"MRI DIFFUSION WEIGHTED IMAGING (DWI) OF THE SPLEEN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION"

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CERTIFICATE

This is to certify that the dissertation **"MRI DIFFUSION WEIGHTED IMAGING (DWI) OF SPLEEN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION"** titled submitted by **Dr.S.KOMALAVALLI** appearing for **M.D (Radiodiagnosis)** degree examination in April 2015 is a bonafide record of work done by her under my guidance and supervision in partial fulfillment of requirement of the TamilNadu Dr. M.G.R Medical University, Chennai. I forward this to the TamilNadu Dr. M.G.R Medical University, Chennai.

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I **Dr.S.KOMALAVALLI**, solemnly declare that this dissertation titled **"MRI DIFFUSION WEIGHTED IMAGING(DWI) OF THE SPLEEN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION"** is a bonafide work done by me at the Barnard Institute of Radiology, Madras Medical College and Government General Hospital, under the guidance of **Dr.S.Babupeter, M.D.,D.N.B** and under the supervision of the **Professor K. Vanitha, M.D., D.M.R.D., D.R.M.,** Director, Barnard Institute of Radiology, Madras Medical College and Rajiv Gandhi Government General Hospital. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of M.D. Degree Radiodiagnosis.

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CONTENTS

MRI DIFFUSION WEIGHTED IMAGING OF THE SPLEEN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION.

ABSTARCT

Aim :
ADC value of the diffusion weighted imaging is a measure of the perfusion of the organ. Portal hypertension (PH) is one of the essential manifestations of chronic liver disease. It was used in previous studies to assess indirectly assessing the fibrosis of the liver. However no studies have evaluated the ADC value of the spleen to assess the PH features in cirrhosis.
We did a preliminary study to find the difference in ADC mapping of normal and cirrhotic patients. Then we analyzed the correlation of ADC value of the spleen in cirrhotic patients, to the severity of PH in the form of clinically significant PH (CSPH) and also the surrogate markers of PH.

Materials and Methods:
We prospectively evaluated 51 patients with chronic liver disease/ cirrhosis and 15 normal liver function patients in our hospital from the month of June 2014 to September 2014 with DWI of the abdomen.Their clinical and laboratory parameters were noted. Using 1.5 tesla, diffusion weighted imaging with ADC mapping was performed with b value of 0, 300, 500 and the ADC value of the spleen and liver were calculated . They were correlated with the severity of the PH in terms of CSPH and PH surrogate markers.

Results:
We found significant difference between the ADC mapping of the spleen in normal and cirrhotic patients (ADC of the spleen is increased in cirrhotics). In chronic liver disease / cirrhotic patients, we also found a significant correlation between ADC value of the spleen and CSPH, as well as PH surrogate markers in the form of grade of esophageal varices and symptomatic hypersplenism. However the ADC of the liver alone correlated significantly with the severity of liver diseases (Child Pugh status and MELD)

Conclusion :
Our study showed that ADC value of the spleen correlated well with the severity of PH. ADC measurements may allow for noninvasive evaluation of portal pressure and even in assessment of treatment response.

Keywords: Cirrhosis, Diffusion weighted imaging, Portal hypertension, Magnetic resonance imaging

INTRODUCTION

Chronic liver disease is a major spectrum of disease due to various etiologies which deteriorates to cirrhosis in significant proportion of these patients. Cirrhosis is complicated by various clinical manifestations in the form of gastrointestinal bleed, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis and hepatorenal syndrome. etc. Portal hypertension (PH) is an essential manifestation of end stage liver disease. It presents in the form of variceal bleed, hypersplenism and splenomegaly. However accurate evaluation of its severity depends on invasive investigations like repeated upper gastrointestinal endoscopy and hepatic venous wedge pressure monitoring. Non invasive investigations like ultrasound (US) abdomen and doppler, though simple, repeatable and cost effective, still it is plagued by its observer variations due to non standardized techniques and inferior cancer surveillance efficiency.[1, 2]

Recently, Magnetic Resonance Imaging (MRI) has been found to have superior safety and efficacy in evaluating severity of chronic liver disease patients and their cancer surveillance. [3, 4] Diffusion weighted imaging and MRI elastography was evaluated to assess the portal hemodynamics and resistance at the liver in chronic liver disease patients and found correlation to the degree of fibrosis. [5, 6] However very few studies have assessed the MRI characteristic of the spleen and its hemodynamics in cirrhosis and portal hypertensive patients. [7, 8]

RATIONALE FOR THE STUDY

Magnetic resonance imaging (MRI) has been used increasingly for the visualisation of anatomical changes in patients with cirrhosis. Further advancement in the form of diffusion-weighted imaging (DWI), has emerged as a promising imaging method for the noninvasive evaluation of liver fibrosis and cirrhosis. The principle of DWI involves measuring the Brownian molecular motion of water, thereby yielding the apparent diffusion coefficient (ADC) as a quantitative measure.

Apparent diffusion co-efficient (ADC) obtained using DWI is a useful parameter in assessing the relative hemodynamics of any organ. It is a measure of diffusion or perfusion calculated mathematically and reduced ADC appears as bright spot in DWI and it indicates restricted diffusion.[9]

Many series and reports have revealed that ADC is significantly reduced in cirrhotics compared to noncirrhotic livers.[9] This is most probably related to the fibrosis and distortion of lobular architecture of the liver, which restricts water molecule motion. Also, these results have shown that ADC values are useful as a predictive marker of liver fibrosis, especially moderate and advanced stage of fibrosis. Differences in imaging technique and parameters are one of the main drawbacks, as ADC values vary significantly between different studies. Several authors have proposed to use the spleen as a reference organ for ADC measurements of liver parenchyma in order to decrease variability of

liver ADC , even though in patients with cirrhosis and portal hypertension suffer from splenomegaly.[10] Recently advances in MRI including, MR elastography observed that the spleen stiffness increase proportionately with the degrees of liver fibrosis and found a linear correlation between them.[11] Possibly, this could be partly due to portal hypertension for this correlation. Hence, the grade of portal hypertension is a indirect prognostic factor for cirrhotic patients.

Similarly, cirrhosis is a state of hyperdymanic circulation and in view of portal hypertension, there is a splanchnic hyperemia. This splanchnic hyperemia is assessed by taking spleen as the representative organ of the splanchnic circulation. [12] Spleen ADC has been found to increase according to the different stages of cirrhosis. However the splanchnic hyperemia is the main contributor of portal hypertension in advanced cirrhosis and ADC value of the spleen should be a true reflection of the portal hypertension rather than the stage of cirrhosis. Portal hypertension necessarily need not correlate with the stages of cirrhosis. Hence we hypothesized that the ADC value of the spleen should be a reliable predictor of the severity of portal hypertension and should correlate well with the portal hypertension parameters in the form of grade of varices, gastrointestinal bleed, spleen size, platelet count, hypersplenism. etc. [13]

AIM OF THE STUDY

PRIMARY OBJECTIVES

1. To analyse the ADC value of the spleen in cirrhotic patients and to compare with a control group with normal liver function test.

2. To analyse the correlation of ADC value of the spleen in chronic liver disease patients, to the severity of portal hypertension in the form of clinically significant portal hypertension (CSPH) and also the surrogate markers of portal hypertension in the form of grade of esophageal varices, incidence of gastrointestinal (GI) bleeds, hypersplenism and size of the spleen.

SECONDARY OBJECTIVES

To analyse the correlation of the spleen and liver ADC to the severity of cirrhosis in terms of Child Pugh's status (CTP) and Model for End Stage Liver Disease (MELD) score.

REVIEW OF LITERATURE

Cirrhosis was initially described in a 4th-century B.C hippocratic aphorism:

"In cases of jaundice it is a bad sign when the liver becomes hard".

Although the harmful effects of ethanol on the liver was appreciated by *Galen* and his contemporaries in 2nd century A.D, "liver disease due to alcoholism", as a separate entity was first described by *Baillie* and other English writers in the 18th century after the "gin plague".[14] Shortly thereafter, *Laënnec* coined the term *cirrhosis,* which got derived from the Greek word *kirrhos,* meaning "orange-yellow." In 19th century, many European and English pathologists were analyzing this topic, including *Carswell* and *Rokitansky*, who described the gross and histopathologic characteristics of the disease.

ETIOLOGY OF CIRRHOSIS

Cirrhosis is the end result of an insult, hepatocellular injury caused by various etiologies which includes toxins, viruses, cholestasis, autoimmune, and genetic disorders (metabolic) (hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency). Recently, Non alcoholic steatohepatitis (NASH) is very much prevalent in India.

Most common causes of cirrhosis	Less common causes of cirrhosis
Alcohol (60%–70%)	Autoimmune chronic hepatitis
Biliary obstruction (5%–10%)	Drugs and toxins
Primary/secondary biliary cirrhosis	Genetic metabolic diseases
Chronic hepatitis B or C virus (10%)	Infection
Hemochromatosis	Vascular abnormalities
Nonalcoholic fatty liver disease (10%)	Veno-occlusive disease
	Idiopathic

Figure 1: Etiology of cirrhosis

Although the mechanisms by which these etiologies are different, the end pathologic response is the same: *"hepatocellular injury followed by fibrosis and regeneration"*. However in clinical situations, each of these elements can exist alone "necrosis, uncomplicated hepatitis; fibrosis, congenital hepatic fibrosis; nodular regeneration, partial nodular transformation", but the presence of *"all three are required for the development of cirrhosis"*. Cirrhosis is a diffuse pathology and can be classified either by etiology or morphologically. Posthepatitic cirrhosis especially due to viral etiology, which is generally macronodular and ethanol related cirrhosis, which is usually micronodular, were the two most common etiologies in the world. Few occasions the cause of the hepatocellular injury cannot be discerned as the pathologic responses to these injuries are the same. They are named as cryptogenic cirrhosis.

PATHOPHYSIOLOGY OF CIRRHOSIS

Figure.2: The pathophysiology of complications of cirrhosis

Cirrhosis exhibits two major clinical manifestations: *"hepatocellular failure and portal hypertension"*. Even though the noxious stimuli is removed from the patient (e.g., alcohol abstinence), the hepatocellular may keep on progressing and results in cirrhosis. Although the mechanism is not clearly understood, they can be related to ischemia, secondary to the diffuse fibrosis especially along the portal tract, intrahepatic and extrahepatic shunts. Autoimmunity can also play a role. Finally in view of the periportal fibrosis and perisinusoidal involvement, the hepatic architecture is distorted and simultaneously cause increased hepatic vascular resistance, *resulting in portal hypertension and its clinical complications such as variceal bleed, hepatic encephalopathy, volume overload, and hypersplenism.*

Progression without treatment
Variable course depending on host factors (e.g., age, sex, genetic predisposition), environmental factors (e.g., alcohol consumption, medications, smoking), and the etiology of liver disease

chronic liver disease → hepatic fibrosis → compensated cirrhosis → hepatocellular carcinoma

may be reversible with treatment   may be reversible with treatment   ca. 1%–5% per year

may be reversible with treatment   progression without treatment

decompensated cirrhosis (e.g., jaundice, ascites, bleeding from esophageal varices)
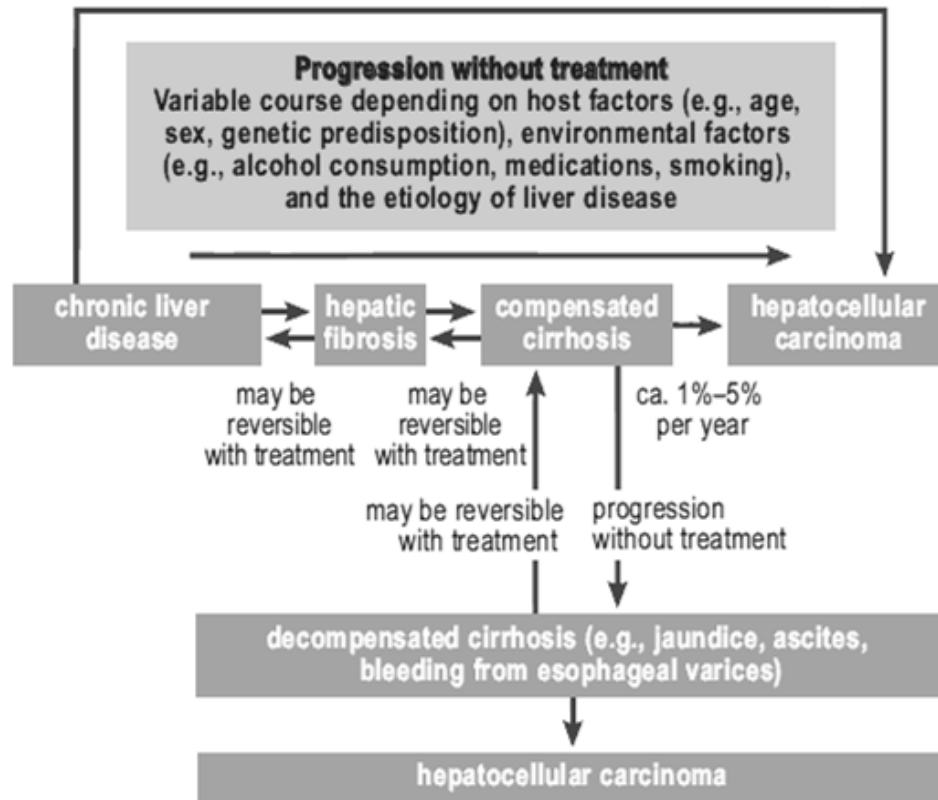
hepatocellular carcinoma

Figure 3: Course in a chronic liver disease patient.

Historically, cirrhosis was managed palliatively with the treatment of portal hypertension complications rather than cirrhosis per se. However, since 1966, after the invention of liver transplantation, which is the definitive treatment modality for cirrhosis, the management of chronic liver disease has been highly effective, with most of them having long-term survival (70%).[15] It is the optimal use of the palliative management initially in managing these patients medically and then deciding on the definitive management (liver transplantation) once the risk for death is more is the challenge of managing these patients.

IMPLICATIONS OF LIVER DISEASES IN INDIA

According to recent survey, liver diseases affect almost one of every 10 Indians. The rising trend of these problems in India is related to the increased prevalence of obesity and diabetes epidemic. As a result of these, there has been an emergence of a recent entity called as non alcoholic related steatohepatitis which resulted from fatty liver in 10% of these patients. [16] This forms a major cause of cirrhosis in India along with viral infections (Hepatitis B and C), apart from alcohol intake. According to the recent WHO report released in April 2011, Liver Disease related deaths in India reached 2 million or 2.3% of the total deaths. Most common cause of death in cirrhosis is hepatic failure, followed by variceal hemorrhage and decompensation.

MANIFESTATIONS OF CIRRHOSIS

A number of physical findings have been described in patients with cirrhosis. They are broadly classified as features of hepatic cell failure or because of portal hypertension. They are schematically described in the diagram shown below.(Fig.4)
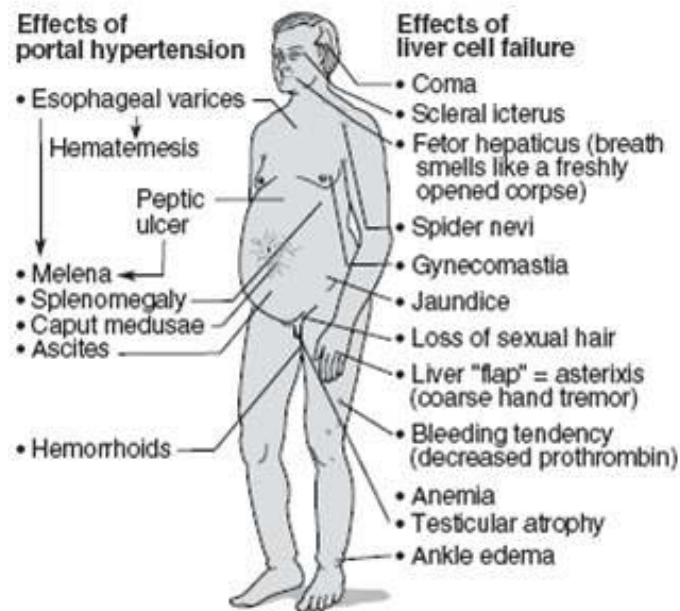
Figure 4: Presentation of cirrhosis and portal hypertension.

ANATOMY, PHYSIOLOGY OF PORTAL HYPERTENSION

The liver is a peculiar organ in that it has a two blood supply through portal vein and hepatic artery.[17]

PORTAL VEIN

The main portal vein is formed behind the neck of the pancreas at L2 level by the confluence of the splenic and superior mesenteric vein. It measures about 60 to 80 mm in length and 9- 10mm in diameter (Fig.5). The left coronary or gastric vein drains the distal oesophagus and lesser curvature of the stomach, and empties into the portal vein just before its formation. The inferior mesenteric vein drains the distal part of the colon and drains into the splenic vein which course posteriorly to the distal part of the pancreas and joins the superior mesenteric vein.
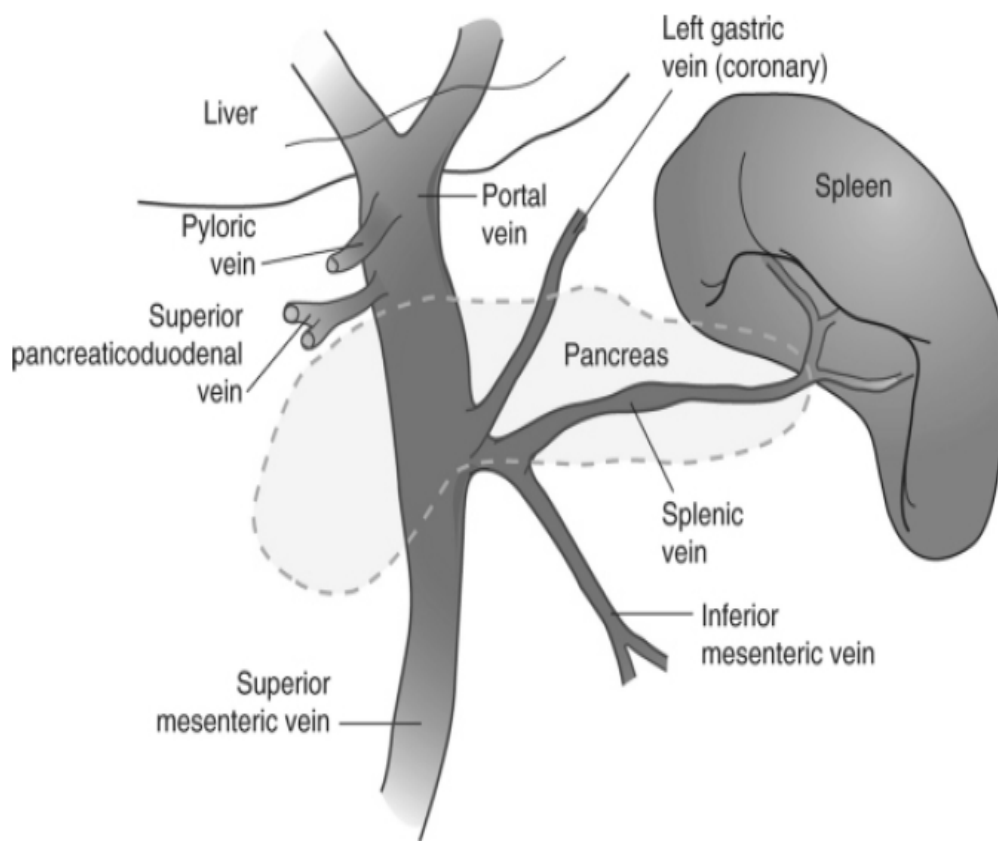
Figure 5: The portal venous circulation

HEPATIC ARTERY

The hepatic artery takes its origin from celiac axis along with splenic and left gastric and course to the left of the bile duct in the hepatoduodenal ligament before it enters the liver.

REGULATION OF BLOOD FLOW

Liver blood flow approximates 1.5 L/min, which forms about 25% of the total cardiac output. The portal flow contributes to 70% of the total liver blood flow, whereas hepatic artery contributes to the main oxygen supply of the liver (> 50%).[17]

The splanchnic circulation is modulated by various vasogenic factors. The volume of splanchnic venous flow is indirectly regulated by vasoconstrictors and vasodilators of the splanchnic arterial bed. However, the hepatic arterioles are directly regulated by the circulating catecholamines from the sympathetic nervous stimulation. There is an autoregulatory system between the hepatic artery and portal circulation called as arterial buffer response, which is the modulation of the hepatic arterial blood flow inversely proportional to the portal blood flow. This response is very critical in situations of intense vasoconstriction such as in shock or disease related or surgically diverted shunts. This response maintains the optimal blood flow to the liver and maintains the functions of the liver.[18]

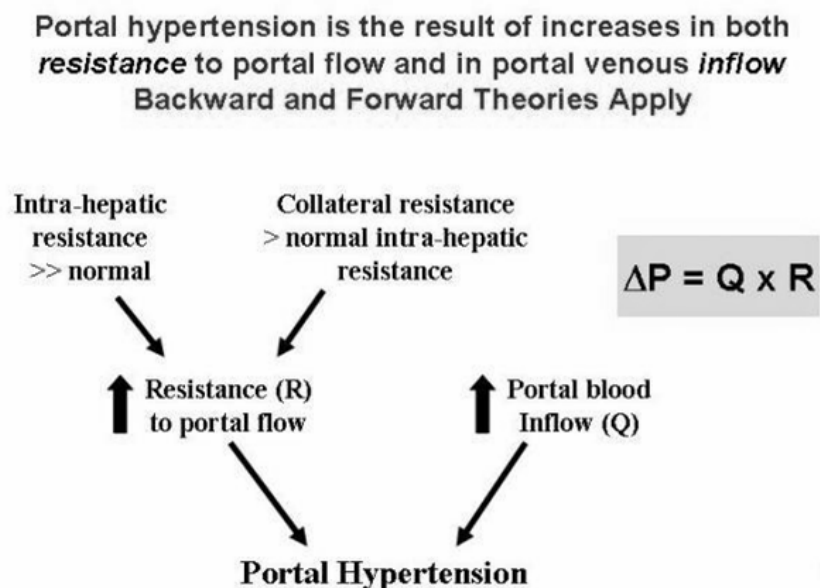## PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Figure 6: Pathophysiology of the mechanism of portal hypertension.

The mechanism behind the effects of portal hypertension is because of two factors.(fig.6) Initially it is the increased resistance to the portal venous blood flow at various levels in the portal circulation, thereby classified according to the site of obstruction. However, in addition to the elevated passive resistance due to portal fibrosis and regenerative nodules, increased vascular resistance at these levels due to active vasoconstriction caused by various agents like endothelin, norepinephrine, and other humoral factors contribute significantly to the increased vascular resistance.[18]

However in the late stages of the chronic liver disease especially in cirrhosis, it is the increased portal blood blow due to the hyperdynamic systemic circulation due to splanchnic hyperemia and this is the predominant contributor for sustaining portal hypertension.[19] The etiology for this hyperdynamic circulation with increased cardiac output and splanchnic hyperemia was not known. However it is the splanchnic hormones, like glucagon, and reduced sensitivity of the splanchnic vascular bed to catecholamines which might play a role. Elevated production of Nitric oxide and prostacyclins by vascular endothelium may also contribute to this.

CLASSIFICATION OF PORTAL HYPERTENSION

According to the level of resistance, the etiologies of portal hypertension have been classified as prehepatic, intrahepatic and posthepatic etiologies.

1. Prehepatic	
	Portal vein thrombosis – independent of cause, splenic vein thrombosis, cavernous transformation of the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly
2. Intrahepatic	
a) presinusoidal	
	Schistosomiasis, chronic viral hepatitis HBV, HCV, cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson's disease, hemochromatosis, amyloidosis, remaining storing diseases, polycystic liver disease, infiltration of liver hilus - independent of cause, benign and malignant neoplasms
b) sinusoidal	
	Liver cirrhosis - independent of etiology, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy
c) postsinusoidal	
	Venous-occlusion disease, alcoholic hyaline sclerosis of central veins
3. Extrahepatic	
	Hepatic veins thrombosis (Budd- Chiari disease), inflammatory/neoplastic infiltration cavering hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency

Table 1: Anatomical classification of portal hypertension

PREHEPATIC PORTAL HYPERTENSION

The most common cause of prehepatic portal hypertension which is predominant in children is the extrahepatic portal vein obstruction. This approximates for almost 50% of cases of PH in children. When the main portal vein gets occluded in the absence of chronic liver disease, collateral vessels will develop over the hepatoduodenal ligament to restore the portal flow to the liver (hepatopetal flow) in order to restore portal perfusion. This transformation is termed as *cavernomatous malformation of the portal vein.* [20] Apart from portal vein, when splenic

vein alone gets thrombosed as secondary to pancreatic neoplasm or inflammation, which is called as left-sided or sinistrial portal hypertension, it results in gastrosplenic segment venous pressure elevation with rest of the splanchnic system with normal portal pressures. Here, the left gastroepiploic vein forms the major collateral and thereby they develop gastric rather than esophageal, varices. This is important to diagnose because, this variant of portal hypertension can be easily treated with splenectomy itself rather than any other shunt surgeries.

INTRAHEPATIC PORTAL HYPERTENSION

The level of increased resistance in the intrahepatic portal hypertension can be at

1. Presinusoidal

2. Sinusoidal, or

3. Postsinusoidal level.

Occasionally, more than one level can be involved.

PRESINUSOIDAL

Though it is rare in India, the most common cause of presinusoidal portal hypertension worldwide is schistosomiasis parasitic infestation. In India, non cirrhotic portal fibrosis is the most common reason which results in presinusoidal portal hypertension. This is due to either infection or autoimmunity.

SINUSOIDAL

This is the most common form of portal hypertension in adults. Ethanol and viral hepatitis are the most common cause of portal hypertension in the India. As earlier mentioned they cause increased resistance at two levels

1. Sinusoidal - due to collagen deposit in the extracellular matrix, especially in the space of Disse and

2. Postsinusoidal - due to regenerating nodules distorting small hepatic venules.

POSTSINUSOIDAL

Postsinusoidal etiologies of portal hypertension are not common as sinusoidal and they include etiologies which affect the hepatic veins or the inferior vena cava causing congestion and portal hypertension.

1. Budd-Chiari syndrome (Inferior vena cava or hepatic vein or both thrombosis),

2. Constrictive pericarditis, and heart failure are the most common causes. [21]

Rarely, increased portal blood flow alone, due to huge splenomegaly (idiopathic portal hypertension) or a Porto arterial fistula can cause portal hypertension.

PORTOSYSTEMIC COLLATERALS

Portal pressure of more than 5 mm Hg is defined as portal hypertension. Portosystemic collaterals develop when portal pressure increases to the range of 8-10 mm Hg. It is well known that collateral vessels develop in places where portal and systemic venous circulations are in close proximity. Examples are in the distal esophagus, fundus of stomach, umbilicus and distal aspect of rectum. (Fig. 7).
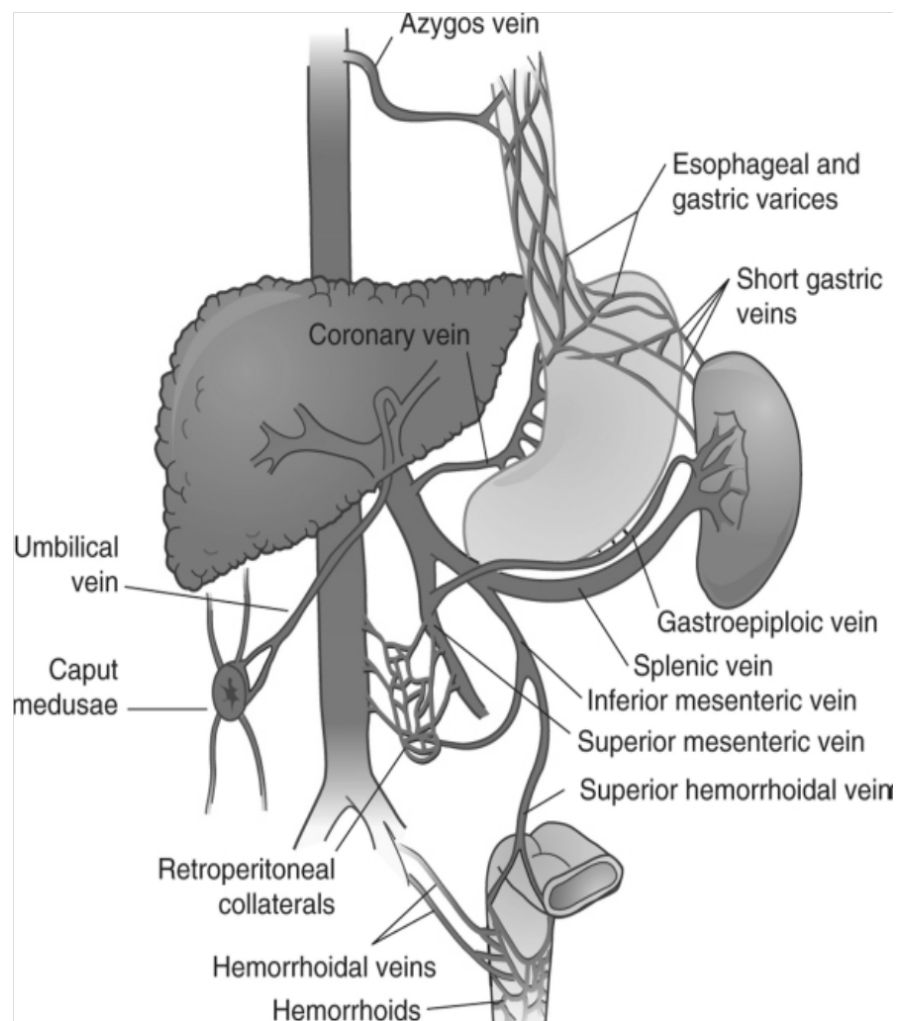

Figure 7: Portosystemic collaterals

Clinically, the most relevant site of porto-systemic collateralization is between coronary and short gastric veins of portal system and the azygos venous system. Collateralisation in this site results in formation of esophagogastric varices. (Fig.8)
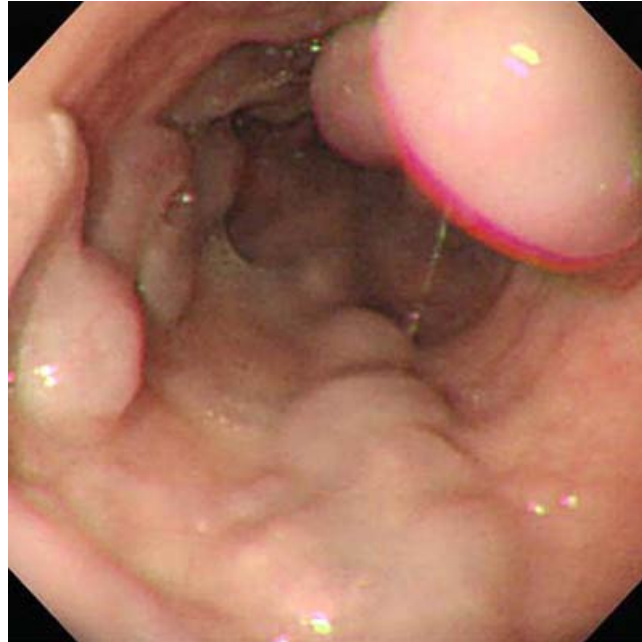
Figure 8: Endoscopic appearance of esophageal varices.

Other well known sites of portosystemic collateralization include recanalized umbilical vein from the left portal vein to the epigastric venous system (caput medusae), retroperitoneal collateral vessels, and the hemorrhoidal venous plexus. Intrahepatic shunts due to capillarization of hepatic sinusoids also form a significant channel of portosystemic shunting. All these factors result in reduction in portal flow through the liver. This leads to increase in hepatic arterial flow to liver. This is termed hepatic artery buffer response.

PORTAL HYPERTENSION- IMPLICATIONS

Most of the clinical manifestations of advanced liver disease are due to portal hypertension. These are gastrointestinal bleeding from esophageal or gastric varices, portal hypertensive gastropathy and colopathy, hyperdynamic circulation, ascites, hypersplenism and hepatorenal syndrome. Some complications of advanced liver disease like spontaneous bacterial peritonitis, hepatic encephalopathy and hepatopulmonary syndrome are multifactorial, but portal hypertension still plays a major role in their pathophysiology.

Normal hepatic venous wedge pressure is 3-6 mmHg. Ascites forms when the pressure is about 8 mm Hg and varices form when pressure is about 12 mm Hg. The most common and life threatening complication of portal hypertension is variceal bleed from esophago-gastric varices. This results in upto one-third of all deaths due to cirrhosis. Uncontrolled bleeding causes death in about a half of patients with bleeding esophageal varices. Rest of the patients die due to liver decompensation that invariably follows an episode of major variceal bleeding. Majority of patients with cirrhosis will develop esophageal varices (90%).[22] About a third of them will develop bleeding and one third to one half of patients with bleeding varices die during the first episode of bleeding.

Ascites occurs commonly in patients who develop significant sinusoidal portal hypertension. Reduction in portal pressure by surgically constructed porto systemic shunts or radiologic shunts like TIPSS (Transjugular Intrahepatic Portosystemic Shunt) leads to resolution or ease in control of ascites.[23] This is the proof of concept that portal hypertension is the causative factor for ascites.

Hypersplenism is another important effect of portal hypertension. Here, there is reduction in one or more blood cell lines in peripheral blood along with an overactive bone marrow. The most common cell line affected is platelets and this results in thrombocytopenia.[19] Mechanism of cytopenias in hypersplenism is sequestration of blood in enlarged spleen. It also is accentuated by immunologic mechanisms and intravascular activation of platelets. Banti first described the peripheral blood picture associated with hypersplenism in the setting of cirrhosis and a large spleen. Hypersplenism occurs in non cirrhotic causes of portal hypertension like non cirrhotic portal fibrosis and extrahepatic portal vein obstruction. The latter fact proves that hypersplenism is merely due to the presence of portal hypertension and can occur in the absence of liver disease.

The outcome of patients with cirrhosis is influenced by many factors like the etiology of cirrhosis, severity of portal hypertension, presence of comorbid conditions and complications of liver disease. There are several prognostication models for predicting outcome of

cirrhosis. Child-Pugh score(CTP), described initially to predict outcome of shunt operation in patients with cirrhosis is one of the earliest described methods. It still remains a very useful method to prognosticate patients with liver disease. Model for end stage liver disease (MELD) score is another commonly used prognostic model and uses a combination of serum bilirubin, serum creatinine and international normalized ratio (INR) of the patient in question. MELD score predicts the 3 month probability of death in patients with cirrhosis. The following table shows the parameters and their use to calculate the "Child-Pugh score and the mathematical formula used to calculate MELD score.

Table 2 :Child-Pugh Criteria for Hepatic Functional Reserve

Clinical and laboratory measurement	1	2	3
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	None	Mild	Moderate
Bilirubin (mg/dL)	1-2	2.1-3	≥3.1
Albumin (g/dL)	≥3.5	2.8-3.4	≤2.7
Prothrombin time (increase, s)	1-4	4.1-6	≥6.1

Grade A, 5-6; grade B, 7-9; grade C, 10-15

MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6

[Ln serum creatinine (mg/dL)]+6.4

where Ln is the natural logarithm."

DIAGNOSIS OF PORTAL HYPERTENSION AND CIRRHOSIS

Chronic liver disease is a heterogeneous and dynamic condition. The exact estimations of the stage and the changes in hepatic fibrosis and PHT are essential in the management of patients with this disease.

Portal hypertension is an essential event in the progression of chronic liver disease when severe fibrosis or cirrhosis develops. [24]Once the portal pressure increases above 10 mmHg it is termed as clinically significant portal hypertension – CSPH, where the risk of developing portal hypertension related complications like variceal bleed or ascites are high. However it is very difficult to estimate this pressure gradient non invasively. Histopathological examination of the liver biopsy samples has been practically considered as the gold standard for assessing the stage and severity of liver fibrosis and for diagnosing cirrhosis. However, it is the invasive nature of this investigation was the major limiting factor in its use. And also sampling error has been seen frequently with liver biopsy, especially wedge biopsy and trucut biopsy. Over the last two decades, various studies have been done to circumvent these problems and have tried to invent non-invasive techniques to evaluate liver fibrosis and cirrhosis along with portal hypertension.[24]

These have been possible after the invention of various non invasive investigations like ultrasound with Doppler, computer tomography, magnetic resonance imaging etc.

The ideal test for assessing liver fibrosis and cirrhosis along with portal hypertension is the one which has to be harmless, easy to do, not expensive, repeatable (between patients and between and within labs). It should give an accurate estimate of the different stages of liver fibrosis from the pre-cirrhotic stage, and early cirrhosis. Also these tests should have a prognostic significance on the prediction of future problems like variceal bleed, hepatic decompensation and most importantly the stage for the requirement of transplantation, and mortality.

PHYSICAL EXAMINATION

The simplest, cheapest and easily available method which can be repeated many times to get information on the diagnosis and staging of cirrhosis and/or of portal hypertension is the routine clinical examination There are lots of clinical stigmata of decompensated liver disease which are helpful in confirming advance stage of chronic liver disease. They are a firm to hard left hepatomegaly , gynecomastia, atrophy of the testes, parotid enlargement, features of hepatic dysfunction like yellowish discolouration of the sclera, urine, angio malformations such as spider naevi, leuconychia, palmar erythema or altered sensorium, visualization of parietal wall collaterals, volume overload in the form of ascites, pedal

oedema and splenic enlargement. Splenomegaly is considered as the most important stand alone physical diagnostic marker of portal hypertension. In view of the increased cardiac output and hyperdynamic circulation, they can present with peripheral vasodilatation, reduced blood pressure and increased pulse rate. These are signs of advance liver diseases. All these clinical signs and symptoms are found in end stage liver disease and they in association are very specific to this syndrome. Portal hypertension usually presents with variceal bleed mostly esophageal or non esophageal bleed, ascites and presence of splenomegaly and large abdominal wall collaterals. In a latest study, where patients with early compensated chronic liver disease were evaluated with hepatic venous wedge pressure gradient (HVPG) and correlated with their clinical signs and symptoms, they found none of them correlated well with HVPG > 10mm Hg. However, the presence of vascular malformations like spider naevi was found to be predictive of oesophageal varices but not their bleeding.

LABORATORY EXAMINATION

Various indirect serum markers of fibrosis has been evaluated like indicators of hepatocyte damage (AST, ALT), impaired bile secretion (γGT, bilirubin), synthetic function markers of hepatocytes (i.e. cholesterol, INR, ApoA1, N-glycans, haptoglobin), and hypersplenism due to splenomegaly (i.e. platelet count). Though in a recent evaluation

by meta-analysis, none of these markers helps in differentiating various levels of fibrosis and severity of portal hypertension. In a recent study, serum hyaluronic acid (HA) has been found to have a prognostic value equivalent to CTP score for the prediction of mortality and cirrhosis complications.[25]

For portal hypertension, CTP score and its objective factors (albumin, bilirubin, INR) correlated well with HVPG. In addition the CTP score correlated well with the severity of portal hypertension in the form of grade of oesophgeal varices and their occurrence in cirrhotic patients. As expected, this correlation is also found in early cirrhotic patients with no history of decompensation, impling that a significant correlation exists between the architectural distortion and the onset of portal hypertension and ultimately, hepatocellular failure.

Platelet count, which is an important component of hypersplenism has been found to correlate independently with the prevalence, grade of oesophageal varices in various studies. This suggests its correlation with severity of portal hypertension and in another study, platelet count to spleen diameter ratio > 909 was found to have 100% negative predictive value for presence of esophageal varices.[26] The author emphasis that it can help in avoiding unnecessary endoscopy.

IMAGING OF CIRRHOSIS AND PORTAL HYPERTENSION

In chronic liver disease, the imaging diagnosis plays several significant roles in patient management, both in terms of diagnosing hepatocellular carcinoma and predicting its progression to cirrhosis. The basic diagnostic imaging modalities consist of ultrasound (US), computed tomography (CT), and magnetic resonance (MR) based methods, and many specific techniques derived from these basic methods are currently being developed to achieve convenient, non-invasive, and accurate diagnosis.

ULTRASOUND AND DOPPLER-ULTRASOUND

Ultrasonography is an inexpensive and harmless technique which can be used as an initial evaluation for the diagnosis and follow-up of liver diseases. US with Doppler were very accurate in diagnosing flow related issues in portal and hepatic veins.[27] Hence, it has the advantage of non invasively evaluating a portal hypertensive patient and finding out the location of the thrombosis, thereby identifying the causes, extrahepatic portal vein obstruction , Budd Chiari syndrome and isolated splenic vein thrombosis. It is advantageous over liver biopsy in terms of non invasiveness, available at all centres, multiple times repeatable, can focus on all the areas of liver especially in Budd Chiari syndrome where there is difference in the liver biopsy taken from obstructed hepatic segment and non obstructed hepatic segment.[2]

Conventional US looks out for the morphological changes of the liver in cirrhosis and the evidence of portal hypertension (Table 2). Conventional US findings are highly specific, in that the findings of cirrhosis can "rules-in" cirrhosis with positive predictive value. They are enough for the establishment of liver disease like cirrhosis. Even then, it cannot differentiate early non shrunken cirrhosis with non cirrhotic portal fibrosis and Budd Chiari syndrome. In contrast on evaluating a patient suspected of liver disease, no individual US findings has good negative predictive value, impling that a negative finding cannot fully rule-out cirrhosis.

The best accurate single US sign for establishing the diagnosis of cirrhosis, is by assessing the liver morphology. Nodularity of the liver surface can be found in early stages of cirrhosis and its has a high predictive value.[28] With the use of high frequency abdominal US probes, diagnostic accuracy has got increased over the conventional US probes, and should be preferred.[29] (Fig.10)
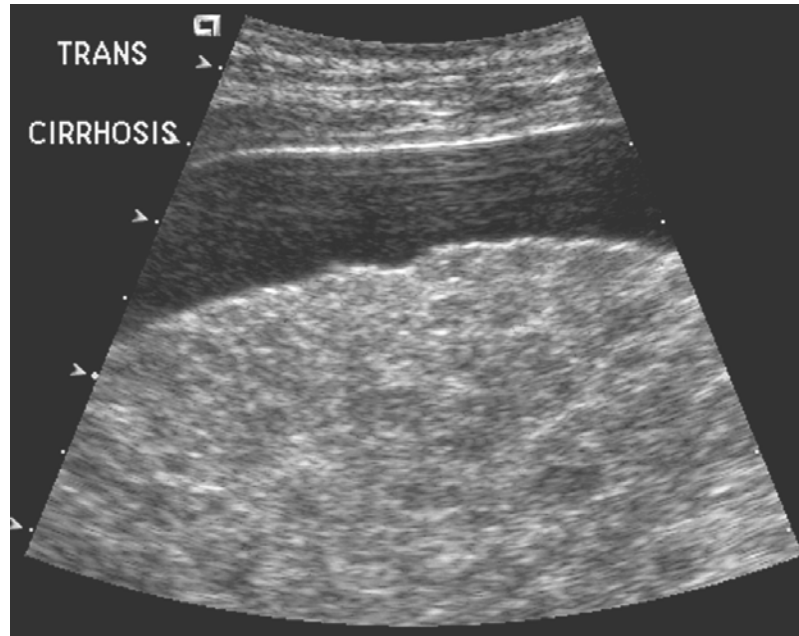
Figure 10: Conventional US abdomen showing nodular liver with ascites suggestive of cirrhosis

In a recent study, the predictive value of combining nodular liver morphology with main portal vein velocity < 12 cm/s (mean) was about 80% in discriminating chronic hepatitis C virus patients with severe grade of fibrosis and those with cirrhosis.[30] In patients, clinically suspicious of cirrhosis , the detection of nodular liver morphology is an excellent method to "rule in" cirrhosis, and then by combining this with transient elastography (TE) favours the best diagnostic performance .[30-32]
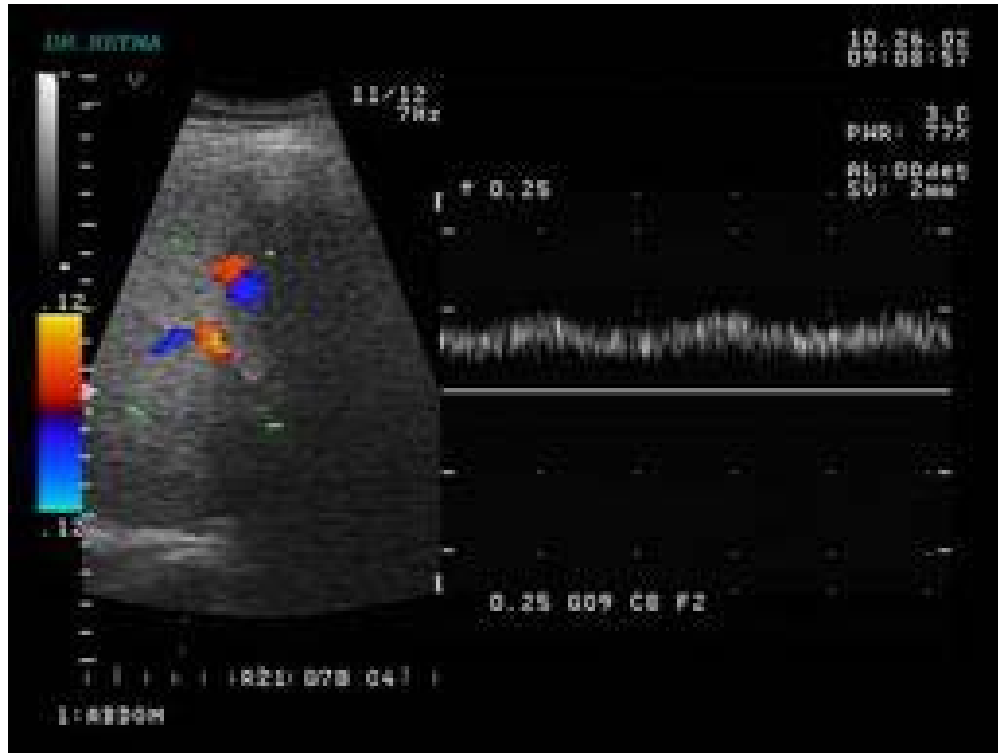
Figure 11: Colour doppler shows normal portal venous spectral waveform.

Figure 12: Colour doppler shows bidirectional flow in portal vein.

Figure 13: Colour doppler demonstrating hepatofugal flow in the main portal vein in advanced cirrhosis.
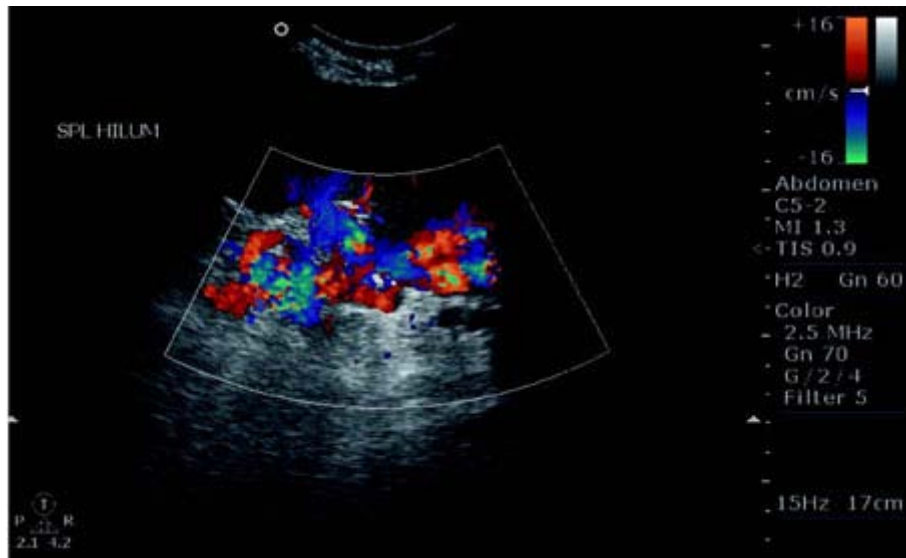
Figure 14: Colour doppler shows splenorenal collaterals.

Figure 15: Doppler US- showing in the sagittal paramedian view, the flow in the coronary vein (CV) is directed superiorly and away from the splenic vein

Figure 16: Doppler US- showing in the sagittal view slightly posterior, the tortuousity of the CV as it extends to the gastroesophageal junction
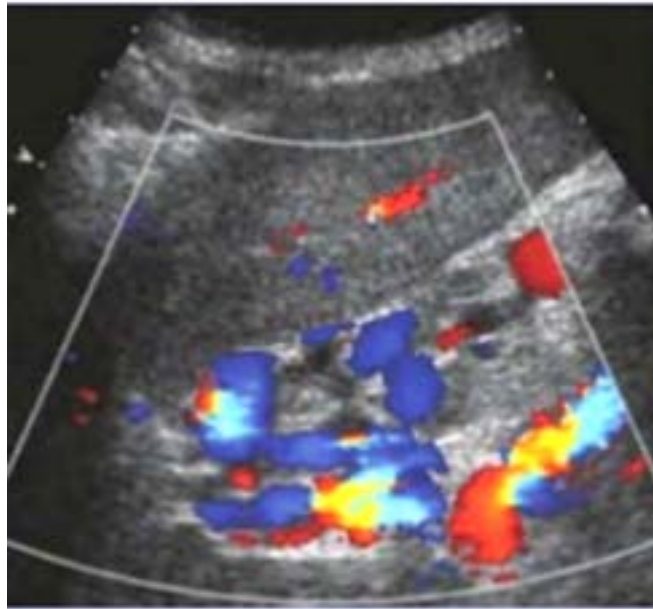
Figure 17: Doppler US, showing in the longitudinal view of the left liver lobe, the gastroesophageal collaterals close to the diaphragm

Figure 18: Ultrasonography of the spleen showing Gandy gamma bodies in congestive spleen

Similarly to the diagnosis of cirrhosis with US, all ultrasound signs of portal hypertension are very specific, though their sensitivity is low, especially in early cirrhosis. Hence the presence of an ultrasound sign or a combination of multiple signs can accurately "rules-in" portal hypertension. However the same signs absence cannot defer the diagnosis. Out of all the US signs for portal hypertension, the measurement of spleen enlargement is the most common sign to be correlated well with the presence and severity of portal hypertension.[33] Their sensitivity is high as proven in various studies, though their specificity value falls to 50–80% in different series. It is an independent predictor of oesophageal varices, and is associated to clinically significant PH in patients with early and compensated cirrhosis.[34]
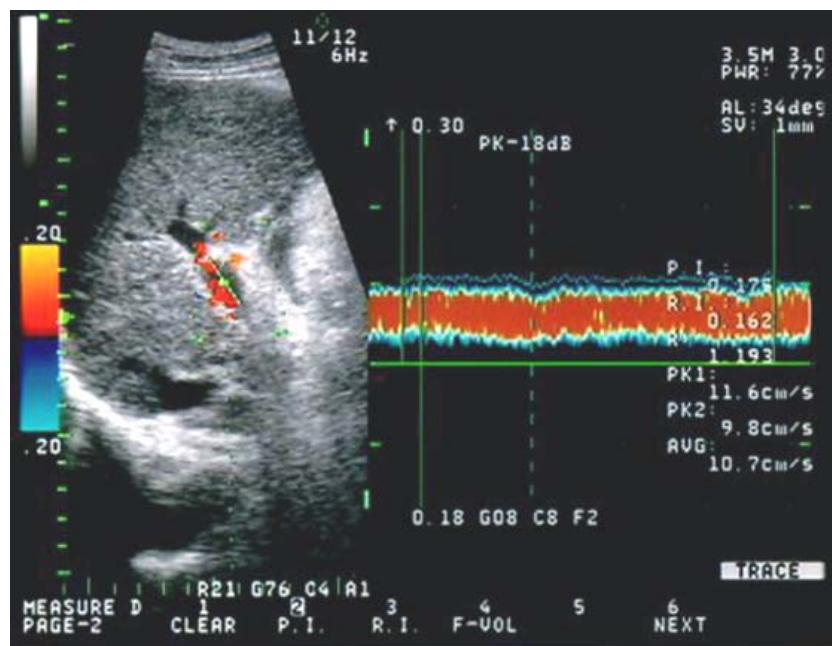
Figure 19: Portal venous velocity measured with Doppler US (10.7 cm/s) in a patient with cirrhosis.
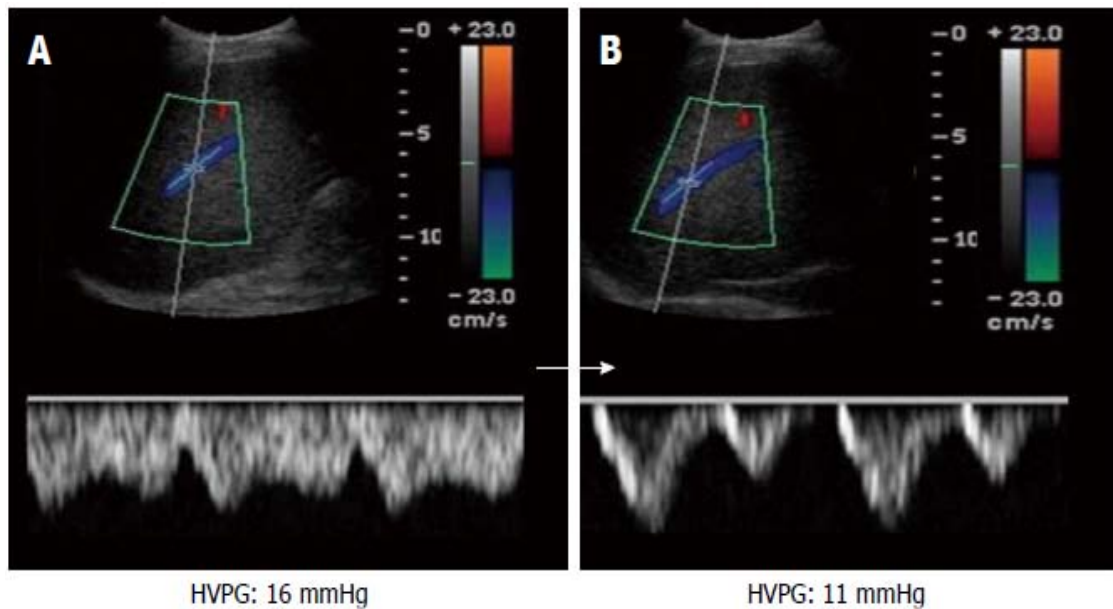
Figure 20: Doppler US showing change in the hepatic vein waveform and damping index (A) before and (B) 3 month after propranolol treatment in a patient with liver cirrhosis

On analyzing the various signs of US for its correlation to the severity of PH (CSPH) , the presence of patent paraumbilical vein, large collateral between left renal vein and splenic vein, dilated and tortuous left coronary and short gastric veins, and the reversal of flow in the portal circulation were 100% specific US signs of CSPH.[35] Other US signs of CSPH include

1.   Dilatation of main portal vein (> 13mm in diameter)

2.   Absence or reduced respiratory variations of splenic and SMV diameter

3   Decreased portal vein mean velocity (< 10–12 cm/s and < 16 cm/s ,mean and maximal velocimetry of main portal vein flow, respectively)

4.   Elevated congestive index of main portal vein

5.   Distorted hepatic venous Doppler pattern

6.   Elevated intraparenchymal splenic and hepatic artery resistance (impedence)

7.   Elevated intraparenchymal renal artery impedance and reduced SMA impedance

HVPG, which is the gold standard for the portal hypertension correlated significantly with few US parameters like main portal vein mean velocity and volume of portal blood flow, hepatic artery RI (resistive index), splenic and renal artery resistance and pulsatility index.

However the degree of correlation between these factors is only mild to moderate and these US signs cannot replace or can apply as useful surrogates for HVPG. Some Doppler signs hold prognostic value in cirrhotic patients.

PREDICTORS OF VARICEAL BLEED

Like the diagnosis of oesophageal varices and variceal formation, their growth and the risk of bleeding, models for the prediction of varices of any size or of large varices involves main portal vein diameter or spleen dimension in association with laboratory tests (platelet count and

INR). This was evaluated in few prospective studies in early cirrhosis which found a good discriminating ability.[35] However, later studies could not validate these parameters for the accurate prediction of varices.

1. Porto-systemic collaterals such as left coronary vein > 3 mm and short gastric vein (collaterals at superior spleen half) reliably suggest the prevalence of oesophageal varices, and their growth/increase in size have been associated with a increased proportion of variceal formation and growth.[36]

2. Progressive splenomegaly can predict variceal formation and growth .

3. In a prospective study, congestive index of the main portal vein (ratio between the cross-sectional area and portal flow velocity) predicts the first variceal bleed in patients with varices .

As for the prediction of first clinical decompensation of any kind, progressive splenomegaly (> 1 cm) on follow up scan might be correlating with a higher possibility of developing the first clinical decompensation of cirrhosis. A main portal vein mean velocity > 15 cm/s was the only sign independently predictive of increased risk of non-malignant PV thrombosis in a prospective study.

Ultrasound is highly accurate in diagnosing and estimating ascites, which is the most common clinical manifestation of decompensated

cirrhosis and it holds a severe prognostic significance. The elevation of intrarenal arteriolar RI in patients with end stage liver disease is related to arterial vasoconstriction (Renin Angiotensin mechanism). It is found in approximately two fifth of patients with ascites and efficacious in diagnosing HRS (hepato-renal syndrome). A shrunken liver, splenomegaly of > 14.5 cm, mean main PV velocity > 10 cm/s and loss of pulsatile pattern (triphasic → biphasic→ monophasic) of hepatic veins have been correlated to higher mortality on follow-up in patients with early cirrhosis.

Contrast-enhanced ultrasound (CEUS)

CEUS imaging represents a new US modality for the assessment of chronic liver disease.[37] Hepatic vein transit times (HVTT) have been shown to be reduced with worsening liver disease. HVTT showed a significantly strong correlation with PHT and the AUROC of HVTT for the diagnosis of clinically significant PHT was 0.973.[38] However, this method also has some limitations, such as the requirements for the injection of a contrast agent, considerable operator skill, and access to the relevant technology.[39, 40] "More intensive studies and validation are needed.

US signs of cirrhosis			
		Sensitivity	**Specificity**
Liver	Nodular liver surface	55–91%	82–95%
	Coarse echopattern	20% overall 51% HBV-HDV	90%
	Left lobe/ right lobe ratio > 1.30	74%	100%
	Caudate lobe/ right lobe ratio ≥ 0.65 (hypertrophy of caudate lobe)	43–84%	100%
	Reduction of the medial segment of left hepatic lobe	74%	100%
Hepatic veins	Narrowing and loss of normal phasicity of flow by Doppler	Not reported	Not reported
	Altered straightness	97%	91% 86%
	Nonuniformity of hepatic vein wall echogenicity	88%	
Hepatic artery	Increased diameter	Not reported	Not reported

US signs of portal hypertension			
		Sensitivity	**Specificity**
Portal venous system	Dilatation of portal vein (≥ 13 mm)	< 50%	90–100%
	Reduction of portal vein blood flow velocity (Max vel < 16 cm/s;)	80–88%	80–96%
	Mean vel < 13 cm/s		
	Inversion of portal vein blood flow	Not reported; sign prevalence: 8.3% of unselected pts	100%
	Increased portal vein congestion index (≥ 0.08)	67–95%	100%
	Dilatation of splenic vein (SV) and superior mesenteric vein (SMV) (≥ 11 mm)	72%	100%
	Reduction of respiratory variation of	79.7%	100%

US signs of portal hypertension			
		Sensitivity	**Specificity**
	diameter in SV or SMV (<40%)		
Spleen	Splenomegaly (diameter > 12 cm and/or area ≥ 45 cm^2	93%	36%
Splenic artery	Increased resistive index of the intraparenchymal branches (≥0.60)	84.6%	70.4%
Hepatic artery	Increased resistive index of artery at the porta hepatis (> 0.78)	50%	100%
Renal artery	Increased resistive index of the right interlobar renal artery	79.5%	59.3%
SMA	Decreased pulsatility index (≥ 2.70)	85.7%	65.2%
Presence of porto-systemic collateral circulation		83%	100%

COMPUTED TOMOGRAPHIC SCAN (CT) and MRI

Cross-sectional imaging studies such as CT and MRI are useful imaging modalities for the diagnosis of cirrhosis. These modalities are considered to be standard methods for the diagnosis of HCC on the background of chronic liver disease, including cirrhosis. The radiologic features of advanced cirrhosis are normally obvious and include surface nodularity, prominent fibrous septa, shrinkage of liver volume, and an enlarged portal venous system including varices and splenomegaly due to PHT. [41]However, it is difficult to diagnose the early stage of cirrhosis. As such, various functional techniques using CTand MRI have been developed recently and described in many hepatology and radiology journals.[42]

However, in the era of multidetector CT, which enables CT scanning at a submillimeter thickness, CT can be used to obtain information not only about the cirrhotic liver itself but also about the PHT caused by cirrhosis. Various portosystemic collateral veins can also be depicted in the CT scan, and physicians can plan a strategy for the treatment of varices, including the insertion of a transjugular intrahepatic portosystemic shunt and balloon-occluded retrograde transvenous obliteration. Moreover, as with endoscopy, demonstrating the presence of esophageal and gastric varices is now possible using CT. The sensitivity and specificity of CT were found to be 96% and 55%, respectively, to detect esophageal varices and 93% and 80%, respectively to detect high-

risk esophageal varices.[43] Using the 1-to 3-mm multiplanar reformat or surface-shaded display can also increase the specificity of CT for the risk stratification of esophageal varices. With regard to gastric varices, the sensitivity and specificity were 83%-89% and 75%-79%, respectively.[44] Although these results are not bad, the accuracy for small varices remains low.
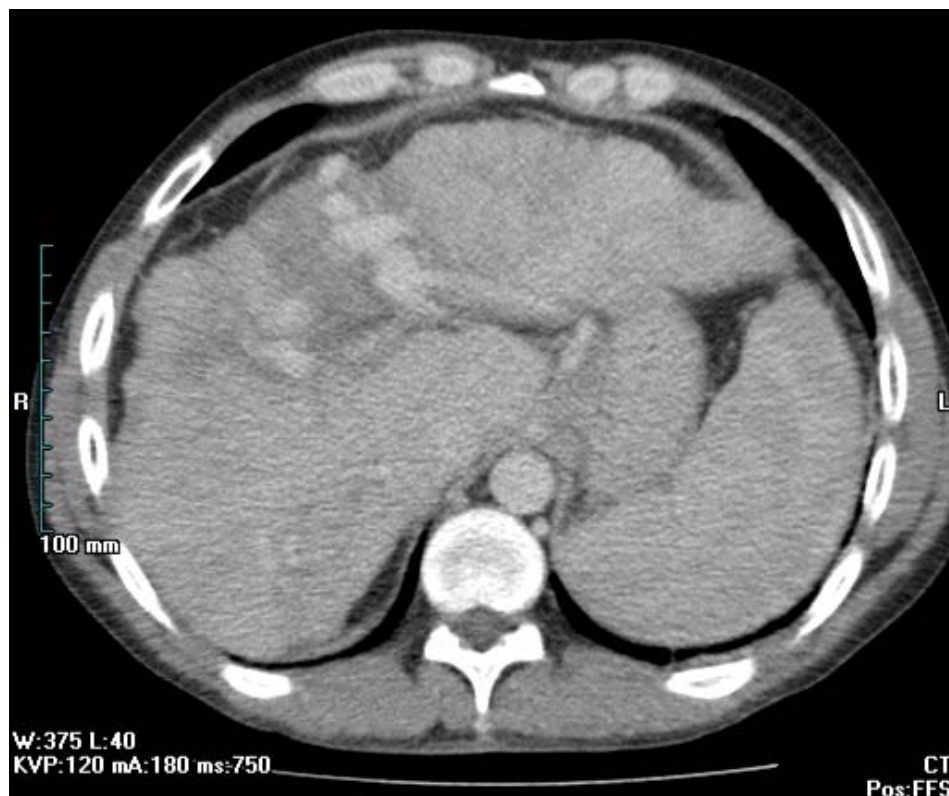
Figure 21: Contrast enhanced CT showing evidence of cirrhosis with nodular liver surface and also portal hypertension with a patent paraumbilical vein and spleen enlargement.
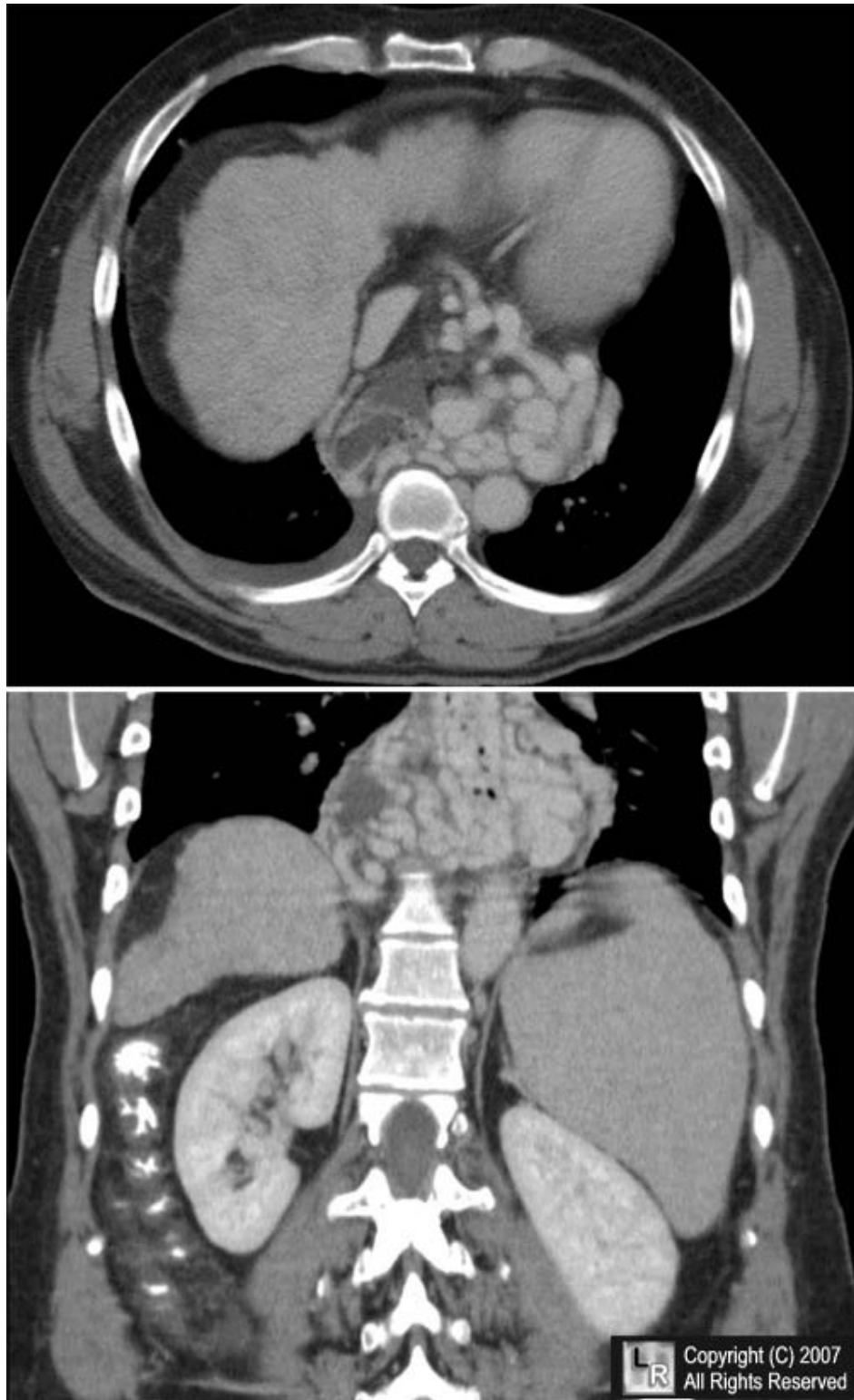
Figure 22: **Contrast enhanced CT images (axial and coronal) showing shrunken nodular liver with tortuous gastro-esophageal collaterals and gross splenomegaly.**

Figure 23: Contrast enhanced CT coronal images showing dilated left coronary vein and forming large oesophageal collaterals

Figure 24: Contrast enhanced CT axial MIP images showing the spontaneous splenorenal collaterals between splenic and left renal vein.

Few large studies have analysed the efficacy of CT, either single detector or multidetector scanning in the assessment of the oesophageal varices in cirrhotic patients. They found CT are reliable in diagnosing large oesophageal varices with specificity (91–100%) and sensitivity (85–100%), though with some inter-observer variations.[45] However, their role or accuracy in diagnosing smaller varices is significantly reduced and they are not recommended for these varices. In a recent study done to analyse the cost-benefit ratio showed that direct computer tomography screening of oesophageal varices was more benefitting than endoscopic visualization and that computer tomography followed by endoscopic visualization is helpful for cirrhotic patients with few small varices visualized or suspected on CT .[46]

Dynamic imaging with contrast CT and MRI imaging (hepatic contrast images after administration of gadolinium chelate and compartmental analysis of intensity versus time curves for MRI images), and phase contrast MR venography helps in the quantitative assessment of the flow in the portal vein and azygous venous system. The importance of assessing azygous venous flow is that it is an indirect predictor of the grade of lower oesphageal porto-systemic collateral flow. [47-50]Azygous venous flow, as measured by phase contrast MR venography, was associated well with the presence of oesophageal varices at endoscopy. It also predicts the risk of variceal bleeding with increased accuracy. Other parameters like portal venous proportion of the hepatic perfusion and the

average transit time in MRI has been found to have a significant correlation with the hepatic venous wedge pressure in a recent study. However, whether any of these highly expensive and sophisticated techniques gives more information, in addition to the physical, biochemical, ultrasound or TE parameters has to be evaluated in further studies.
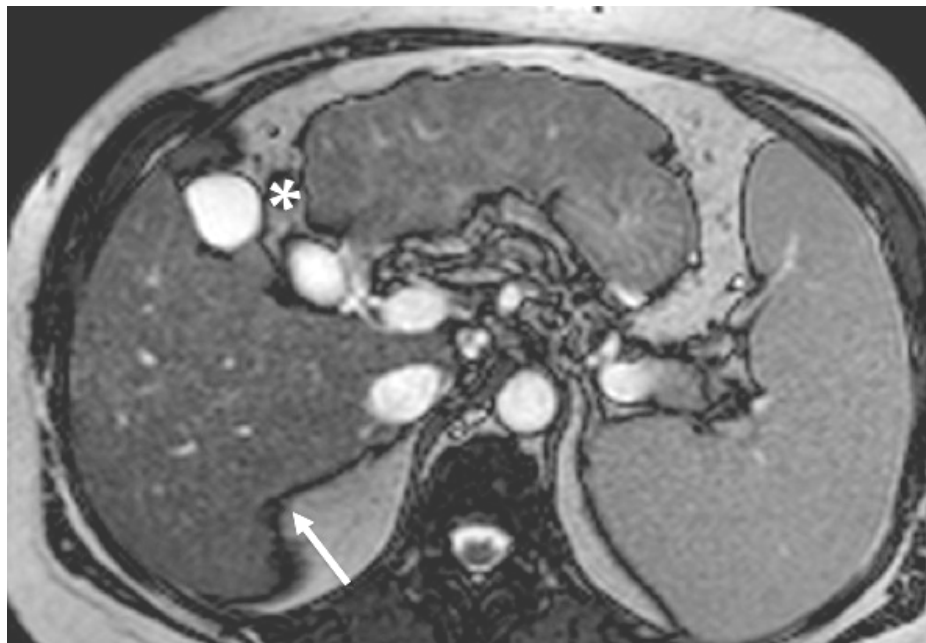
Figure 25: MRI axial image shows a nodular surface liver with splenomegaly and enlarged left liver and edematous gallbladder fossa (asterisk), notching of the right lobe (arrow).
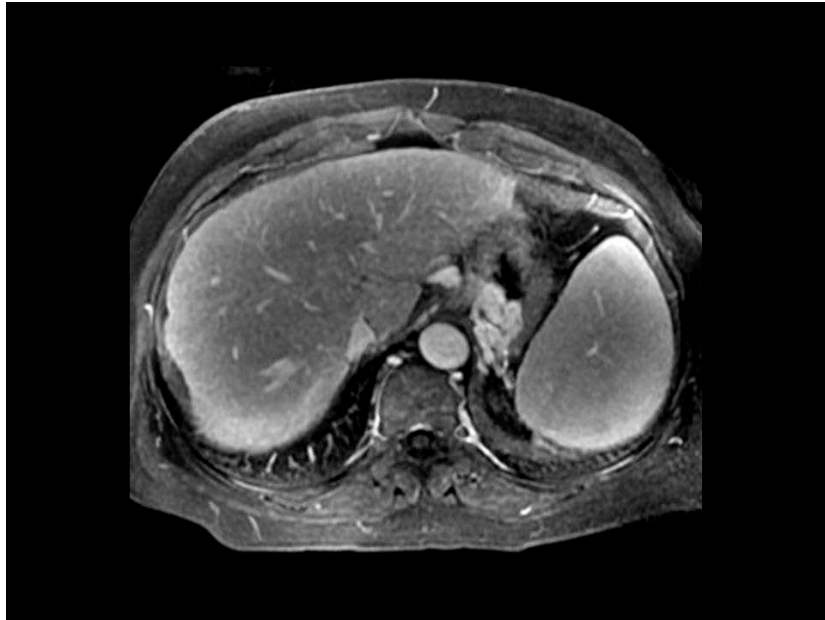
Figure 26: Postcontrast T1 weighted MRI abdomen shows varices in the fundus of the stomach.

Figure 27: MRI postcontrast T1W shows paraesophageal collaterals projecting outside the oesophagus.

Figure 28: MRI abdomen shows hypointense gammagandy nodules diffusely scattered in spleen in portal hypertension.
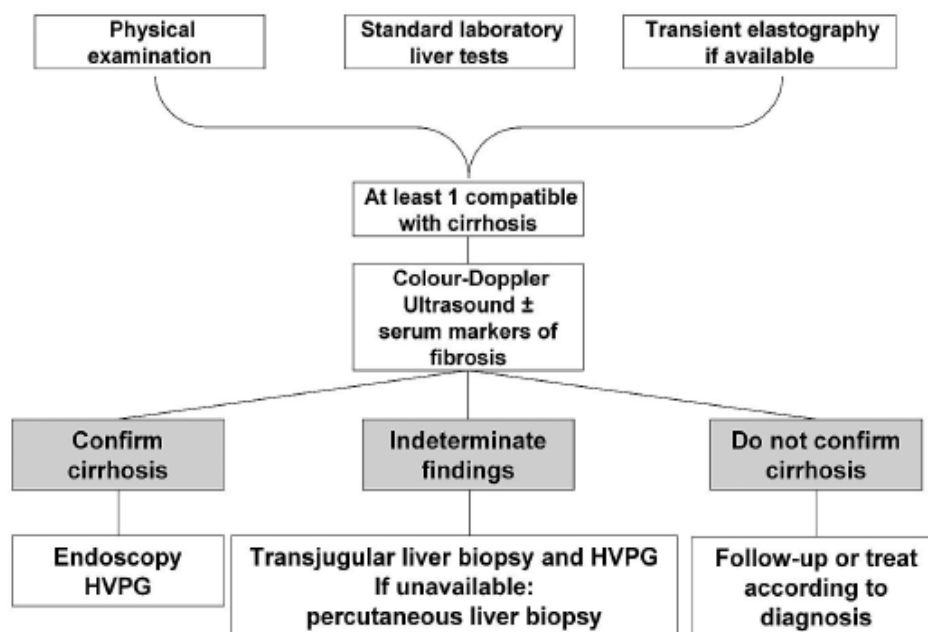
Figure 29:Algorithm for clinical suspicion of cirrhosis with portal hypertension

NON INVASIVE ASSESSMENT OF LIVER FIBROSIS

Regardless of its underlying etiology, fibrosis is the main component of chronic liver damage that directly relates to the severity and prognosis of the disease. Hepatic fibrosis and its secondary result, portal hypertension (PHT) are currently viewed as a dynamic process that can be reversible in some situation, if the underlying insult that has caused the fibrosis and cirrhosis has been removed. Over time, the excess fibrous tissue of cirrhotic liver may also regress. Therefore, an accurate estimation of the severity of fibrosis and PHT is essential to evaluate the disease state and prognosis and is the first step towards the optimization of the treatment and estimation of its response .[51-56]

SERUM MARKERS

Direct markers such as serum laminin levels, serum hyaluronic acid and procollagen type Ⅲ propeptide were evaluated in an old small population studies and laminin and hyaluronic acid showed correlation with HVPG, however these markers has limitations in clinical application because of low predictive values for the presence of severe PHT.[57, 58]

ELASTOGRAPHY

Transient elastography (TE), popularly called as Fibroscan, has been introduced recently for assessing the stiffness of the liver , non invasively which matches the accuracy of the liver biopsy in assessing the grade of fibrosis.[59-65] It is done by the following method.

1. An US transducer probe, which was built on the longitudinal plane of a vibrator was used. Through this, a low frequency and mild amplitude signal is transmitted. This produces a wave that propagates through the hepatic tissue.

2. A pulse-echo acquisitions were done to quantify the spped of the wave propagation through the liver tissue, which is found to correlate with the liver stiffness.
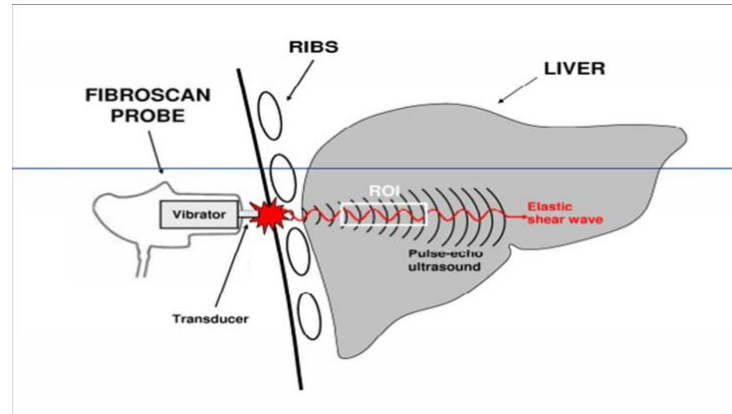
Figure 30: Showing the mechanism of Fibroscan and reading of a grade 4 fibrotic liver with liver stiffness score of 49.6 kPa

The area of the hepatic parenchyma which can be evaluated by Fibroscan is approximately hundred times larger than that estimated by biopsy. Hence there is a low potential for sampling error. As the liver gets fibrosed during the course of the chronic liver disease / cirrhosis, the stiffness level of the organ increases proportionately and hence transient elastography has been used to evaluate the presence of fibrosis and cirrhosis, and was found to be an effective analysing tool in this setting. Stiffness of the liver is measured as kilopascals (kPa) or centimeters per

second (cm/s). However to get a single cut-off value to differentiate chronic liver disease from cirrhosis is difficult, as the liver stiffness varies with the etiology of the chronic liver disease and its also varies between different geographical location. However, a cut-off value of 12.6 kPa and over has been estimated to differentiate cirrhosis, in a recent prospective study done in patients with chronic liver disease.[66] Stiffness of the liver has been shown to correlate best with the viral etiologies, especially Hepatitis C and correlates well with the severity of the fibrosis.[67]

The effectiveness of transient elastography in the non-invasive estimation of portal hypertension and CSPH have also been analysed. In a recent study done in patients with recurrent hepatitis C infection post liver transplantation, liver stiffness measured, was found to have excellent correlation with the degree of fibrosis and with HVPG. They found that, a liver stiffness value of 8.73 kPa had a sensitivity and specificity of 91% and 80% for the diagnosis of any grade of portal hypertension (HVPG 6 mmHg). Along with this, in cirrhotic patients, liver stiffness has been found to correlate well with the presence of high grade oesophageal varices. In the prospective study by Kazemi et al, they found a liver stiffness value above 19.5 kPa predicted the presence of high grade oesophageal varices.[68] In another recent study, though published as an abstract, a significant correlation has been shown between HVPG and liver stiffness in a population of uncomplicated alcoholic and HCV-related cirrhotic patients; they found a cut-off value

of 17.2 kPa had a sensitivity of 92% for the clinically significant portal hypertension.[68, 69] In addition two further studies showed the cut-off values of respectively, 23.4 and 13.5 kPa had a good accuracy to predict the presence of CSPH (HVPG > 12mmHg) in patients with chronic liver disease.[70, 71] However, it has been stressed in the study by Vizzutti and colleagues, that at the threshold value of 13.7 kPa there was no good correlation between liver stiffness and CSPH, probably because once portal hypertension progresses above a the threshold HVPG value of 10–13mmHg, porto-systemic collaterals forms and thereby, the hepatic fibrosis is not the only mechanisms maintaining portal hypertension, as porto-systemic collateral flow increases and significantly contributes.[72] In a recent study done, transient elastography was evaluated for the diagnosis of CSPH in the setting of resectable hepatocellular carcinoma patients.[73-75] Their result showed that TE is not an accurate method to rule-out or confirm CSPH in this population, and they recommended TE not is used as a non-invasive surrogate marker for indicating or contraindicating surgery. To conclude from these observations, though it has been estimated that higher values of liver stiffness at TE showed strong predictive value for cirrhosis and the presence of CSPH, the technique is not effective enough to analyse the severity of portal hypertension.

MR ELASTOGRAPHY (MRE)

MRE is a recent technique with novel MRI technology to evaluate liver stiffness. The parameters are obtained by synchronizing motion-sensitive imaging series with the application of acoustic signals in the tissue media. It has been evaluated in humans, and the initial report has shown satisfactory results supporting its practicability in estimating the stage of hepatic fibrosis in patients with chronic liver disease.[76] MR elastography can be repeated multiple times and changes correlate well with the progression of tissue fibrosis. MR elastography has also been evaluated for estimation of the spleen stiffness, which was highly correlated with hepatic stiffness.[77] And spleen stiffness was found to have a close correlation with portal pressure. Even though MRE has some technical superiority over Fibroscan (no need an acoustic window, a freely-oriented view field, no sensitivity to body habitus) it is not cost effective, as it is more expensive and time consuming. Also it will only used when the patient is already subjecting to undergo MRI for some other reasons.
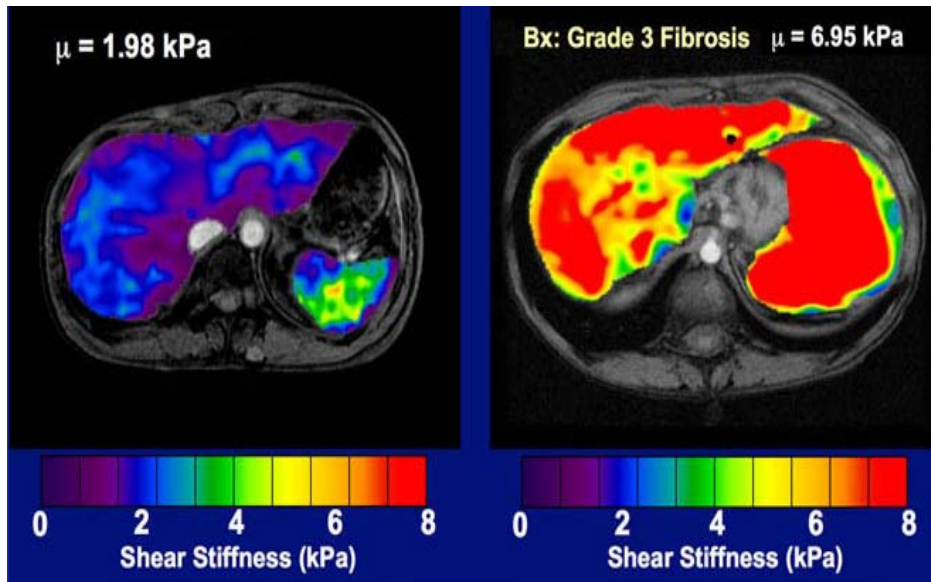
Figure 31: MR Elastography-An elastrogram of a healthy patient showing a post processed value of 1.98 kPa corresponding to normal tissue stiffness. An elastogram of the liver of a patient with Grade 3 fibrosis, with a shear stiffness value of 6.95 kPa.

ACOUSTIC RADIATION FORCE IMPULSE IMAGING (ARFI)

ARFI is a recent novel technology that gives information about the elasticity of the tissues *in real-time*. Short duration ($\sim$ 263 μs) acoustic signals are produced and cause the propagation of shear waves which cause minimum displacements within the local tissue. The shear wave velocity (metre per second) is analysed in a little area of the hepatic parenchyma (11 mm long $\times$ 5 mm wide). It has the advantage of being associated with a conventional US system, thereby allowing control of the sampling location within the hepatic parenchyma. Recent meta analysis showed that ARFI can be same accuracy as TE by Fibroscan for evaluating the severity of liver fibrosis and detection of cirrhosis in patients with chronic liver diseases.[78]

HEPATIC VENOUS PRESSURE GRADIENT

HVPG measurement through the internal jugular vein route is the gold standard method to evaluate the presence and grade the severity of portal hypertension. However the fact that it is invasive and more so that it is not available in all centres across the country to assess and to evalaute the progression of the liver diseases has been the main limiting factor for its use as a common practical tool. Also patients are unwilling to subject themselves to an invasive investigation when other non invasive methods are available and they can get a fairly a rough estimate of the severity of the liver disease. This is even more important when the procedure needs to be repeated to monitor treatment response. These problems have created more interest to non-invasively estimate when CSPH is present, so allowing defining the patient population who are prone for developing portal hypertension-related complications.
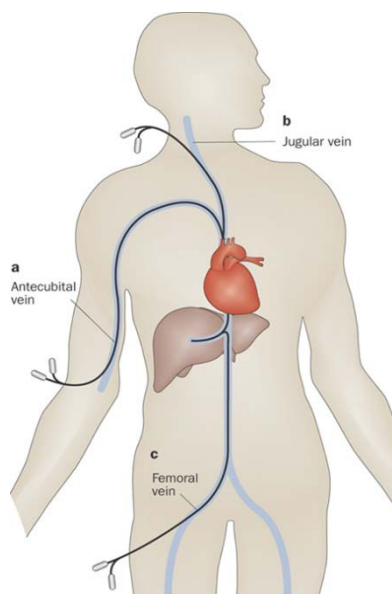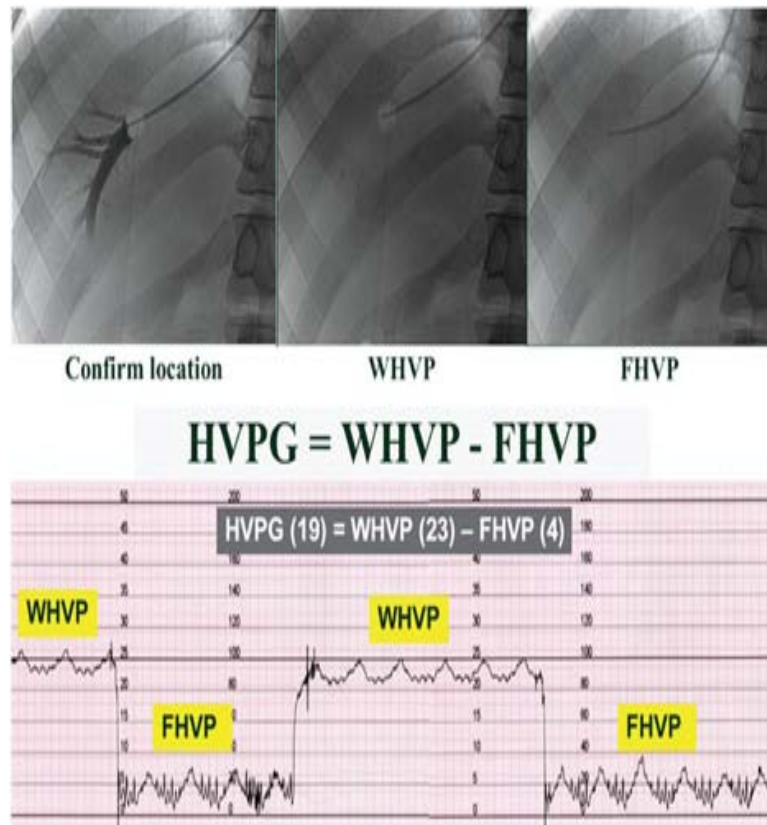
Figure 32: **Schematic diagram showing the procedure of measuring HVPG and their readings.**

RECENT ADVANCES - MRI IN ASSESSMENT OF CIRRHOSIS AND PORTAL HYPERTENSION

Recently, various MR imaging based techniques have been evaluated in assessment of hepatic fibrosis, including conventional contrast MR imaging, including double contrast-enhanced MR imaging, MR perfusion imaging, diffusion-weighted imaging and MR spectroscopy.[79-81]
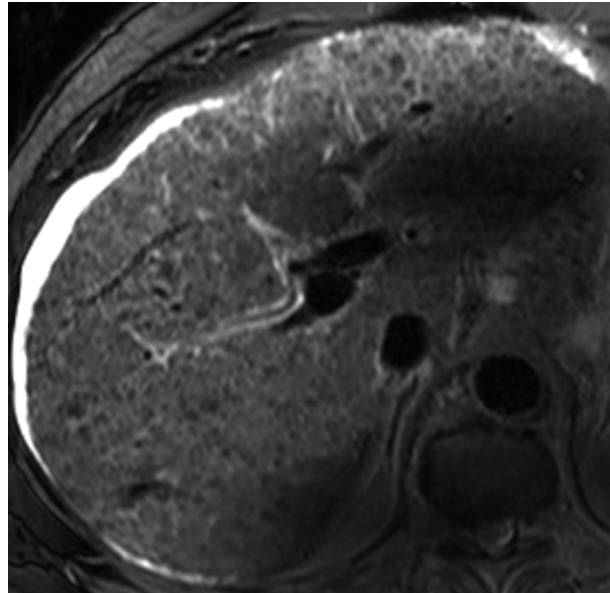
Figure 33: Fat suppressed axial T2W FSE image showing diffuse reticular network throughout the liver, indicating fibrosis

DIFFUSION-WEIGHTED IMAGING

Diffusion is random movement of water protons and the process by which water protons moves in space is called BROWNIAN MOTION.[82]
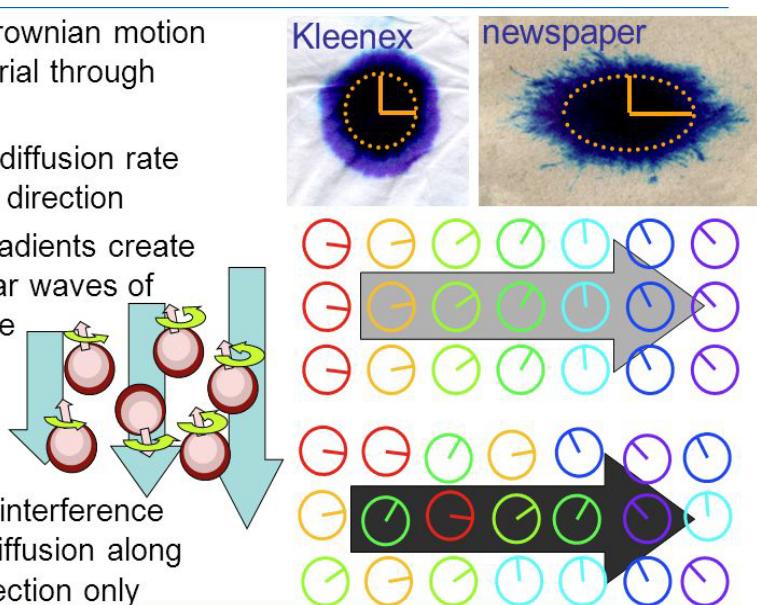
Figure 34: Showing the mechanism of diffusion weighted imaging.

Diffusion-weighted imaging helps in assessing the diffusion of protons within local tissue by application of various motion sensitizing gradients that cause the diffusing protons to lose signal. This signal loss is quantified and it is affected by two variables.

1. Influenced by the strength of the diffusion weighting b value of the sequence is the diffusion sensitivity parameter and

2. The ability of the protons to diffuse through the local tissue.
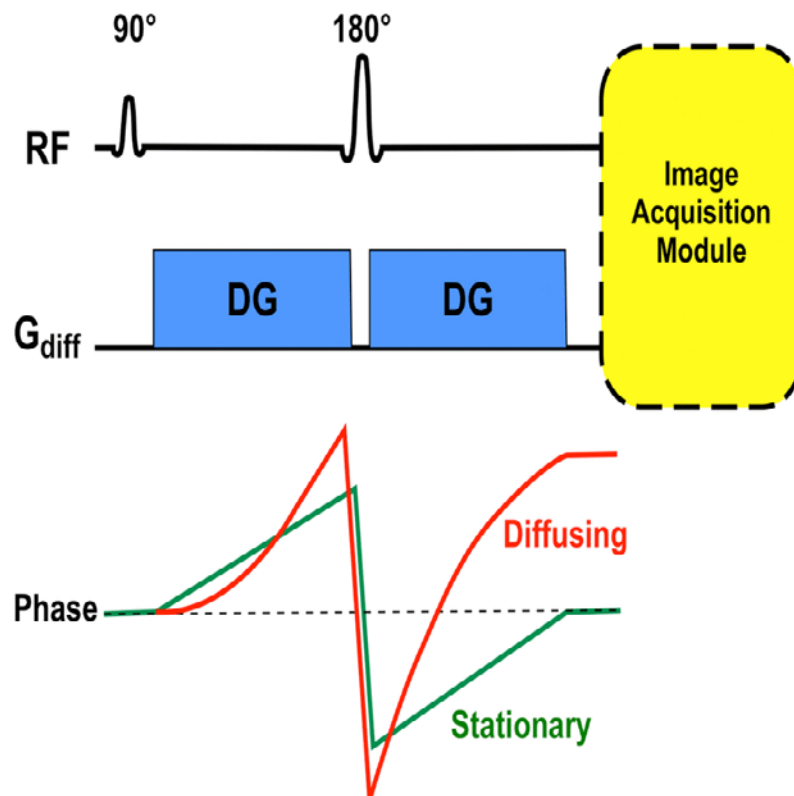
Figure 35: The basis of current diffusion-weighted imaging-The Stejskal-Tanner technique.

Until recently, higher quality liver DWI was not attainable because of the relatively short T2 of the liver. Also the unavoidable physiologic motion in the abdomen, the susceptibility effects, and other factors. However, the recent implements of high performance gradients and parallel imaging, the image acquisition has improved tremendous, increasing the quality of diffusion-weighted imaging of the liver.

In view of its efficacy in evaluating the changes in the brain density and the different pathologies, initially DWI was applied as an experimental study in the assessment of hepatic fibrosis. A central background behind use of diffusion weighted imaging for this purpose is that water diffusion is restricted by fibrosis. However, till date hepatic DWI was not to achieve a good image quality has not achieved sufficient image quality to permit direct visualization of fibrosis, and interpretation relies on estimation of the ADC.[83]

APPARENT DIFFUSION COEFFICIENT

ADC is a measure of diffusion. It is calculated from b-value zero and higher b-values. Diffusion restricted areas appears bright on diffusion weighted images and dark areas on ADC maps. The ADC is calculated by analysing the signal lost between the two images obtained with various b values. Atleast two b values are needed to see the difference. However most of the units have used three or more b values. In the calculation leverage was given for the decay due to Monoexponentiality. The directional vector of the motion-sensitizing gradient has no influence on the images, and anisotropy was not seen yet. [84]
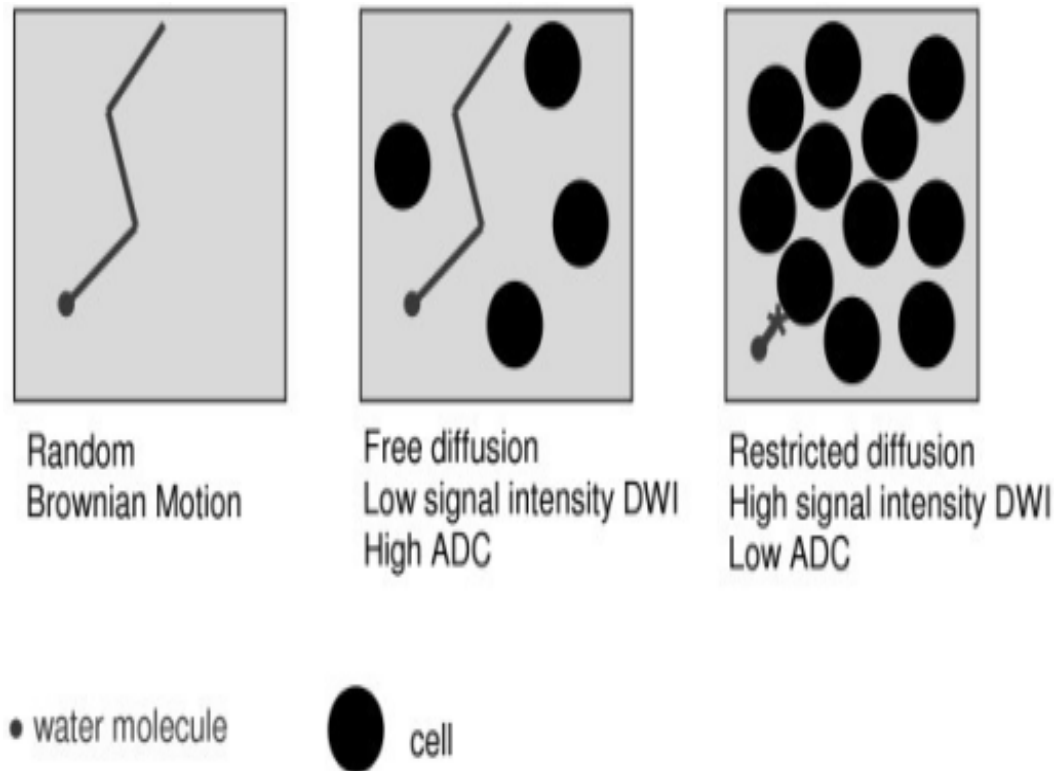
Figure 36: Illustration of the free and restricted diffusion of water in different tissues.

Initial DWI studies on the liver used fat-suppressed DWI sequence which revealed decreased ADC in cases of chronic liver disease compared to other causes. This paid the way for development of various technique and protocol for staging the chronic liver disease by finding the different stages of fibrosis. However, initial studies with few number of patients and hardware and sequencing issues showed inconsistent results for staging liver fibrosis with diffusion-weighted imaging.
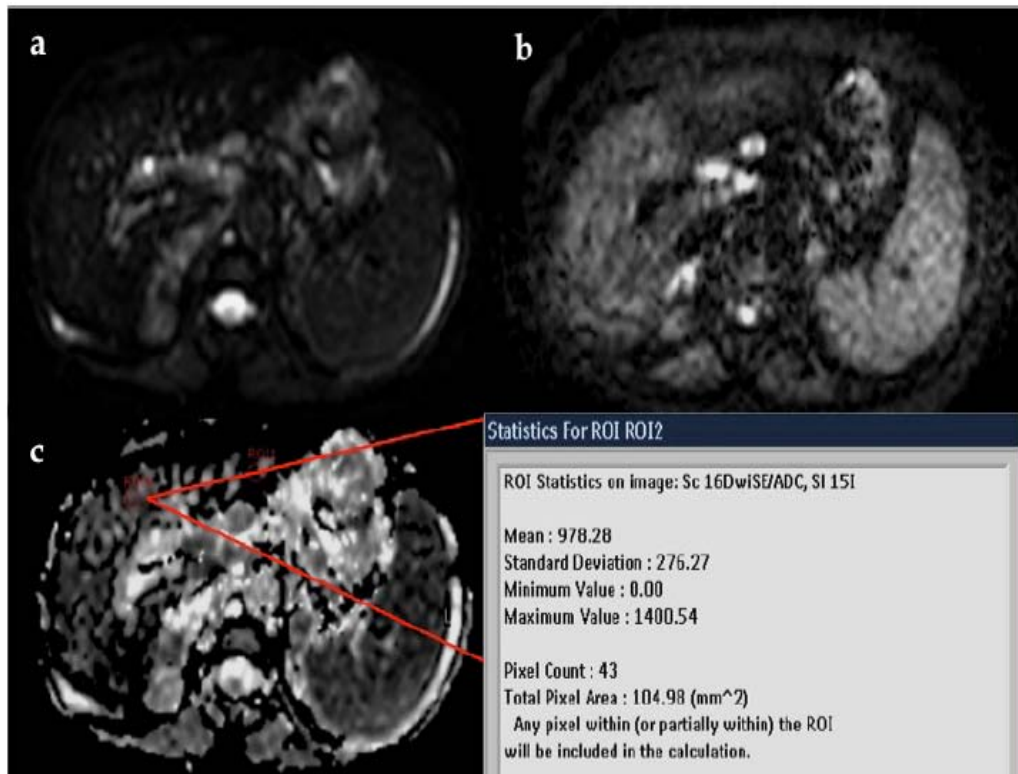
Figure 37: A patient with hepatitis C and related stage III fibrosis. DWI obtained with b value of 0 (a) and 800 (b) s/mm2 and ADC map (c) are shown. Mean ADC value was 0.98 $\times$ 10−3 mm2/s.

There are several challenges in use of diffusion as a surrogate marker for fibrosis. Interpretation of the ADC is complex because there are several potential confounding factors, including perfusion effects, hepatic steatosis, hepatic iron, and liver inflammation.[85, 86] In addition, despite technical improvements in diffusion-weighted imaging, the method remains sensitive to susceptibility and motion-related artifacts, and it is difficult to obtain images with sufficient quality for reliable quantitative analysis on a consistent basis. More important, the ADC depends on imaging parameters. Field strength, repetition time, echo

time, and b values all affect the ADC. The manner in which a particular b value is achieved is also relevant. The b value indicates magnitude of diffusion weighting. It is expressed in sec/cm. It is determined by the gradient strength, gradient duration, and gradient separation. Different combinations of gradient strength, gradient duration, and gradient separation may achieve the same b value but yield dissimilar ADC measurements. In general, for a fixed b value, increasing the gradient separation reduces the ADC. Because technical factors lead to differences in estimated ADC, reported ADCs are variable, with considerable overlap between normal and abnormal ranges . Thus, there is a need to develop site- and technique-specific normal ranges and to standardize methods across imaging centers.
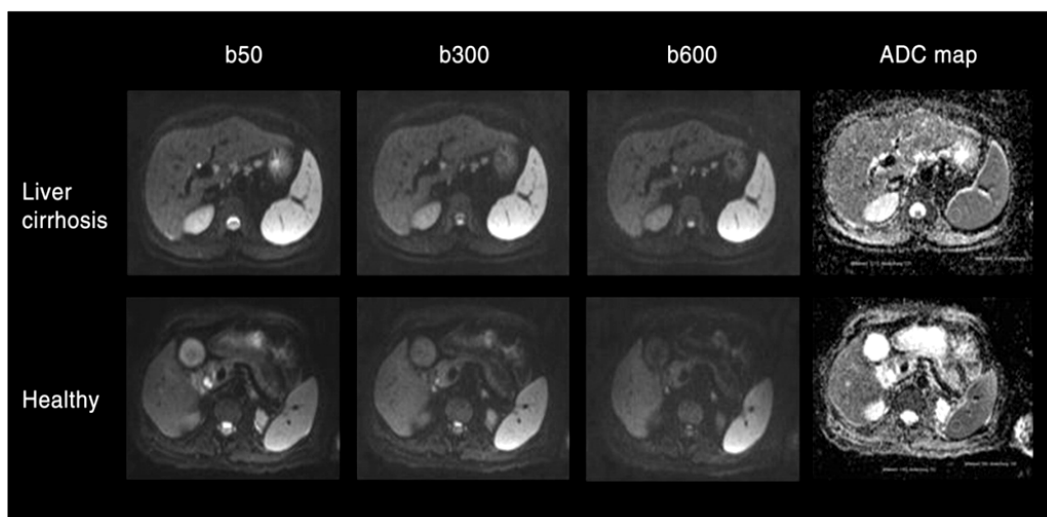
Figure 38: Axial echo planar diffusion-weighted images with different b values and ADC mapping in healthy and cirrhotic patients

ADC LIVER AND LIVER FIBROSIS STAGE

Recent studies have shown that the liver ADC value of patients with liver fibrosis is lower than that of healthy subjects.[8] It has been suggested that this decrease in the ADC value can be explained by the accumulation of glycosaminoglycane, proteoglycane and collagen fibres in the liver resulting in restricted water molecule diffusion with liver fibrosis. In a study by Koinuma et al. using 128 s/mm^2 b value, a significant negative correlation was found between ADC and fibrosis score. The most limiting factor of this study is that the b value is low.

The hepatic mean ADC value of patients at different stages of chronic liver disease was found to be low compared to that of healthy individuals in a study by Talwalkar et al. [85] Bakan et al. found that ADC values decreased as the fibrosis stage increased. However, there were no statistically significant differences in terms of the mean liver ADC values between stages 0 and 1 and stages1 and 2. [87]Though DWI was helpful in differentiation of later fibrosis stages and intermediate fibrosis stages, DWI was not reliable in discriminating between early fibrosis stages. This situation can be explained by the localisation and small amount of fibrosis in F1 and F2 groups. In chronic hepatitis, fibrosis starts in the portal areas so in F1 and F2. In F3, the bridging fibrosis which connects the portal tracts are the parenchymal distortion first detected.
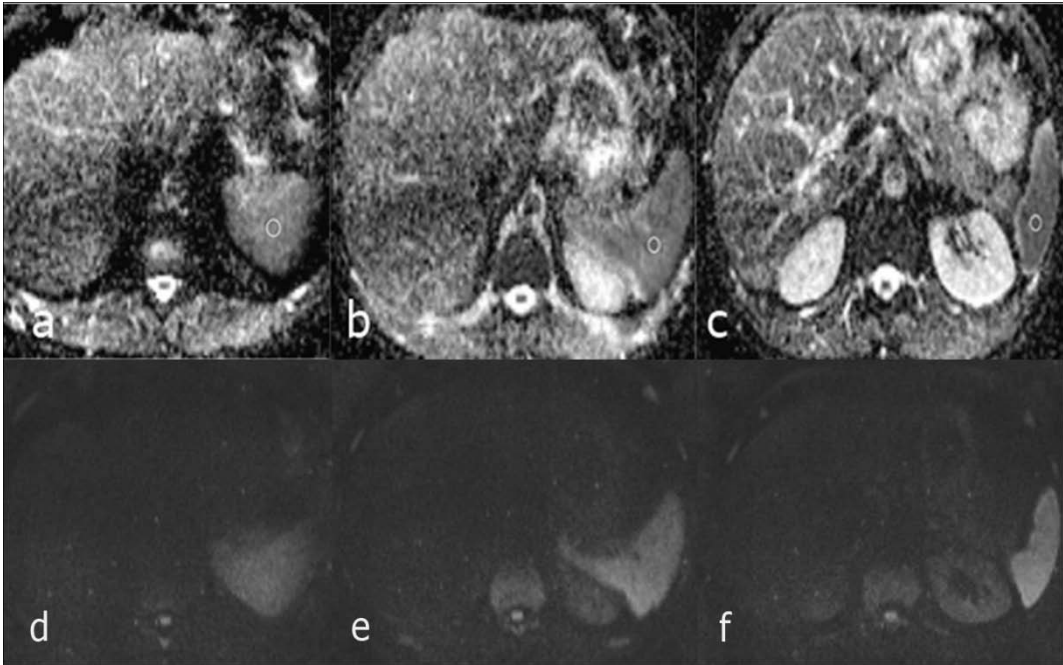
Figure 39: (a–c) MRI upper abdominal ADC mapping images of cirrhotic patient with stage F3 fibrosis. (d–f) DWI images at same sections.

MATERIALS AND METHODS

Study design - Prospective Observational

Sampling - Simple random sampling

Place of Study

Rajiv Gandhi Government General Hospital, Madras Medical College.

Duration of Study

June 2014 to September 2014.

Inclusion Criteria

Case

- Patients admitted with cirrhosis of various etiology were evaluated

- Age > 20 yrs was evaluated.

Control

- Patients with normal liver function test.

- No history of chronic or acute liver disease.

Exclusion criteria

- Patients taking treatment for portal hypertension

- Absolute contraindication to MRI

- Patient refusing MRI

Study Methodology

This prospective study was performed after obtaining clearance from our institutional ethical committee.

As this study is the first of its kind done on portal hypertension patients, we initially planned to find out any difference and the characteristics of the MRI spleen findings of chronic liver disease / cirrhosis patients compared to a control group with no liver disorders.

Patients admitted with clinical and examination findings of chronic liver disease/ cirrhosis were evaluated with detailed history and clinical examination involving the symptoms of cirrhosis like gastrointestinal bleeding, index bleed, ascites, therapeutic paracentesis and hepatic encephalopathy along with the etiology of cirrhosis. Their investigations were reviewed to confirm the etiology, evidence of hypersplenism (hemoglobin,white blood cell count and platelet count), Child Pugh's status and Model for End stage Liver Disease (MELD) score (Serum bilirubin in mgms%, serum albumin in gms%, serum creatinine in mgms%, International normalized ratio (INR)) to assess the severity of chronic liver disease. Upper gastrointestinal endoscopy findings of the patient done at the initial visit or the highest grade of the esophageal varices were noted along with USG abdomen findings of the size and echotexture of the liver along with spleen size, portal vein diameter and grade of ascites (no/moderate/ severe). Patients undergoing treatment for portal hypertension were not evaluated as this might be an confounding variable on the ADC value. Finally the patients were subjected for MRI examination after informed consent. The protocol will be as follows:

Using 1.5 tesla, diffusion weighted imaging/opposed / inphase imaging was performed in cirrhotic and control patients.

1. b value of 0, 300, 500 are used. Time to repeat (TR) of 100 millisecond(ms) and Time to echo (TE) of 2.1ms for opposed phase and 4.2 ms for inphase were used. Slice thickness of 5mm, matrix size of 256*256 are used.).

2. ADC value of the spleen along with liver was calculated

3. In phase and opposed phase of the liver and spleen was also calculated

For control, patients who undergo MRI abdomen investigation for other reasons with normal liver function test were included and the above mentioned values were calculated.

DEFINITIONS

1. "A diagnosis of Chronic liver disease/cirrhosis was made based on the combination of clinical presentation, doppler findings, and liver function test.

2. Esophageal varices were graded according to Conn's classification.[88]

    - Grade 1 – Small varices, only detectable on performing Valsalva maneuver

    - Grade 2 – Small varices (1-3mm) visible without a valsalva maneuver

    - Grade 3 – Varices of moderate size (4-6mm)

    - Grade 4 – Large varices (> 6mm)"

3. Clinically significant portal hypertension

    "Clinically significant portal hypertension was defined as the presence of either oesophageal or gastric variceal bleed, portal hypertensive gastropathy, or thrombocytopaenia (platelet count <100000/cu.mm) associated with splenomegaly."

4. Child Pugh class of Chronic liver disease

"Child-Pugh Criteria for Hepatic Functional Reserve

Clinical and laboratory measurement	1	2	3
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	None	Mild	Moderate
Bilirubin (mg/dL)	1-2	2.1-3	$\geq$3.1
Albumin (g/dL)	$\geq$3.5	2.8-3.4	$\leq$2.7
Prothrombin time (increase, s)	1-4	4.1-6	$\geq$6.1

Grade A, 5-6; grade B, 7-9; grade C, 10-15

5. MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6 [Ln serum creatinine (mg/dL)] + 6.4 where Ln is the natural logarithm"

6. Hypersplenism [89]

    "It was defined as the presence of splenomegaly with a defect in any one of the peripheral cell lines (anaemia - hemoglobin less than 8 gm/dL with normocytic and normochromic appearance in peripheral smear; a leukocyte count of <3500/mm^3 and a platelet count of <150000/mm^3). "

7. Symptomatic hypersplenism. [90]

    "Symptomatic hypersplenism was defined as requirement of repeated blood transfusions or symptoms of anemia with no obvious cause, recurrent infections, spontaneous bleeding episodes (epistaxis, gum bleed, menorrhagia etc)."

8.   Degree of splenomegaly was classified using Hackett's classification. "Class Findings on palpation

    0.   Spleen not palpable even on deep inspiration

    1.   Spleen palpable below costal margin, usually on deep inspiration.

    2.   Spleen palpable, but not beyond a horizontal line half way between the costal margin and umbilicus, measured in a line dropped vertically from the left nipple.

    3.   Spleen palpable more than half way to umbilicus, but not below a line horizontally running through it.

    4.   Palpable below umbilicus but not below a horizontal line half way between umbilicus and pubic symphysis.

    5.   Extending lower than class 4."

Hackett's classes 1 and 2 were considered as mild splenomegaly, class 3 as moderate splenomegaly, and classes 4 and 5 as massive splenomegaly

9.   Ascites

    Grade 1: mild, only visible on ultrasound and CT

    Grade 2: detectable with flank bulging and shifting dullness

    Grade 3: directly visible, confirmed with the fluid wave/thrill test

10. Hepatic encephalopathy - The severity of hepatic encephalopathy is graded with the "West Haven Criteria[91]

Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction

Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour

Grade 3- Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation

Grade 4- Coma (unresponsive to verbal or noxious stimuli)"

STATISTICAL ANALYSIS

Statistical analysis was done using Graphpad instat ver.3.0.

Student's *t* tests was used in the comparison of numerical variables (mean ages,liver size, spleen size, PV diameter, laboratory values, liver and spleen ADC values) between the patient group and the control group. Differences were considered to be statistically significant at $p < 0.05$.

Mann U Whitney test was used in comparison of different stages of liver fibrosis, Grades of varices, Child Pugh class and MELD grade to the ADC value of the patients.

Chi square test was used in comparison of the ADC value of the patient to different portal hypertension surrogate markers and CSPH.

Mann U Whitney test was performed in the comparison of mean ADC values of the patients at different stages (non parametric variables) and the control group. Differences were considered to be statistically significant at $p < 0.05$

RESULTS

MRI SPLEEN - CONTROL VS CHRONIC LIVER DISEASE PATIENTS

We initially compared 15 patients from each group (case and control) to analyse the difference in MRI findings of the spleen in DWI. The 15 control patients were selected ruling out any liver pathology in them by clinical, biochemical and imaging findings.

We analysed the demographics of both group and found both group to be matched with no significant difference between the age and sex of the patients. Table.1

Table 1: Demographics of the matched case and control group

Variable	Case (15)	Control (15)	P value
Age (yrs)	43 (32-60)	42 (22-59)	0.9
M:F	12:3	10:5	0.6

CHARACTERISTICS OF THE CHRONIC LIVER DISEASE PATIENTS

We analysed 15 chronic liver disease patients, of which most of them are Child Pugh class A patients (7), with alcohol as the predominant etiology. 10 out of the 15 were GI bleeders and eight of them had hypersplenism (Table.2)

Table . 2 – Characteristics of the case group.

VARIABLE	
Child's Pugh status (A:B:C)	**7:5:3**
Etiology	**Alcohol- 7** **Viral = 5** **NASH- 2** **Cryptogenic- 1**
History of GI bleed	**Bleeder- 10/15**
History of hypersplenism	**8/ 15**

NASH – Non alcoholic steatohepatitis, GI- Gastrointestinal

COMPARISION OF THE CHARACTERISTICS OF CASE AND CONTROL GROUP

When the clinical and biochemical parameters were compared between the two groups, there were significant differences in parameters of chronic liver disease like hypersplenic features, liver span, spleen span and serum bilirubin, serum creatinine and INR (Table.3)

Table.3- Comparision of the clinical and biochemical parameters

VARIABLES	Case (15)	Control (15)	p value
Hemoglobin (gm/dL)	8.4 ±2	11.9 ± 1.3	0.04
WBC (cu.mm)	5120 ±1392	6710 ± 1151	0.12
Platelet count (cu.mm)	102000 ± 25000	316000 ± 11200	0.016
Liver size (cm)	10.4± 2.4	13.2 ± 0.5	0.01
Spleen size (cm)	15.6 ± 2.4	9 ± 0.7	0.01
Portal vein diameter(mm)	13.7 ± 1.1	9.3 ± 0.4	0.04
Serum Bilirubin (mg/dL)	5.6 ± 2.3	0.74 ± 0.7	0.001
INR	1.7 ± 0.5	1.04 ± 0.1	0.02
Serum creatinine	1.2 ± 0.5	0.79 ± 0.4	0.04

INR- International normalized ratio, WBC – white blood count (cu.mm)

ADC CHARACTERISTICS OF THE SPLEEN AND LIVER

When the ADC value of the spleen and liver was analysed between the case and control group, we found significant difference in the ADC values. ADC value of the spleen increased (117.4 ± 28.4 Vs 80.7 ± 9.1, *p=0.04)* significantly in chronic liver disease patients whereas ADC value of the liver significantly decreased (107.2 ± 41.8 Vs 338.9 ± 31.1, *p=0.001)*   in the case group. We also analysed the Inphase and Oppose phase of the liver and spleen and found significant difference between both groups.

Table : 4 ADC spleen and Liver (mm2/s)– Case Vs Control

VARIABLES	Case (15)	Control (15)	*p* value
ADC LIVER(mm^2/s)	107.2 ± 41.8	338.9 ± 31.1	0.001
ADC SPLEEN(mm^2/s)	117.4 ± 28.4	80.7 ± 9.1	0.04
Inphase Liver	131.1 ±54.3	206 ± 11.3	0.001
Inphase spleen	78.7 ± 21.1	148.3 ± 13.9	0.02
Oppose Liver	124.2 ± 46.7	205.8 ± 28.9	0.01
Oppose spleen	70.1 ± 21.5	157.8 ± 9.3	0.03

ADC SPLEEN AND CHRONIC LIVER DISEASE

We analysed the 51 chronic liver disease patients managed in our hospital from July 2014 - September 2014. Their clinical and biochemical parameters were analysed with their imaging findings and after informed consent underwent DWI of the abdomen.(Figure.1)

Figure 1: Etiology of the 51 chronic liver disease patients
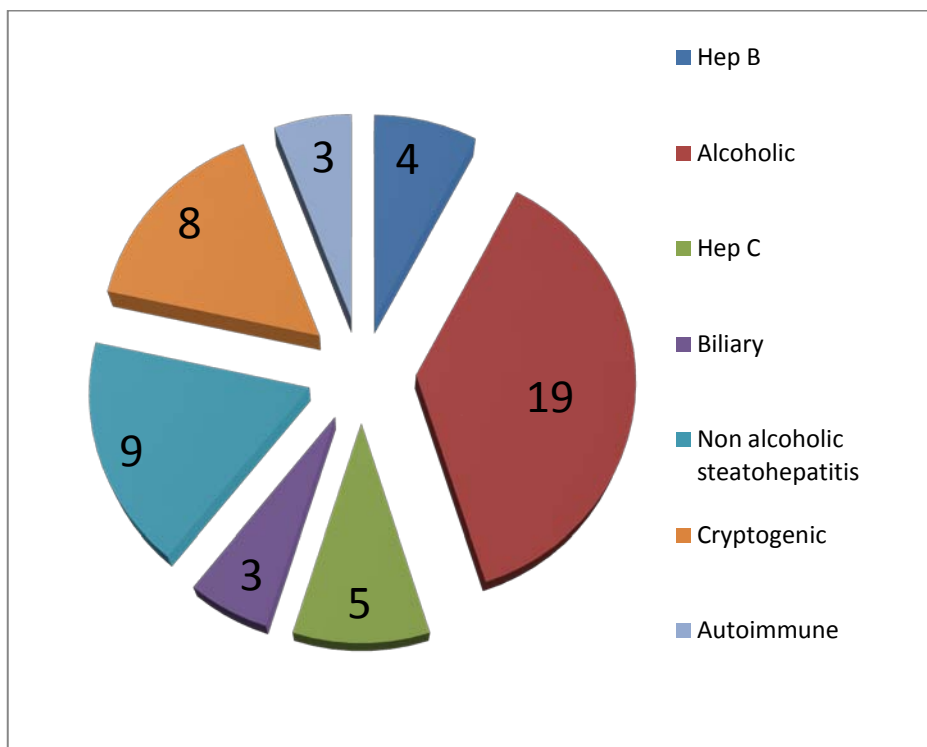
DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF THE PATIENTS

Out of the 51 chronic liver disease patients, most of them belong to Child Pugh's class A (29/51) status with 9 patients of Child's class C status. Their mean age was 49.6 ± 12.3 with 38 of them males. (Figure.2)

Figure 2: Child Pugh class of the 51 patients
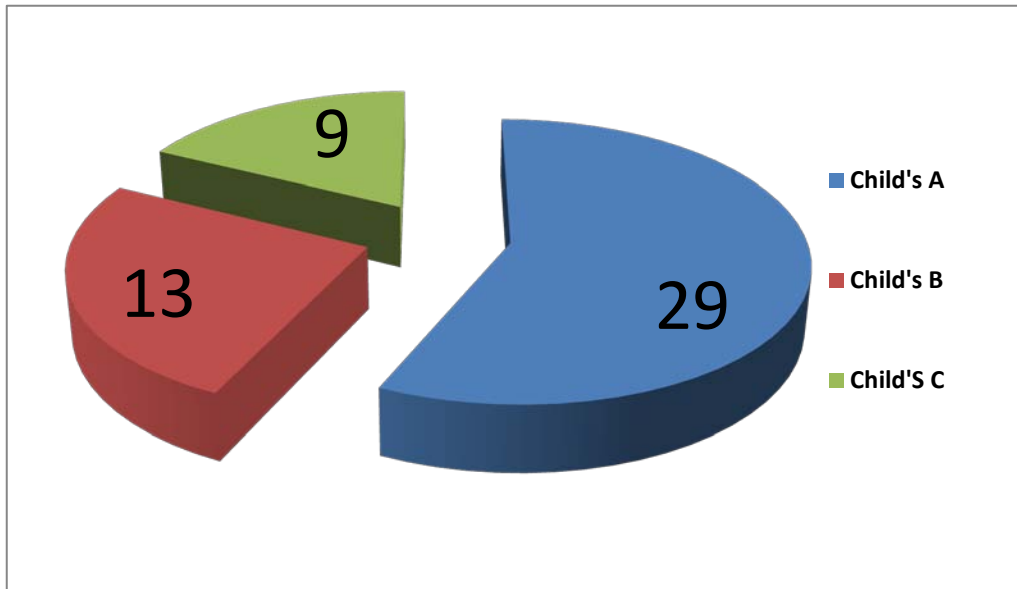
Figure 3: X Y scatter diagram of the age distribution in the CLD patients
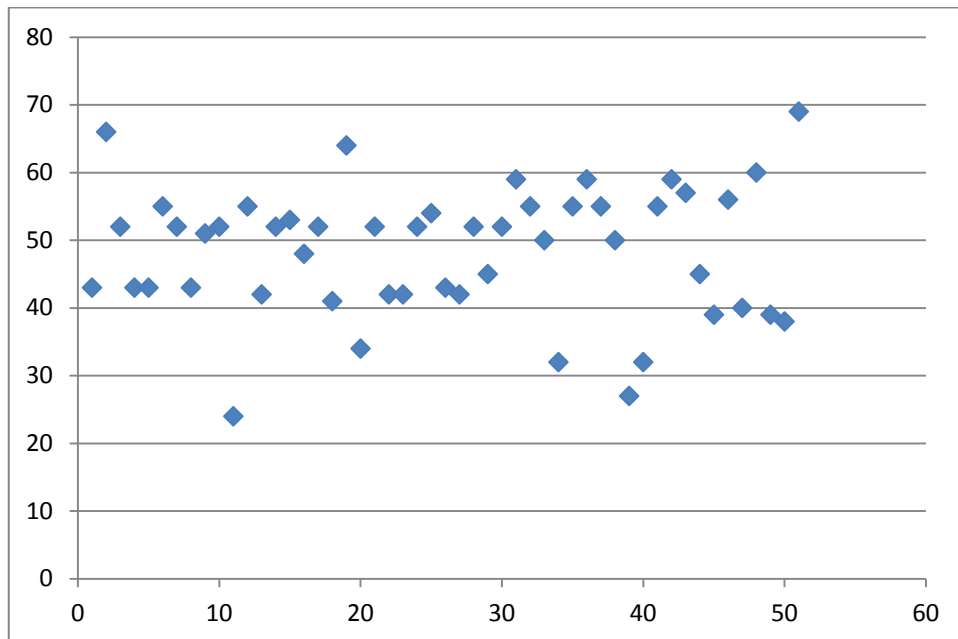
Figure 4: Sex distribution of the CLD patients
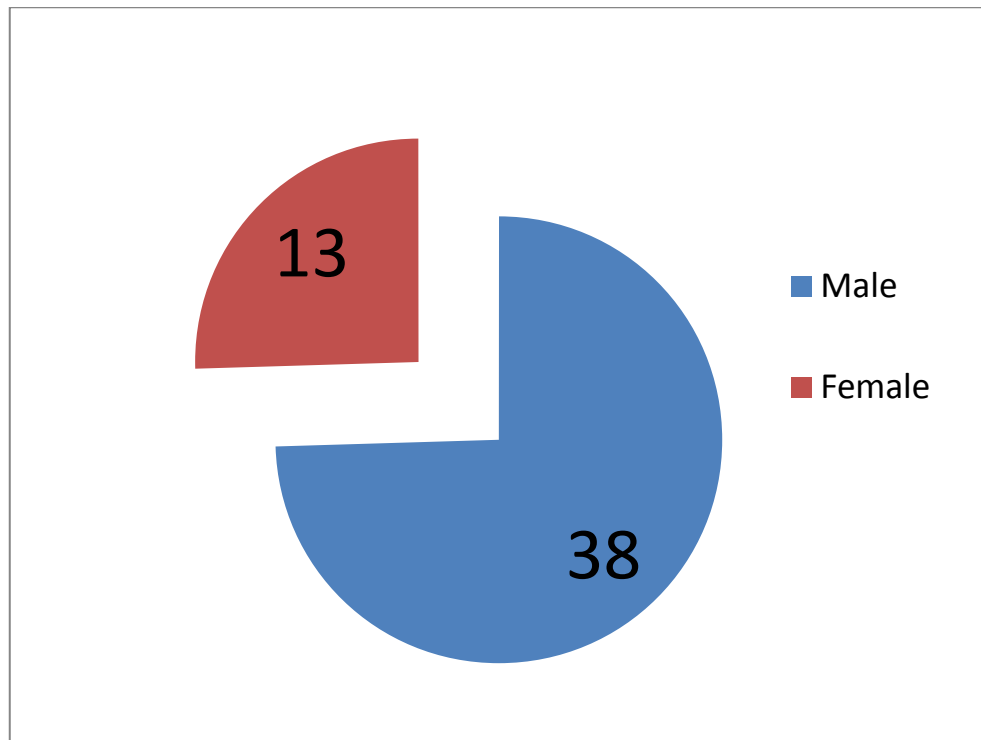
CLINICAL and BIOCHEMICAL CHARACTERISTICS OF THE CLD PATIENTS

All 51 patients were reviewed of their medical history and their biochemical parameters were analysed. Since 29 patients belong to Child's A status, there were no ascites in any of them. Most of them had hypersplenism with their mean hemoglobin of 8.42 ± 2.1gms%, WBC count of 5820 ± 1720/ cu.mm and platelet count of 100313 ± 25189 / cu.mm. Out of the 51 patients, 32 patients were bleeders with 4 patients having grade 4 varices. Their median MELD score 11.

Table 5: Clinical and biochemical characteristics of the CLD patients

VARIABLES	Value
Esophageal varices Grade 1-4	16/15/15/4
Hemoglobin(gms%)	8.42 ± 2.1
WBC(cu.mm)	5820 ± 1720
Platelet count(cu.mm)	100313 ± 25189
Liver span(cms)	9.79 ± 2.37
Spleen size(cms)	15.4 ± 2.32
Portal vein diameter(cms)	1.35 ± 0.1
Splenomegaly No: Mild: Moderate: Severe	9: 22:15:5
Ascites No:Mild: Moderate: Severe	29:4:13:5
Se.Bilirubin(mg%)	3.5 ± 1.6
Se.Creatinine (mg%)	1.1 ± 1.3
INR	1.35 ± 0.9
Se.Albumin(gm/dL)	2.8 ± 1.2

PORTAL HYPERTENSION FEATURES OF THE CLD PATIENTS

We also analysed the portal hypertensive surrogate features of these 51 patients and found that most of them are hypersplenic (42/51= 82%) with 37% of them are symptomatic hypersplenism. Only 10 patients have suffered mild grade of encephalopathy.

Table 6: Portal hypertensive features of the CLD patients

VARIABLES	Yes	No
History of GI bleed	32	19
Hypersplenism	42	9
Symptomatic Hypersplenism	19	32
Hepatic encephalopathy	8	43
Controlled ascites	38	13

ADC OF THE SPLEEN WITH SEVERITY OF PORTAL HYPERTENSION

We analyzed the ADC mapping of the spleen for the 51 patients and compared it between the 39 patients who had clinically significant portal hypertension (CSPH) to the group of 12 patients who had no CSPH. We found the ADC value of the spleen was significantly higher (125.2 ± 29.6 vs 84.1 ±1.6, p value=0.05) in the CSPH group, however the ADC value of the liver is non significantly lower (84.1 ±1.6 vs 125.2 ± 29.6, p value=0.09) in the CSPH group compared to the non CSPH group.

Table 7 : Correlation between ADC value of spleen/ Liver to Clinically significant Portal hypertension

VARIABLE	ADC spleen (mm2/s)	ADC Liver (mm2/s)
CSPH (39)	125.2 ± 29.6	89.2 ± 20.1
NO CSPH (12)	84.1 ±1.6	134.3 ± 11.4
p value	0.05	0.09

ADC OF THE SPLEEN AND PORTAL HYPERTENSION SURROGATE MARKERS

We also analysed the ADC value of the spleen with the different portal hypertension surrogate markers and found that though ADC of the spleen were non significantly higher in the presence of increased severity of portal hypertension, it is the esophageal varices>grade 2 and symptomatic hypersplenism which had significantly higher spleen ADC compared to the other group. Chi square test was used for the analysis.

Table 8: ADC of the spleen and portal hypertension surrogate markers

Portal hypertension surrogates	ADC spleen (mm2/s)	p Value
Bleeder (32) Vs non bleeder (19)	120.2 ± 29.6 Vs 86.1 ±1.6	0.06
Grade of varices (<=2 Vs > 2)	93.1 ± 9.9 Vs 126.6 ± 20.2	0.04
Symptomatic hypersplenism (19 Vs 32)	123.3 ± 23.1 Vs 90.2 ± 11.3	0.02
PV diameter (<= 13mm Vs > 13 mm)	112.3 ± 23.1 Vs 123.3 ± 8.9	0.12
Splenomegaly (<= 13cm Vs > 13cm)	109.5± 9.1 Vs 123.4 ± 7.8	0.23

ADC SPLEEN/LIVER VS SEVERITY OF CHRONIC LIVER DISEASE

As evaluated in the past studies, we also analysed the ADC value of the spleen and liver for different Child Pugh's class patients and found that as the severity of the Child class worsens, the ADC value of the liver decreased (140.1 ± 13.4 vs 120.2 ± 11.3 vs 82.0 ± 9.3, *p value = 0.05*) which was statistically significant. However, though the ADC of the spleen increased proportionately to the Child Pugh status (85.9 ± 9.4 vs 101.4 ± 11.4 vs 121.6 ± 14.2, *p value =0.12*) , it was not statistically significant.

Table 9: ADC Spleen / Liver Vs Severity of chronic liver disease

Child Pughs Class	ADC LIVER (mm^2/s)	ADC SPLEEN (mm^2/s)
A	140.1 ± 13.4	85.9 ± 9.4
B	120.2 ± 11.3	101.4 ± 11.4
C	82.0 ± 9.3	121.6 ± 14.2
p value	0.05	0.12

ADC SPLEEN / LIVER Vs Model for End Stage Liver Diseases (MELD)

We in addition analysed the ADC value of the spleen and liver to different levels of MELD score and again found that the ADC value of the liver significantly decreased(135.1 ± 11.4 vs 113.2 ± 16.3 vs 83.9 ± 10.3, p value = 0.04) according to the increasing MELD score. Here also the ADC of the spleen was non significantly increasing (89.9 ± 9.4 vs 99.4 ± 11.4 vs 127.6 ± 14.2, p value = 0.09) to the increasing MELD score.

Table 10: ADC SPLEEN/LIVER Vs MELD

MELD	ADC Liver (mm2/s)	ADC Spleen (mm2/s)
> 15	135.1 ± 11.4	89.9 ± 9.4
16 - 25	113.2 ± 16.3	99.4 ± 11.4
>25	83.9 ± 10.3	127.6 ± 14.2
p value	0.04	0.09

ADC SPLEEN / LIVER AND LIVER FIBROSIS SCORE

We could retrieve the liver biopsy findings from 10 out of the 51 patients and found atleast one patients in every grade of fibrosis. Though the numbers were very small for analysis, we found that ADC of the liver decreased (135.1 ± 11.4 vs 113.2 ± 16.3 vs 100.3 ± 12.3 vs 83.9 ± 10.3) according to increasing severity of the grade of fibrosis.

Table 11: ADC spleen / liver and liver fibrosis score

Fibrosis score	ADC Liver (mm2/s)	ADC Spleen (mm2/s)
F1	135.1 ± 11.4	89.9 ± 9.4
F2	113.2 ± 16.3	99.4 ± 11.4
F3	100.3 ± 12.3	111.3 ± 10.4
F4	83.9 ± 10.3	127.6 ± 14.2

MRI CORONAL IMAGING OF A NORMAL LIVER PATIENT

MRI ABDOMEN (BOTH T1W AND T2W) IMAGES SHOWING NORMAL SPLEEN

T1Weighted – Normal spleen hypointense than the liver

T2 Weighted – Normal spleen hyperintense than the liver

DWI AND ADC MAPPING OF A NORMAL STUDY

ADC SPLEEN IS 72.5 MM2/S AND ADC LIVER IS 290.2 MM2/S
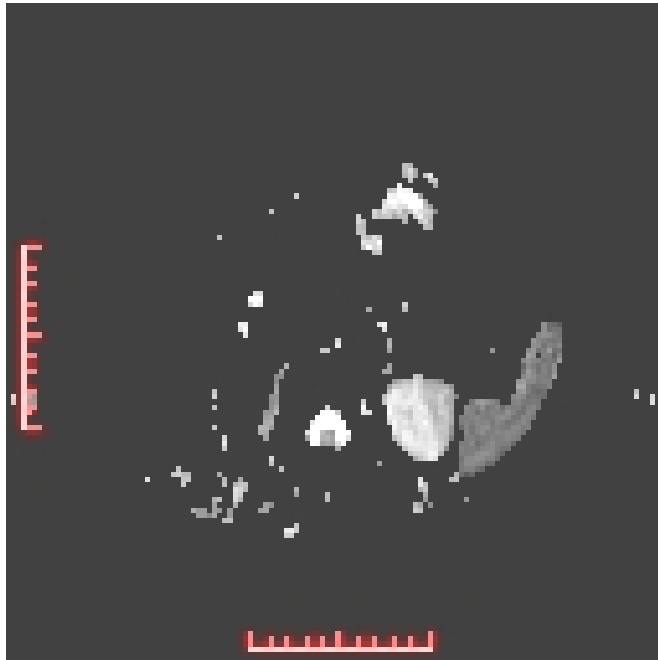
MRI SHOWING THE FEATURES OF CIRRHOSIS
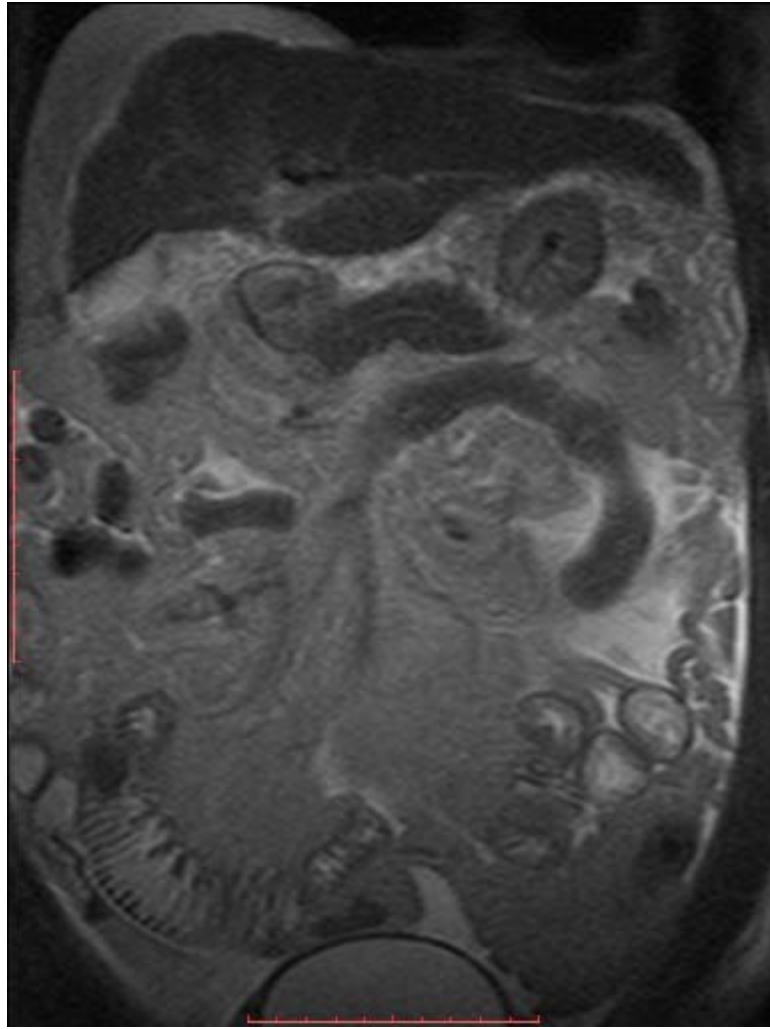
MRI T2W CORONAL FSP IMAGE OF A F3 FIBROTIC LIVER PATIENT SHOWING GROSS SPLENOMEGALY
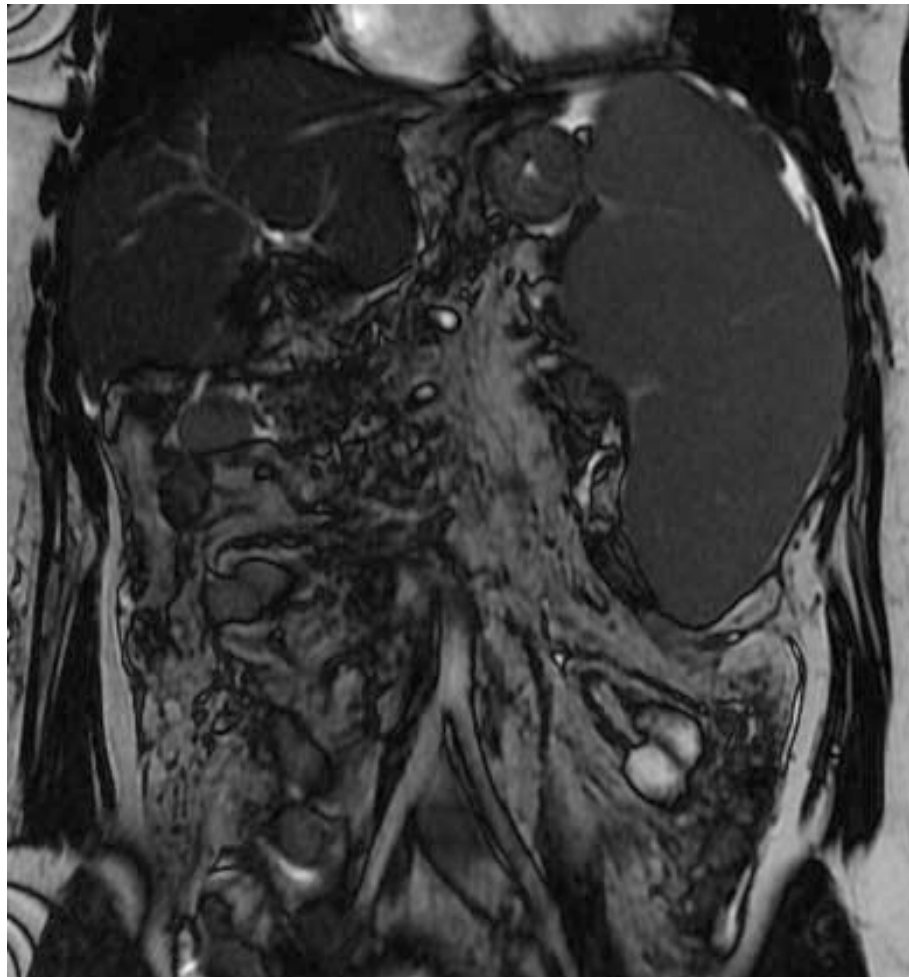
DWI AND ADC MAPPING OF A CIRRHOTIC PATIENT

SPLEEN ADC OF 167.8 mm^2/S

CHILD C CIRRHOSIS
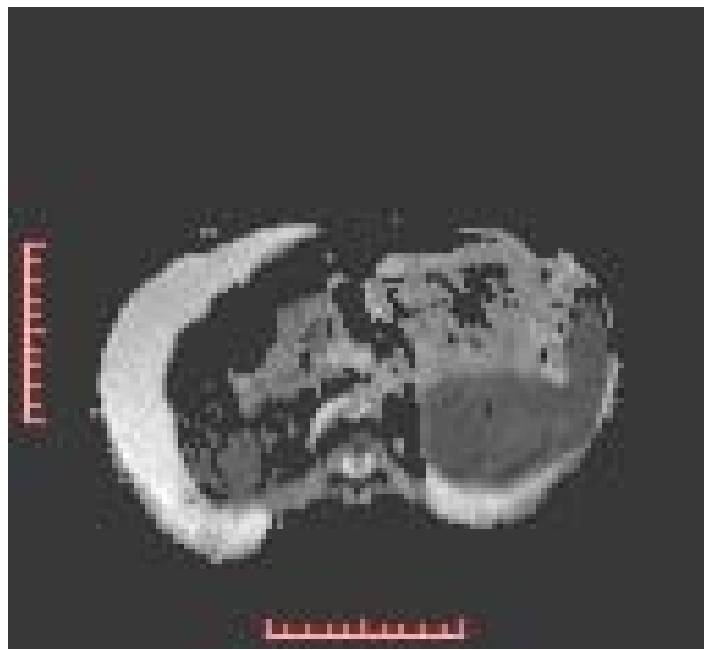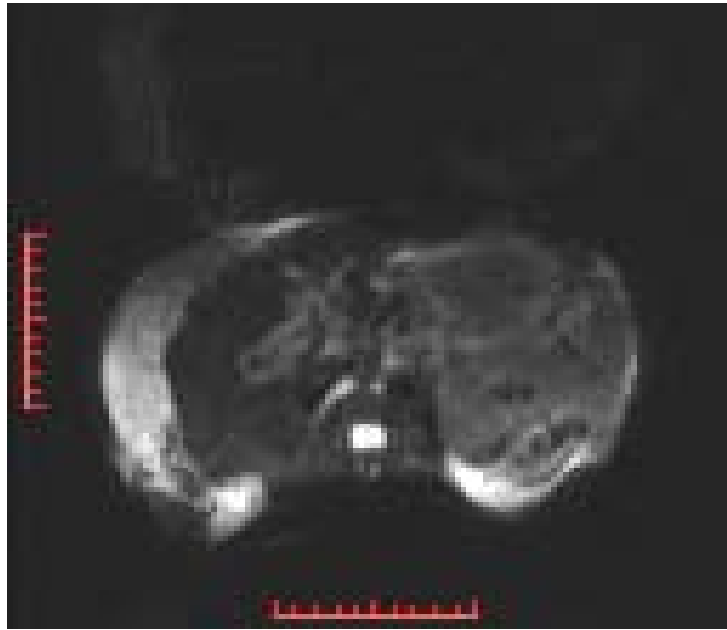
DWI AND ADC MAPPING OF CIRRHOTIC PATIENT

SPLEEN ADC OF 120.2 mm^2/S

CHILD'B CIRRHOSIS
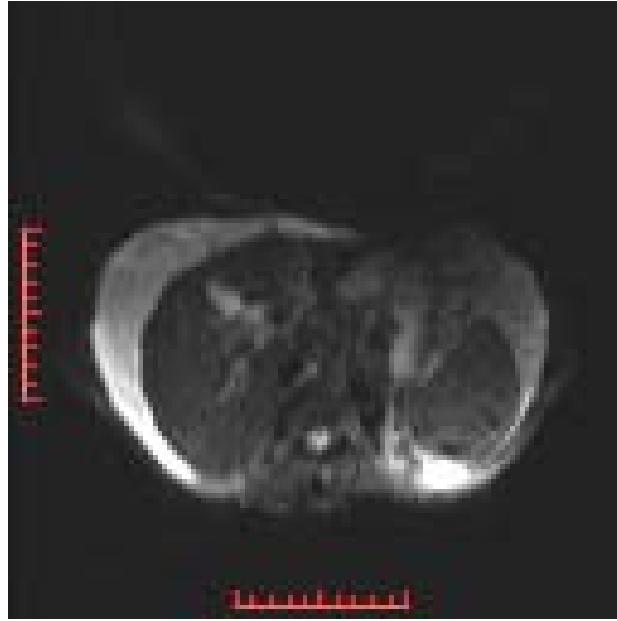
DWI AND ADC MAPPING OF A CIRRHOTIC PATIENT

SPLEEN ADC OF 89.5 mm^2/S

CHILD'S A CIRRHOSIS
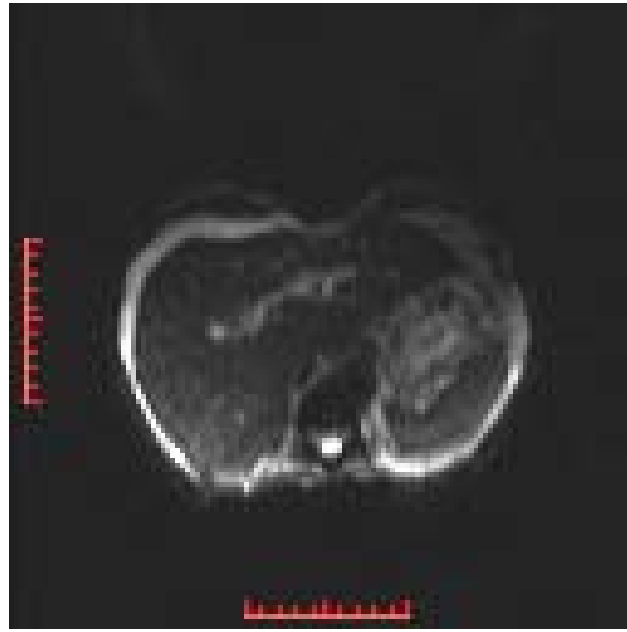
DISCUSSION

DWI has been used extensively in chronic liver disease patients and liver ADC has been found to be a useful adjunct in predicting the degree of fibrosis especially in patients with viral etiology. This is due to the reduced perfusion in a fibrotic liver and the degree of ADC reduction implies the severity of fibrosis in the liver. Similarly, cirrhosis is a state of hyperdynamic circulation and in view of portal hypertension, there is a splanchnic hyperemia. This splanchnic hyperemia is assessed in our study by taking spleen as the representative organ of the splanchnic circulation.

In our study, we found that when compared to normal patients, Liver ADC is significantly reduced in chronic liver disease patients. A growing body of literature had demonstrated that the ADC of cirrhotic livers is significantly lower than that of normal livers.[8, 92-97] In current study, we confirmed this results, as we found that the mean liver ADC value in patients with hepatic fibrosis was significantly lower than that of volunteers (1.59 · 103 mm2/s vs. 1.67 · 103 mm2/s, p =0.01). This can be attributed to the presence of fibrous tissue. The main component of fibrous tissue is collagen that associated with restricted diffusion and subsequent diminished ADC values. However we also found that found that spleen ADC is significantly increased in patients with chronic liver disease correlating to their splanchnic hyperemia. However this is in contradiction to the earlier reports except the one by Klasen who found that the negative correlation between spleen and liver ADC in cirrhosis patients.[7] In chronic liver disease patients, ADC liver decreases due to liver fibrosis and spleen ADC increases in view of splanchnic hyperemia.

Normalization of ADC using a reference organ which remains relatively constant among patients have been used in earlier studies to aid in reduction of ADC calculation variability.[8, 12, 95, 98] Earlier studies used spleen as a reliable internal standard wherever quantitative analysis using ratios is required as in assessing degree of signal intensity loss in adrenal masses in MRI. However the same spleen was used for normalization in studies which correlated liver fibrosis with liver ADC. Our study has proven the negative correlation between the ADC of liver and spleen in chronic liver disease and this suggest that spleen cannot be taken as a reference organ in chronic liver disease patients and this might have confounding influence on the results.

Though earlier studies have used spleen ADC as a reference organ and one recent study correlated spleen ADC with severity of chronic liver disease, our study is the first to correlate spleen ADC to the severity of portal hypertension in chronic liver disease patients. On analysis, we found a significant correlation to the CSPH to the spleen ADC and also to the surrogate markers of portal hypertension like grade of varices, symptomatic hypersplenism . The mechanisms behind the significant positive correlation between Spleen ADC and portal hypertension have not been fully elucidated. In theory, elevated portal blood pressure may lead to vasogenic edema due to sinusoidal congestion and dilatation. As explained earlier there are two mechanisms for portal hypertension in chronic liver disease patients. One is the increased portal venous resistance at the sinusoidal and post sinusoidal level is usually the

initiator of portal hypertension. However, increased portal venous inflow secondary to a hyperdynamic systemic circulation and splanchnic hyperemia is a major contributor to the maintenance of portal hypertension as portosystemic collaterals develop. The cause of the elevated cardiac output and splanchnic hyperemia is not known, but splanchnic hormones, such as glucagon, and decreased sensitivity of the splanchnic vasculature to catecholamines probably play a role. Increased production of nitrous oxide and prostacyclin by vascular endothelium is also an important factor. In our study , this splanchnic hyperemia may be reason for the significant association of ADC value of spleen to CSPH. The high ADC values are consistent with highly mobile water in areas of vasogenic edema. When we analysed the liver ADC to the severity of portal hypertension, we couldn't find any significant correlation, impling the heterogeneous correlation of the severity of portal hypertension and severity of chronic liver disease. Similarly we found that Spleen ADC doesnot correlate with the severity of chronic liver disease (Child Pugh's class). These two findings suggest that the spleen ADC is an indirect marker of splanchnic hyperemia, thereby portal hypertension and liver ADC is an indirect marker for the severity of liver fibrosis. This was also confirmed in our study as well, when we found Liver ADC decreased in cirrhotic patients as evident in previous studies and it correlated with Child Pughs class. "Even more in our study, where we could get 10 patients liver biopsy, there was a correlation to the grade of liver fibrosis and liver ADC and not to spleen ADC.

One of the greatest challenges to widespread adoption of DWI in the body is the lack of standardization.[92] In a prior study[99], two different diffusion sequences were used with b values of 0, 150, 250 and 400 mm2/s and 600 and 800 mm2/s, while in another study, b values of 0 and 500 mm2/s were applied. As a consequence, there is a difference on reported ADC values of the spleen and the normal and cirrhotic liver. As the b values increase, ADC approaches the true diffusion coefficient, thus minimizing the influence of convective motion processes that are sensitive to diffusion-highlighting gradients, mainly perfusion in the randomly organized capillary network. As a general rule, lower b values correspond to higher mean ADCs, overestimated due to signal contribution from other intravoxel incoherent motions (mainly microvascular perfusion). On the contrary, higher b values lead to lower ADC values as a consequence of the gradient-enhanced signal degradation that eliminates fast diffusion contributions. Some investigators recommended the use of higher b values, possibly larger than 400 s/mm2, to reduce the T2 shine-through effect and make the ADCs determined approach the true diffusion coefficient. We took b value of 0, 300, 500 for finding out the true diffusion co efficient.

Our study is the largest series to correlate spleen ADC to the severity of chronic liver disease and portal hypertension. "However there are few limitations in our study. We didn't use normalization of the spleen ADC with a reference organ to have some standardization to the MRI protocol in view of technical difficulties. Secondly, it was difficult to get patients who were not on medications for portal hypertension

CONCLUSION

In conclusion, our results showed that

1. Liver and Spleen ADC values vary among patients with liver cirrhosis and control subjects. Liver ADC value decreases, whereas Spleen ADC increases with cirrhosis.

2. ADC values in the spleen correlated well with the severity of portal hypertension like clinically significant portal hypertension and portal hypertension surrogate markers.

3. ADC values in the spleen does not correlate significantly with the degree of liver disease.

Also, the spleen might only be of limited value for normalization of liver ADC values to determine cirrhosis.

4. ADC values in the liver correlate significantly with the degree of liver disease.

ADC measurements may allow for noninvasive evaluation of portal pressure and even in assessment of treatment response.

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ABBREVATIONS

CTP	-	Child Turcotte Pugh's class
ADC	-	Apparent diffusion co-efficient
US	-	Ultrasound
CT	-	Compjuter tomography
MRI	-	Magnetic resonance imaging
DWI	-	Diffusion weighted imaging
ARFI	-	Acoustic Radiation Force Impulse Imaging
TE	-	Transient Elastography
PH	-	Portal hypertension
TE	-	Time to echo
TR	-	Time to repeat
F1	-	Fibrosis score of 1
MRE	-	MR elastography.
HVTT	-	Hepatic vein transit times.
RI	-	Resistive index.
INR	-	International normalized Ratio
HA	-	Hyaluronic acid
HVPG	-	Hepatic venous wedge pressure gradient
TIPSS	-	Transjugular Intrahepatic Portosystemic Shunt
NASH	-	Non alcoholic steatohepatitis
MELD	-	Model for End Stage Liver Disease
CSPH	-	Clinically significant portal hypertension.

PROFORMA

MRI DIFFUSION WEIGHTED IMAGING OF SPLEEN IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION.

Name:	
Age:	
Sex:	
Ip/ op number:	
Address:	
Contact number:	

History

1. Variceal bleed – y/n
2. Number of episodes-
3. Index bleed-
4. Abdominal distention with free fluid-
5. History of hepatic encephalopathy-
6. History of breathlessness.
7. Symptoms of hypersplenism.
8. History of etiology - alcoholism / viral hepatitis (b and c) / diabetic/ hypertension/ others

Examination findings.

Signs of liver cell disease- y/n

Mention the positive findings-

1.

2.

3.

4.

Investigation

Investigations	Values
1. Hemoglobin	
2. White blood cell count	
3. Platelet count	
4. Serum bilirubin	
5. Serum albumin	
6. Serum creatinine	
7. INR	

8. **Upper GI scopy findings –**

      1. Esophageal varices-grade-   columns-

      2. Esophageal varices – grade-   columns-

9. **USG abdomen – Liver- size echotexture**

      Spleen size

      Portal vein diameter flow

      Ascites

10. **DWI MRI**

Parameters	
ADC liver	
ADC spleen	
Inphase liver	
Inphase spleen	
Opposed phase liver	
Opposed phase spleen	

PATIENT INFORMATION SHEET

INFORMED CONSENT

We are conducting a study **"MRI Diffusion weighted imaging(DWI) of spleen in patients with cirrhosis and portal hypertension"** among those who attend Government General Hospital, Chennai.

Cirrhosis is the advanced stage of liver disease and it is manifested in the form of blood vomiting, fluid in the abdomen, altered sensorium, splenomegaly, etc. Portal hypertension (increased blood pressure in the bllod supply to the liver) is one of the manifestation of cirrhosis.

The purpose of this study is to observe the changes in spleen by DWI MRI in these patients and to find any correction with the severity of portal hypertension.

By taking part in the study, you have to undergo MRI examination which is the same as any routine MRI examination with no extra drugs.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefit to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Investigator   **Signature of the Participant**

ஆராய்ச்சி தகவல் தாள்

நுண்கதிரியியல் மருத்துவ பகுதி

செ ன்னை அரசு பொதுமருத்துவமனைக்கு வரும் கல்லீரல் பாதிப்படைந்த நோயாளிகளின் மண்ணீரலை எம்.ஆர்.ஐ (MRI) லம் ஆராய்ச்சி செய்தல்.

கல்லீரல் பாதிப்படைவதால் போர்டல் என்னும் சிரையில் உயர் இரத்த அழுத்தம் ஏற்படுகின்றது. அது வயிற்றில் நீர்கட்டுதல், இரத்த வாந்தி, மண்ணீரல் வீக்கம், சுயநினைவு தப்பிப்போதல் போன்றவைகளாக வெளிப்படுகின்றது. இதில் மண்ணீரலில் ஏற்படுகின்ற மாற்றத்தை எம்.ஆர்.ஐ ஆராய்ச்சியின் லம் கண்டறிந்து ஆராய்கிறோம்.

இதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்   பங்கேற்பாளர் கையொப்பம்

தேதி:

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

கல்லீரல் பாதிப்படைவதால் போர்டல் சிரையில் ஏற்படுகின்ற உயர்இரத்த அழுத்தத்தினால் மண்ணீரலில் ஏற்படுகின்ற மாற்றத்தினை எம்.ஆர்.ஐ ஆராய்ச்சி லம் கண்டறிதல்.

பெயர்	**உள்நோயாளின் எண்.**
வயது	**ஆராய்ச்சி சேர்க்கை எண்.**
பால்	

இந்த ஆரயர்ச்சியின் விவரங்களும் அதன் நோக்கங்களும். முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கின்றேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன். மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்காலம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் "கல்லீரல் பாதிப்பால் மண்ணீரலில் ஏற்படுகின்ற மாற்றத்தை எம்.ஆர்.ஐ யின் லம் கண்டறிதல்" பற்றி இந்த ஆராய்ச்சிகான விவரங்களைக் கொண்ட தகவல்களைப் பெற்றுக் கொண்டேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கின்றேன்.

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கையொப்பம்

</div>

MASTER CHART- CASE (51 patients)

Name	Child Pugh status	Sex	Age	Variceal bleed	Hep encep	Hypersplenism	Etiology	Hb	WBC	Platelet	Bilirubin	Albumin	creatinine	INR	Eso varices grade	Liver echo	Liver size	Dopp spleen	Dopp PV	Ascites	ADC liver	ADC spleen	Inphase liver	Inphase Spleen	Opposed liver	Opposed spleen
Kulandivelu	A	M	43	no	no	no	Alcoholic	6.8	7600	135000	3.4	2.7	1.1	1.4	2	Coarse	10	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Palani	A	M	42	no	no	no	HBV	7.8	5700	185000	2.1	3.2	0.8	1.3	1	Coarse	9	13	14.9	no	113	100.2	88.2	81.3	107.4	93.6
Sugirtham	A	F	52	yes	no	no	Alcoholic	11.9	4200	87000	2.4	3	0.7	1.2	1	Coarse	12.5	19.5	12	no	167	89	200	98	149	92
Deivaraj	A	M	38	yes	no	yes	Alcoholic	6	8600	56000	2.3	3.8	1.1	1.4	2	Coarse	9	15.5	13	no	142	90	82.5	42	84.7	44.4
Anandaraj	A	M	43	no	no	no	Alcoholic	6.8	7600	175000	2.1	3	0.6	1.1	2	Coarse	10	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Periaswamy	A	M	42	no	no	yes	HCV	7.8	5700	45000	2.1	3.2	0.9	1.3	2	Coarse	11	13	14.9	no	123	100.2	88.2	81.3	107.4	93.6
Latha	A	F	52	yes	no	yes	Crytogenic	11.9	4200	87000	1.6	3	1.1	1.2	1	Coarse	9	19.5	12	no	167	101	200	98	149	92
Saravanan	A	M	43	no	no	no	Alcoholic	6.8	7600	135000	1.6	3	0.8	1.2	2	Coarse	11	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Pechimuthu	A	M	42	no	no	yes	HCV	7.8	5700	78000	2.1	3.2	1.1	1.2	2	Coarse	11	13	14.9	no	112	100.2	88.2	81.3	107.4	93.6
Lakshmi	A	F	52	yes	no	no	Crytogenic	11.9	4200	87000	1.5	3	0.8	1.3	1	Coarse	9	19.5	12	no	156	103	200	98	149	92
Durai	A	M	38	yes	no	no	Alcoholic	6	8600	180000	1.4	3.8	1.1	1.2	1	Coarse	10	15.5	13	no	142	123	82.5	42	84.7	44.4
Sridhar	A	M	43	no	no	no	Alcoholicic	6.8	7600	135000	1.2	3	0.9	1.1	2	Coarse	9	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Naluswamy	A	M	42	no	no	yes	HBV	7.8	5700	45000	2.3	3.7	1.1	1.1	1	Coarse	11	13	14.9	no	98	100.2	88.2	81.3	107.4	93.6
Savathri	A	F	52	yes	no	no	Biliary	11.9	4200	87000	1.5	3	0.8	1.1	1	Coarse	9	19.5	12	no	167	128	200	98	149	92
Periakarupan	A	M	43	no	no	no	Crytogenic	6.8	7600	150000	1.5	3	0.9	1	2	Coarse	9	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Pari	A	M	42	no	yes	yes	HCV	7.8	5700	67000	1.4	3.2	0.9	1.3	2	Coarse	11	13	14.9	no	98	100.2	88.2	81.3	107.4	93.6
Mariammal	A	F	52	yes	no	no	NASH	11.9	4200	87000	1.5	3	0.9	1.3	1	Coarse	12.5	19.5	12	no	145	112	200	98	149	92
Senthil	A	M	38	yes	yes	yes	NASH	6	8600	56000	1.4	3.8	0.6	1.2	2	Coarse	9	15.5	13	no	142	132	82.5	42	84.7	44.4
Nagendran	A	M	43	no	no	no	Cryptogenic	6.8	7600	135000	1.6	3	0.7	1.3	2	Coarse	13	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Anandaraj	A	M	42	no	no	yes	HBV	7.8	5700	125000	1.7	3.2	0.6	1.4	1	Coarse	9	13	14.9	no	102	100.2	88.2	81.3	107.4	93.6
Rajendran	A	M	52	yes	no	no	Alcoholic	11.9	4200	87000	2.1	3	1.1	1.1	1	Coarse	9	19.5	12	no	182.7	112	200	98	149	92
Kumar	A	M	43	no	no	no	Crytogenic	6.8	7600	135000	2.2	3	1.1	1.3	2	Coarse	13	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Nandhakumar	A	M	42	no	no	yes	HCV	7.8	5700	125000	3.4	3.2	1.3	1.4	2	Coarse	12	13	14.9	no	108	100	88.2	81.3	107.4	93.6
Muniammal	A	F	52	yes	no	no	Alcoholic	11.9	4200	87000	1.8	3	1.4	1	1	Coarse	9	19.5	12	no	188	119	200	98	149	92
Sethu	A	M	38	yes	no	yes	NASH	6	8600	107000	1.4	3.8	1.1	1.2	1	Coarse	12	15.5	13	no	142	124	82.5	42	84.7	44.4
Kaliappan	A	M	43	no	no	no	Crytogenic	6.8	7600	135000	1.9	3	1.2	1.5	1	Coarse	13	13.5	13.2	no	110	98	89.8	62.8	110	68.6
Pechiswamy	A	M	42	no	no	yes	Biliary	7.8	5700	125000	2.1	3.2	1.3	1.2	1	Coarse	16.5	13	14.9	no	112	100.2	88.2	81.3	107.4	93.6
Aruna	A	F	52	yes	no	no	Alcoholic	11.9	4200	87000	1.9	2.6	1.6	1.2	1	Coarse	9	19.5	12	no	190	108	200	98	149	92
Dasan	A	M	38	yes	no	yes	Alcoholic	6	8600	107000	1.4	3.8	1.4	1	2	Coarse	9	15.5	13	no	142	99	82.5	42	84.7	44.4
Selvi	B	F	37	yes	no	no	NASH	8.8	9800	120000	2.4	2.6	1.7	1.3	3	Coarse	8.2	15.5	14.8	Mild	84	102	72	48.8	62	50
Duraipandian	B	M	59	yes	no	no	Crytogenic	10	4500	100000	3.4	2.5	1.1	1.3	1	Coarse	9	17	14	Moderate	89	79.9	200	92.3	99	56
Ramamurthy	B	M	55	yes	no	no	Alcoholic	7.8	9000	100000	8	3.3	1.6	1.5	3	Coarse	8.8	15	13.5	Moderate	130	112	166.4	100.6	134.9	95.7
Rangachary	B	M	50	yes	no	no	Alcoholic	10.3	7500	108000	4.2	2.9	0.9	1.9	3	Coarse	10	12.5	12	Moderate	133.6	134	148.7	117.7	198.7	27.3
Sudhakar	B	M	32	yes	yes	no	Alcoholic	6.5	6200	67000	2.8	2.2	0.9	1.7	2	Coarse	8	13.5	13	Moderate	50.2	110	120.9	60.1	100.7	62.3
Devagi	B	F	37	yes	no	no	NASH	8.8	4500	120000	4.2	2.2	1	1.7	4	Coarse	8.2	15.5	14.8	Mild	78	102	72	48.8	62	50
Sudhakar	B	M	59	no	no	no	Alcoholic	10	11400	100000	3	2.2	1	1.6	3	Coarse	9	17	14	Mild	82	79.9	200	92.3	99	56
Rangarajan	B	M	55	yes	no	yes	NASH	7.8	5500	100000	6.2	2.7	1.1	2.05	3	Coarse	8.8	15	13.5	Moderate	123	121	166.4	100.6	134.9	95.7
Rangachary	B	M	50	yes	no	no	Alcoholic	10.3	4400	108000	3.2	2.9	1.1	1.2	2	Coarse	10	12.5	12	Moderate	134	112	148.7	117.7	198.7	27.3
Chinnaswamy	B	M	32	yes	yes	yes	Biliary	6.5	6200	56000	2.2	2.2	1	1.39	3	Coarse	8	13.5	13	Moderate	57	110	120.9	60.1	100.7	62.3
Srinivasan	B	M	32	yes	yes	yes	HCV	6.5	3400	56000	2.7	2.2	1	1.39	3	Coarse	8	13.5	13	Moderate	54	110	120.9	60.1	100.7	62.3
Akila	B	F	37	no	no	no	NASH	8.8	1900	120000	1.9	2.4	1.1	1.4	3	Coarse	8.2	15.5	14.8	mild	84	102	72	48.8	62	50
Arunpandian	B	M	59	yes	no	no	Crytogenic	10	5500	100000	2.2	2.5	1	1.3	3	Coarse	9	17	14	moderate	89	79.9	200	92.3	99	56
Bimala	C	F	40	yes	no	no	HBV	7.2	4000	70000	2.3	2.4	1	1.2	3	Coarse	8.8	18.9	13.9	moderate	58	100	95	73	99	61.8
Prabhakar	C	M	45	yes	yes	no	Biliary	9	1900	78000	12	2	2.1	1.4	4	Coarse a	8	13	14	moderate	60	84.9	72.5	63.5	99	59.2
Saravanan	C	M	39	yes	yes	yes	NASH	6.6	3400	67000	18.4	2.4	1.1	1.54	3	Coarse	9	18	13.8	Moderate	78	135	238	77.2	247	72
Kuppan	C	M	48	yes	yes	yes	Autoimmune	6.2	2500	69000	9	2.2	1.9	1.68	3	Coarse	9	14.5	14	massive	63	150	185	80.3	146.5	92.6
Jamuna	C	F	40	yes	no	no	Alcoholic	12.5	4400	120000	7	2	3.1	1.7	3	Coarse	8	18.5	14	massive	105	120	110	80.6	119	74.5
Vijayakumar	C	M	60	no	yes	no	Alcoholic	8.6	6400	58000	5.2	2.8	1.7	1.25	3	Coarse	10	16	16	massive	122	106.9	97	102	106	100.2
Saravanan	C	M	39	no	no	yes	HBV	6.6	2300	67000	10.4	2.4	1.1	1.54	4	Coarse	10	18	13.8	Moderate	90	145	238	77.2	247	72
Senthil	C	M	48	yes	yes	yes	Crytogenic	6.2	3500	80000	8	2.2	1.1	1.68	3	Coarse	9	14.5	14	massive	63	150	185	80.3	146.5	92.6
Sarala	C	F	40	yes	no	yes	NASH	12.5	6000	120000	5.5	2.1	1.5	1.67	4	Coarse	8	18.5	14	massive	67	143	110	80.6	119	74.5

MASTER CHART- CONTROL (15 patients)

Name	Age	Sex	Hb	WBC	Platelet	Bilirubin	Albumin	creatinine	INR	Liver echo	Liver size(cm)	Doppler spleen(cm)	Doppler PV(mm)	ADC liver	ADC spleen	Inphase liver	Inphase Spleen	Opposed liver	Opposed spleen
Govindaraj	27	M	14	6500	230000	0.9	3.2	0.6	1	Normal	12.9	9	9	324	70.9	221	159	239	161
Krishnan	42	M	13	7500	340000	0.6	3.4	0.7	1	Normal	12.5	8	9	300	72.9	200	159	228	171
Chinnapillai	38	M	16	5500	540000	0.6	3.5	1	1	Normal	14	10	10	350.9	90	192	126	176	151
Ramayee	42	F	13	5000	440000	0.7	3.5	0.6	1.1	Normal	13.5	9	9.2	380.9	89	211	149	180	148
Madhi	22	M	11	4500	430000	0.8	3.5	0.8	1	Normal	12.9	9	9	324	70.9	221	159	239	161
Alagar	34	M	12	6700	250000	0.6	3.7	0.7	1	Normal	12.5	8	9	300	72.9	200	159	228	171
Chinnathai	39	F	12	7300	180000	1	3.4	0.7	1.2	Normal	14	10	10	350.9	90	192	126	176	151
Kuppammal	56	F	12	8400	340000	0.9	3.5	0.8	1	Normal	13.5	9	9.2	380.9	89	211	149	180	148
Venkatesan	54	M	10	7200	280000	0.6	3.5	0.8	1.2	Normal	12.9	9	9	324	70.9	221	159	239	161
Murthi	34	M	10	6500	210000	0.8	3.5	0.9	1	Normal	12.5	8	9	300	72.9	200	159	228	171
Suresh	51	M	11	7800	290000	0.7	3.5	0.9	1	Normal	14	10	10	350.9	90	192	126	176	151
Priya	36	F	9.9	7600	310000	0.8	3.2	0.9	1.1	Normal	13.5	9	9.2	380.9	89	211	149	180	148
Narayanan	59	M	12	8700	300000	0.6	3.4	0.8	1	Normal	12.9	9	9	324	70.9	221	159	239	161
Kala	45	F	12	4500	300000	0.7	3.4	0.8	1	Normal	12.5	8	9	300	72.9	200	159	228	171
Ramalingam	44	M	11	6700	300000	0.8	3.4	0.9	1	Normal	14	10	10	350.9	90	192	126	176	151

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

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

CERTIFICATE OF APPROVAL

To
Dr. S. Komalavalli,
Post Graduate,
Barnard Institute of Radiology,
Madras Medical College,
Chennai – 600003.

Dear Dr. S. Komalavalli,

   The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"MRI diffusion weighted imaging of the spleen in patients with Cirrhosis and Portal Hypertension"** No.18062014
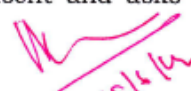
   The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

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

Sd/Chairman & Other Members

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

MEMBER SECRETARY
Member Secretary, Ethics Committee
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PLAGIARISM