMed] [Google Scholar]

4. Timoh T, Protano MA, Wagman G, Bloom M, Vittorio TJ. A perspective on cirrhotic cardiomyopathy. Transplant Proc. 2011;43:1649–1653. [PubMed] [Google Scholar]

5. Gaskari SA, Liu H, Moezi L, Li Y, Baik SK, Lee SS. Role of endocannabinoids in the pathogenesis of cirrhotic cardiomyopa-thy in bile duct-ligated rats. Br J Pharmacol. 2005;146:315–323. [PMC free article] [PubMed] [Google Scholar]

6. Chen X, Zhang X, Kubo H, Harris DM, Mills GD, Moyer J, et al. Ca2+ influx-induced sarcoplasmic reticulum Ca2+ overload causes mitochondrial-dependent apoptosis in ventricular myocytes. Circ Res. 2005;97:1009–1017. [PubMed] [Google Scholar]

7.Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997; 349: 1498–1504.

8,Predicting Clinically Significant Portal Hypertension Atif Zaman, MD, MPH reviewing Berzigotti A et al. Am J Gastroenterol 2008 May

9.. Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol. 1985;1:325–37. [

10. Fernandez M, Vizzutti F, Garcia-Pagan JC, et al. Anti-VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. Gastroenterology. 2004;126:886–

11. Endocannabinoids in liver disease. Tam J1, Liu J, Mukhopadhyay B, Cin ar R, Godlewski G, Kunos G.

12. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennnec's cirrhosis. J Clin Invest 1953; 32: 1025-33.

13. Abelmann WH, Kowalski HJ, McNeely WF. The hemodynamic response to exersize in patients with Laennec's cirrhosis. J Clin Invest 1955; 34: 690-5.

14. Bayley TJ, Segel N, Bishop JM. The circulatory changes in patients with cirrhosis of the liver at rest and during exersize. Clin Sci 1964; 26: 227-35.

15. Claypool JG. Hemodynamic studies in patients with Laennec's cirrhosis. Am J Med Sci 1957; 234: 48-55.

16. Murray JG, Dawson AM, Sherlock S. Circulatory changes in chronic liver disease. Am J Med 1958; 24: 358-367.

17. Gould L, Sharrif M, Zahir M, Lieto MD. Cardiac hemodynamics in alcoholic patients with chronic liver disease and a presystolic gallop. J Clin Invest 1969; 58: 860-8.

18. Limas CJ, Guiha NH, Lekagui O, Cohn JN. Impaired left ventricular function in alcoholic cirrhosis with ascites. Circulation 1974; 49: 755-60.

19. Caramelo C, Fernandez-Munoz D, Santos JC, Blanchart A, Rodriguez- Puyol D, Lopez-Novoa JM, Hernando L. Effect of volume expansion on hemodynamics , capillary permeability and renal function in conscious, cirrhotic rats. Hepatology 1986; 6: 129-34.

20. Lee SS, Marty J, Mantz J, Samain E, Braillon A, Lebrec D. Desensitization of myocardial β-adrenergic receptors in cirrhotic rats. Hepatology 1990; 12: 481-5.

21.Ingles AC, Hernandez I, Garcia-Estan J, Quesada T, Carbonell LF. Limited cardiac preload reserve in conscious cirrhotic rats. Am J Physiol 1991; 260: H1912-17.

22.Lee SS. Cardiac abnormalities in liver cirrhosis. West J Med 1989; 151: 530-5.

23.Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. Hepatology 1996; 24: 451-9.

24.Liu H, Lee SS. Cardiopulmonary dysfunction in cirrhosis. J Gastroenterol Hepatol 1999; 14: 600-8.

25.Myers RP, Lee SS. Cirrhotic cardiomyopathy and liver transplantation. Liver Transpl 2000; 6(suppl 1): s44-52.

26.Kim MY, Baik SK. Cirrhotic cardiomyopathy. Korean J Hepatol. 2007 Mar;13(1):20-6.

27.Soon Koo Baik And Samuel S Lee. Cirrhotic cardiomyopathy: causes and consequences. Journal of Gastroenterology and Hepatology (2004) 19, S185–S190.

28.Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. Semin Liver Dis. 2008 Feb;28(1):59-69

29.Garcia-Tsao G. Portal hypertension. Curr Opin Gastroenterol 2003; 19: 250-258

30.Groszmann RJ. Hyperdynamic circulation of liver disease 40 years later: pathophysiology and clinical consequences. Hepatology 1994; 20: 1359-1363

31.Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. Gastroenterol Clin Biol 2002; 26: 842-847

32.Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. Hepatology 1996; 24: 451-459

33.Weigert AL, Martin PY, Niederberger M, Higa EM, McMurtry IF, Gines P, Schrier RW. Endothelium-dependent vascular hypo- responsiveness without detection of nitric oxide synthase induction in aortas of cirrhotic rats. Hepatology 1995; 22: 1856-1862

34.Bomzon A, Blendis LM. The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. Hepatology 1994; 20: 1343-1350

35.Martin PY, Xu DL, Niederberger M, Weigert A, Tsai P, St John J, Gines P, Schrier RW. Upregulation of endothelial constitutive NOS: a major role in the increased NO production in cirrhotic rats. Am J Physiol 1996; 270: F494-F499

36.Gordon GG, Olivo J, Rafil F, Southren AL. Conversion of androgens to estrogens in cirrhosis of the liver. J Clin Endocrinol Metab 1975; 40: 1018-1026

37.Longcope C, Pratt JH, Schneider S, Fineberg E. Estrogen and androgen dynamics in liver disease. J Endocrinol Invest 1984; 7: 629-6234

38.Weiner CP, Lizasoain I, Baylis SA, Knowles RG, Charles IG, Moncada S. Induction of calcium-dependent nitric oxide synthases by sex hormones. Proc Natl Acad Sci USA 1994; 91: 5212-5216

39.Xu L, Carter EP, Ohara M, Martin PY, Rogachev B, Morris K, Cadnapaphornchai M, Knotek M, Schrier RW. Neuronal nitric oxide synthase and systemic vasodilation in rats with cirrhosis. Am J Physiol Renal Physiol 2000; 279: F1110-F1115

40.Biecker E, Neef M, Sagesser H, Shaw S, Koshy A, Reichen J. Nitric oxide synthase 1 is partly compensating for nitric oxide synthase 3 deficiency in nitric oxide synthase 3 knock-out mice and is elevated in murine and human cirrhosis. Liver Int 2004; 24: 345-353

41. Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a patho physiological review of circulatory dysfunction in liver disease. Heart 2002; 87: 9-15.

42. Hall EM, Olson AY, Davis FE. Portal cirrhosis: clinical and pathological review of 782 cases from 16,600 necropsies. Am J Pathol 1953; 29: 993-1027.

43. Lunseth JH, Olmstead EG, Forks G, Abboud F. A study of heart disease in one hundred and eight hospitalized patients dying with portal cirrhosis. Arch Inter Med 1958; 102: 405-413.

44. Ma Z, Miyamoto A, Lee SS. Role of altered ²-adrenergic receptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. Gastroenterology 1996; 110: 1191-1198.

45. Kempler P, Szalay F, Varadi A, Keresztes K, Kadar E, Tanczos E, Petrik J. Prolongation of theQTc-interval reflects the severity of autonomic neuropathyin primary biliary cirrhosis and in other non-alcoholic liver diseases. Z Gastroenterol 1993; 31 (Suppl. 2): 96-8.

46. Finucci G, Lunardi F, Sacerdoti D, Volpin R, Bortoluzzi A, Bombonato G, Angeli P, et al. Q-T interval prolongationin liver cirrhosis. Reversibility after orthotopic liver transplantation. Jpn Heart J 1998; 39: 321-9.

47. Henriksen JH, Bendtsen F, Hansen EF, Moller S. Acute nonselective beta-adrenergic blockade reduces prolonged frequencyadjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol 2004; 40: 239-46.

48. Henriksen JH, Fuglsang S, Bendtsen F, Christensen E, Moller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. J Hepatol 2002; 36: 513-20.

49. Silver MA, Maisel A, Yancy CW, McCulough PA, Burnett JC,Francis GS, Mehra MR, et al. BNP Consensus Panel 2004 : A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail 2004; 10(5 Suppl 3): 1- 30.

50. Pateron D, Beyne P, Laperche T, Logeard D, Lefilliatre P, Sogni P, Moreau R, et al. Elevated circulating cardiac troponin I in patients with cirrhosis. Hepatology 1999; 29: 640-3

51. Wong F, Siu S, Liu P, Blendis LM. Brain natriuretic peptide: is it a predictor of cardiomyopathy in cirrhosis?

52. Torregrosa M, Aguadé S, Dos L, Segura R, Gónzalez A, Evangelista A, Castell J, Margarit C, Esteban R, Guardia J, Genescà J.

PATIENT PROFORMA

Name:

Age:

Sex:

Chief complaints:

Duration of illness:

Past history:

Comorbid conditions: TYPE 2 DM/SHTN/CAD/COPD/CCF

Personal history:Alcoholism/ Smoking/ Substance abuse

Family History:

Examination : Vitals : BP: PR: SpO2 :

CVS:

RS:

ABDOMEN: Ascites +/_

CNS:

Investigations:

Hb: TC/DC: Platelets:

LFT:

RFT:

Serum Electrolytes:

HbsAg, HCV, HIV status:

ECG:

USG abdomen:

Ascitic fluid analysis:

OGD scopy:

ECHO: Systolic dysfunction:

Diastolic dysfunction:

EF:

EDV:

ESV:

E/A ratio:

Slno	Sex	Age	Etiology	Child Turcotte pugh class	Ascites	Varices	Diastolic Dysfunction	E/A ratio	End Diastolic Volume	End Systolic Volume	Ejection Fraction	Cirrhotic caridio myopathy
1	F	38	HBV	Class A	1	1	1	<1	>90	< 38	64	1
2	F	34	HBV	Class A	1	1	1	<1	>90	< 38	63	1
3	M	52	IDIO	Class B	1	1	1	<1	<90	< 38	62	1
4	F	42	HBV	Class A	0	1	0	<1	<90	< 38	67	0
5	F	36	IDIO	Class A	1	1	1	<1	<90	< 38	69	1
6	M	33	HBV	Class B	1	1	1	>1	>90	< 38	62	1
7	F	44	IDIO	Class A	0	1	0	<1	<90	>38	65	0
8	F	47	IDIO	Class A	0	1	0	<1	>90	< 38	61	0
9	M	32	HBV	Class A	1	1	1	<1	<90	< 38	66	1
10	F	55	IDIO	Class A	1	1	1	>1	>90	< 38	69	1
11	F	48	PBC	Class B	1	1	1	<1	>90	>38	66	1
12	F	45	HBV	Class A	0	1	0	<1	<90	< 38	62	0
13	M	52	IDIO	Class A	1	1	1	<1	<90	< 38	68	1
14	F	43	IDIO	Class A	1	1	1	<1	<90	< 38	69	1
15	M	44	HBV	Class B	1	1	1	>1	>90	< 38	64	1
16	F	52	HBV	Class A	1	1	1	<1	<90	< 38	63	1
17	F	30	IDIO	Class B	1	1	1	>1	>90	< 38	62	1
18	F	59	HBV	Class A	1	1	1	<1	<90	< 38	68	1
19	F	42	IDIO	Class A	1	1	1	<1	>90	>38	67	1
20	F	60	HCV	Class A	0	1	0	<1	<90	< 38	61	0
21	M	44	IDIO	Class B	1	1	1	>1	>90	< 38	65	1
22	F	32	IDIO	Class A	1	1	1	<1	>90	< 38	66	1
23	F	58	HBV	Class B	1	1	1	<1	<90	< 38	52	1
24	M	33	HBV	Class A	1	1	1	<1	<90	>38	62	1
25	F	45	IDIO	Class A	1	0	1	<1	>90	< 38	68	1
26	F	34	IDIO	Class A	0	1	0	<1	<90	< 38	61	0
27	F	63	HBV	Class A	0	1	0	<1	>90	< 38	66	0
28	F	47	HBV	Class A	1	1	1	<1	>90	>38	69	1
29	M	52	IDIO	Class B	1	1	1	<1	<90	< 38	66	1
30	F	46	HBV	Class A	1	0	1	>1	>90	>38	63	1
31	F	68	HBV	Class A	1	1	1	<1	<90	< 38	50	1
32	F	32	IDIO	Class B	1	1	1	<1	<90	< 38	64	1
33	F	56	IDIO	Class A	1	1	1	<1	>90	>38	64	1
34	F	49	HBV	Class B	1	0	1	<1	<90	< 38	63	1
35	M	34	IDIO	Class A	1	1	1	<1	>90	>38	62	1
36	F	39	IDIO	Class B	1	1	1	<1	<90	< 38	68	1
37	F	62	PBC	Class A	1	1	1	<1	<90	< 38	67	1
38	F	42	IDIO	Class A	0	1	0	<1	>90	< 38	61	0
39	F	33	HCV	Class B	1	0	1	<1	<90	< 38	65	1
40	F	35	IDIO	Class A	1	1	1	<1	<90	< 38	64	1
41	M	45	IDIO	Class B	1	1	1	>1	>90	< 38	62	1

Slno	Sex	Age	Etiology	Child Turcotte pugh class	Ascites	Varices	Diastolic Dysfunction	E/A ratio	End Diastolic Volume	End Systolic Volume	Ejection Fraction	Cirrhotic caridio myopathy
42	M	59	HBV	Class A	1	1	1	>1	<90	>38	66	1
43	F	56	IDIO	Class B	1	1	1	<1	>90	< 38	68	1
44	F	35	HBV	Class A	0	1	0	<1	<90	< 38	66	0
45	F	38	IDIO	Class A	1	1	1	<1	>90	< 38	63	1
46	M	42	HBV	Class A	1	1	1	<1	<90	< 38	68	1
47	F	44	IDIO	Class A	0	1	0	>1	>90	< 38	66	0
48	F	48	HBV	Class B	1	1	1	<1	<90	< 38	64	1
49	F	55	IDIO	Class A	1	0	1	<1	<90	>38	63	1
50	F	62	HBV	Class B	1	1	1	<1	>90	< 38	69	1
51	F	38	IDIO	Class A	1	1	1	<1	>90	< 38	66	1
52	F	36	HBV	Class B	1	1	1	<1	<90	< 38	62	1
53	F	42	IDIO	Class A	0	1	0	<1	<90	< 38	65	0
54	M	47	HBV	Class A	1	1	1	<1	>90	< 38	69	1
55	F	31	IDIO	Class A	0	1	0	<1	<90	< 38	66	0
56	F	43	HBV	Class A	0	1	0	<1	<90	< 38	62	0
57	F	67	HCV	Class A	0	0	1	<1	<90	< 38	53	1
58	M	64	HBV	Class B	1	1	1	>1	<90	< 38	63	1
59	F	30	HBV	Class B	1	1	1	<1	>90	< 38	68	1
60	M	42	IDIO	Class A	1	1	1	>1	<90	< 38	66	1
61	F	35	HBV	Class B	1	1	1	<1	<90	< 38	66	1
62	M	57	IDIO	Class A	1	0	1	<1	>90	< 38	63	1
63	F	34	IDIO	Class B	1	1	1	<1	<90	< 38	64	1
64	F	58	IDIO	Class A	1	1	1	<1	>90	< 38	66	1
65	M	62	HBV	Class B	0	0	1	>1	>90	< 38	62	1
66	F	39	IDIO	Class A	1	1	1	<1	<90	< 38	65	1
67	F	45	HBV	Class A	1	0	1	<1	<90	< 38	69	1
68	M	41	IDIO	Class B	1	1	1	>1	>90	< 38	61	1
69	F	62	IDIO	Class A	1	1	1	<1	>90	< 38	62	1
70	F	48	HBV	Class B	0	0	1	<1	>90	< 38	68	1
71	F	32	IDIO	Class A	1	1	1	<1	>90	< 38	66	1
72	F	62	IDIO	Class A	1	0	1	<1	<90	< 38	64	1
73	F	46	HBV	Class B	1	1	1	<1	>90	< 38	68	1
74	F	51	IDIO	Class A	1	1	1	<1	<90	< 38	65	1
75	M	57	HBV	Class B	0	0	1	<1	>90	< 38	61	1
76	F	44	IDIO	Class A	1	1	1	<1	>90	< 38	68	1
77	F	32	IDIO	Class A	1	1	1	<1	<90	< 38	67	1
78	F	44	HBV	Class B	1	0	1	<1	<90	< 38	64	1
79	F	30	HBV	Class A	1	1	1	<1	<90	< 38	62	1
80	F	50	IDIO	Class A	1	1	1	<1	>90	< 38	69	1
81	M	62	IDIO	Class B	1	0	1	>1	<90	< 38	61	1
82	F	34	IDIO	Class A	1	1	1	<1	>90	< 38	68	1

Slno	Sex	Age	Etiology	Child Turcotte pugh class	Ascites	Varices	Diastolic Dysfunction	E/A ratio	End Diastolic Volume	End Systolic Volume	Ejection Fraction	Cirrhotic caridio myopathy
83	F	37	HBV	Class A	0	0	1	<1	>90	< 38	61	1
84	F	48	IDIO	Class B	1	1	1	<1	>90	< 38	64	1
85	M	41	IDIO	Class A	1	1	1	<1	<90	< 38	66	1
86	F	39	HCV	Class B	1	1	1	<1	<90	< 38	63	1
87	M	61	HBV	Class A	1	1	1	<1	>90	< 38	68	1
88	M	40	IDIO	Class A	1	1	1	>1	<90	< 38	62	1
89	F	45	IDIO	Class B	1	1	1	<1	>90	< 38	69	1
90	M	53	HBV	Class A	0	0	1	<1	<90	< 38	61	1
91	F	57	HBV	Class A	1	1	1	<1	<90	< 38	67	1
92	F	48	IDIO	Class A	1	1	1	<1	>90	< 38	63	1
93	M	36	IDIO	Class A	1	1	1	>1	<90	< 38	61	1
94	F	43	PBC	Class B	0	0	1	<1	<90	< 38	65	1
95	F	30	IDIO	Class A	1	1	1	<1	>90	< 38	69	1
96	M	44	PBC	Class A	1	1	1	>1	<90	< 38	63	1
97	F	38	HBV	Class B	1	1	1	<1	>90	< 38	62	1
98	M	52	IDIO	Class A	1	1	1	<1	<90	< 38	64	1
99	F	31	IDIO	Class A	1	1	1	<1	>90	< 38	68	1
100	F	62	HBV	Class A	1	1	1	<1	>90	< 38	55	1

Note

Ascites - 1- Present, 0-Absent

Varices - 1- Present, 0-Absent

Diastolic Dysfuncti - 1- Present, 0-Absent

cardiomy opathy - 1- Present, 0-Absent