DISSERTATION TITLED

"DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS"

Submitted in partial fulfillment of

Requirements for

M.D.DEGREE EXAMINATION BRANCH-I GENERAL MEDICINE

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY CHENNAI

INSTITUTEOFINTERNALMEDICINE

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CHENNAI - 600 003.

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CERTIFICATE

This is to certify that the dissertation entitled **A STUDY ON "DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS"** is a bonafide work done by **DR.S.MUTHUKANI**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch–I General Medicine, under our guidance and supervision, during the academic year 2011-2014.

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DECLARATION

I solemnly declare that the dissertation entitled "**A STUDY ON DIFFERENTIATION OF BENIGN AND MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS"** is done by me at Madras Medical College, Chennai-3 during May 2013 to November 2013 under the guidance and supervision of Prof. S.TITO, M.D., to be submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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ABBREVATIONS

HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C virus.
HCC	Hepatocellular carcinoma.
GBWT	Gallbladder wall thickness.
MELD	Model for End Stage Liver Disease.
NASH	Non alcoholic steato hepatitits
NAFLD	Non alcoholic fatty liver disease
PT	Prothrombin time
INR	International normalized ratio
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANTI-LKM	Anti liver kidney microsomal antibody
ANA	Anti nuclear antibody.
ANTI-SMA	Anti smooth muscle antibody

PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
LFT	Liver function tests
ECG	Electrocardiogram
USG	Ultrasonogram

CONTENTS

“DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS”

ABSTRACT:

BACKGROUND:

The conventional diagnostic method for most of the causes of ascites is diagnostic tapping of the ascitic fluid (paracentesis). This method is an invasive method. It is also a time consuming method.Ultrasonography has positive predictive value of 93-95% in determination of gallbladder wall thickness if the thickness is 1 mm. It is nearly 100% sensitive when the thickness is > 1.5 mm.

AIMS:

In our study we aim to find out the diagnostic value of ultrasonographic measurement of gallbladder wall thickness in differentiation of cirrhotic ascites from peritoneal carcinomatosis induced ascites. We also study the relationship between serum albumin levels and gallbladder wall thickness

PATIENTS AND METHODS:

We have included 60 patients in our study. Patients admitted with chronic liver disease with ascites, malignant induced ascites at medical wards, Institute of Internal medicine.Patients are subjected to routine blood investigations like complete blood count,renal function tests, liver function tests, PT-INR.Patients Gallbladder wall thickness will be assessed by Ultrasonography after 8 hours of

fasting with fill gallbladder. Three measurements of gallbladder wall thickness were taken at each site and average measurement was used for analysis. A single operator performed all the ultrasound examinations both in cirrhotic patients and peritoneal carcinomatosis patients. Real time bidimensional and Doppler ultrasound examinations were performed by using 3.5 MHz transducer. Thickness more than 3 mm was considered significant.

CONCLUSION:

According to our study, thesonographic study of the gallbladder will be helpful as a simple and initial screening tool in differentiating between cirrhosis induced and peritoneal carcinomatosis induced ascites.

Hypoalbuminemia is correlated well with the development of thickened gallbladder in cirrhosis induced ascites.

KEYWORDS:

Gallbladder wall thickness, Serum Albumin, Prothrombin time, International normalized ratio,Ultrasonogram.

INTRODUCTION

INTRODUCTION

Ascites is the term derived from greek word ‘askos’ which means ‘bag like’. Ascites denotes when there is pathological accumulation of fluid inside the peritoneal cavity. There are multiple causes of ascites. Alcoholic liver disease is the commenest of cirrhosis worldwide which is contributing to about 80-85 % of the cases. Another devastating cause of ascites is peritoneal carcinomatosis induced ascites.

Malignant ascites is an important sign of peritoneal carcinomatosis. The common etiologies for malignant induced ascites are gastric malignancy, ovary, colorectum, lung, breast, pancreas, uterus, lymphoma. Malignant ascites accounts for 10% of the causes of ascites. The presence of ascites is a worst prognostic sign in peritoneal carcinomatosis. The average life expectancy is approximately 20-24 weeks after the diagnosis of malignant ascites(3) in a patient.

The early diagnosis of peritoneal carcinomatosis induced ascites is very important in the diagnosis and management of primary malignancy.

The conventional diagnostic method for most of the causes of ascites is diagnostic tapping of the ascitic fluid (paracentesis). This method is an invasive method. It is also a time consuming method.

Ultrasonography has positive predictive value of 93-95% in determination of gallbladder wall thickness if the thickness is 1 mm. It is nearly 100% sensitive when the thickness is > 1.5 mm. The normal gallbladder will be appearing as a pencil thin line on ultrasonogram which is echogenic (4).

Several studies have reported that gallbladder wall is getting thickened in cirrhosis induced ascites. . Hypoalbuminemia causes edema and structural changes in the gallbladder wall. It leads to gallbladder wall thickening. It also affects the gallbladder contractility(1). So the mechanisms which are responsible for gallbladder wall thickening might occur earlier in the pathogenesis of cirrhosis. Hypoalbuminemia precedes the onset of portal hypertension.

In our study we aim to find out the diagnostic value of ultrasonographic measurement of gallbladder wall thickness in differentiation ofcirrhotic ascites from peritoneal carcinomatosis induced ascites. We also study the relationship between serum albumin levels and gallbladder wall thickness.

AIM AND OBJECTIVE

AIMS AND OBJECTIVES

- To study the usefulness of measuring gallbladder wall thickness in the Differentiation of cirrhotic ascites from malignant induced ascites.

- To study the correlation between serum albumin levels and gallbladder wall thickness.

REVIEW
OF
LITERATURE

REVIEW OF LITERATURE

Ascites is the term derived from greek word ‘askos’ which means ‘bag like’. Ascites denotes when there is pathological accumulation of fluid inside the peritoneal cavity. The peritoneum is a serous membrane that forms the inner lining of the abdominal cavity. It is composed of a layer of mesothelium which is supported by a thin layer of connective tissue.

There are two layers of peritoneum. The outer layer is parietal peritoneum which lines the abdominal cavity. The inner layer is visceral peritoneum which lines the internal organs. The potential space between these two layers is called as peritoneal cavity. It is filled with a small amount of serous fluid(approximately 30-50 ml). Mild ascites will be difficult to appreciate clinically.

But moderate to severe ascites will produce abdominal distension. Most experts recommend a diagnostic tapping of the ascitic fluid(diagnostic paracentesis) should be performed to know about the etiology of ascites. The fluid is then analysed for gross appearance of the ascitic fluid and its protein level, albumin, cell count, microbiological culture, gram stain, cytology.

The Serum Ascites- Albumin Gradient (SAAG) is most useful in determining the etiology of ascites. A high SAAG (>1.1 g/dl) indicates the ascites is due to portal hypertension. A high SAAG ascites is further classified depending upon the ascitic fluid protein concentration. When the SAAG is less than 1.1 g/dl , it is called as low SAAG ascites.

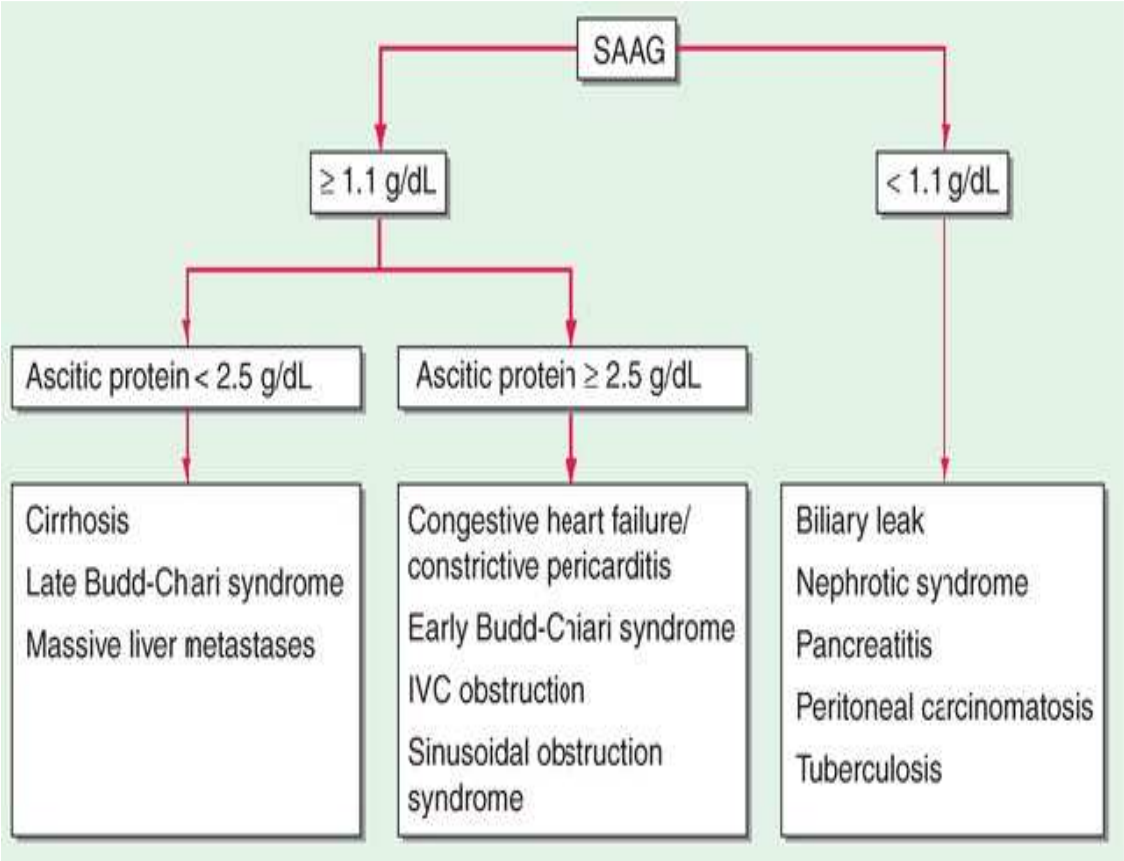


Fig : Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG). IVC, inferior vena cava.

The commonest cause of ascites around the world is cirrhosis. It accounts for 80-84% of the cases of ascites. Congestive cardiac failure, peritoneal carcinomatosis and mixed ascites resulting from cirrhosis and a second disease account for 10-15% cases(2). Less common causes includes infection, massive hepatic metastasis, pancreatitis and renal failure. The ascites can also be classified as either exudative or transudative. There are some diseases which can cause both exudative or transudative ascites. This diseases includes tuberculous peritonitis, purulent peritonitis, congestive cardiac failure, pancreatitits, peritoneal carcinomatosis.

The pathogenesis of ascites is complex. The most recent theory among the postulations is peripheral arterial vasodilatation hypothesis. It has conveyed that both older overfill and underfill theories are correct. But each theory is operative at a different levels of ascites formation.Ascites in patients with cirrhosis is the result of portal hypertension followed by renal salt and water retention. Portal hypertension signifies elevation of the pressure within the portal venous system. According to Ohm's law, pressure is the product of resistance and flow. Increased hepatic resistance occurs by several mechanisms.

At first, there is development of hepatic fibrosis, which defines cirrhosis, disrupts the normal architecture of the hepatic sinusoids and impedes normal blood flow through the liver. Second,there is activation of hepatic stellate cells, which mediate fibrogenesis, leads to smooth muscle contraction and fibrosis. Finally, cirrhosis is associated with a decrease in endothelial nitric oxide synthetase (eNOS) production in the liver, which results in decreased nitric oxide production and increased intrahepatic vasoconstriction(7).

The development of cirrhosis is also associated with increased systemic circulating levels of nitric oxide (contrary to the decrease seen intrahepatically) as well as increased levels of vascular endothelial growth factor and tumor necrosis factor that result in splanchnic arterial vasodilatation(5). Vasodilatation of the splanchnic circulation results in pooling of blood and a decrease in the effective circulating volume, which is perceived by the kidneys as hypovolemia.

As already stated above,The first abnormality that eventually leads to fluid retention is peripheral arterial vasodilatation and it is mediated by nitric oxide. It leads to intravascular hypervolemia which leads to suppression of Renin-Angiotensin-Aldosterone system and vasopressin , norepinephrine concentration. As the state of vasodilatation worsens , there will be reduction in renal blood

supply and then renal function deteriorates. Then plasma levels of vasoconstrictor increases, RAAS is activated and sodium , water retention occurs. This stage is called as decompensated stage. Hepato-renal syndrome development is an extreme form of this condition(6).

Cirrhosis represents an advanced stage of fibrosis and characterized by distortion of hepatic parenchymal anatomy and formation of regenerative nodules and fibrotic bands. The pathogenesis of fibro genesis is activation of stellate cell which is the cardinal feature of hepatic fibrosis. The stellate cells lies within the space of disse which is in direct contact with the hepatocytes, inflammatory cellthey store vitamin A in normal liver, about 40- 70% of body retinoid is stored in stellate cell.

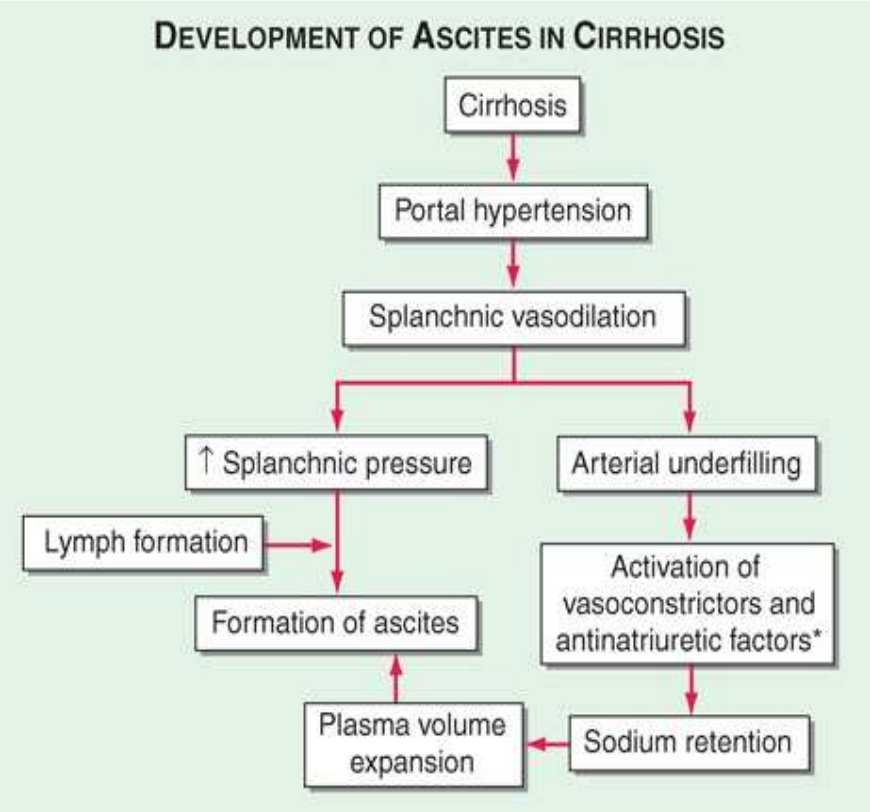


Fig : The pathogenesis of ascites development in cirrhosis.

Intrahepatic portal hypertension plays a necessary role in the formation of ascites. Patients with presinusoidal hypertension do not develop ascites commonly. Due to the large hydrostatic pressure gradient in the liver leads to loss of intravascular volume into the sinusoidal space of disse. This fluid from the space, then weep out into the abdominal cavity, as extravasated lymph. Then the underfilling theory takes over in the propogation of ascites. The sequestration of fluid in the abdomen leads to decreased effective circulatory volume and triggers the release of anti diuretic hormone, renin, aldosterone, further stimulation of

sympathetic system. This all leads to further aggravation of sodium and water retention. This cycle becomes vicious which increases the fluid collection in the peritoneal cavity.Chronic liver disease and cirrhosis is becoming very common(12), and its burden is increasing worldwide. Up to forty percentages of patients with cirrhosis were asymptomatic until the occurrence of decompensation in the form of variceal bleed, hepatic encephalopathy, and SBP (spontaneous bacterial peritonitis). Previously fibrosis and cirrhosis was thought to irreversible .But recent studies are showing that fibrosis might be reversible in some but not all patients with chronic hepatitis B, hemochromatosis.

Scar formation is mediated through increased proliferation of hepatic stellate cells, chemo taxis, fibro genesis, altered degradation of collagen matrix and interaction between hepatic stellate cells and immune system and secretion of inflammatory mediators. The extracellular matrix during fibro genesis consists of collagen and glycoproteins and hyaluronic acid. TGF beta 1 is the central molecule in mediating fibro genesis and TIMP-1 plays a huge role in initiation , progression and regression of fibro genesis. The importance of TIMP-1 can be understood from the fact that overexpression of human TIMP-1 in mice increased CCL4 induced fibrosis by seven fold.

The three features which define cirrhosis pathologically are,

1. Presence of bridging fibrosis / fibrotic bands.
2. Micro architectural distortion.
3. Regenerative macro/ micro nodules.

Fatty liver is the first response to many hepato toxic stimuli including alcohol. The initial accumulation of fat in the perivenular hepatocytes , is due to localisation of the enzyme alcohol dehydrogenase in that region. Continuous ingestion of alcohol leads to diffuse hepatic steatosis. The transition between steatosis and alcoholic hepatitis is less clear. Alcoholic hepatitis is characterised by spotty necrosis, ballooning degeneration of hepatocytes and infiltration of polymorphonuclear cells. Mallory bodies are often present though they are not specific for alcoholic hepatitis. They are eosinophilic intracytoplasmic inclusions of intermediate filaments like keratin. Both hepatic steatosis and alcoholic hepatitis are reversible after alcohol abstinence. cirrhosis is present in upto 50% of the patients with alcoholic hepatitis and its regression is uncertain(9).

ETIOLOGY AND RISK FACTORS:

Alcoholic liver disease is the most common cause of cirrhosis worldwide contributing to about 80-85 % of the cases.

NAFLD AND NASH (Nonalcoholic fatty liver disease and nonalcoholic steatohepatitits): around 2-3% of those with NAFLD will progress to NASH of which about 10% will progress to cirrhosis.

RISKFACTORS:

1.Heavy alcohol consumption- in males 40-80 g/day produces hepatic steatosis. > 160 g/day for 10-20 yrs produces hepatitis or cirrhosis.

Only 10-20% of alcoholics will develop alcoholic hepatitis(10).

2. Health care professionals.

3. Obesity

4. Tattooing

5. Unprotected sexual intercourse

6 .Toxic and chemical exposures

7. Certain medications like methotrexate, sodium valproate etc.

8. IV drug abusers sharing intravenous needles

9. Blood transfusion.

ETIOLOGY:

1.Alcoholic liver disease- most common cause.

2. Viral:

- Chronic hepatitis B.
- Chronic hepatitis C.
- Cytomegalovirus.
- Epstein barr virus.

3.Metabolic:

- NAFLD/NASH.
- Hemochromatosis.
- Wilson’s disease .
- Alpha 1 anti-trypsin deficiency.
- Cystic fibrosis.
- Tyrosinosis.
- Hereditary fructose intolerance.
- Glycogen storage diseases.

4. Drug induced:

- Amiodarone .
- Methotrexate .
- Nitrofurantoin.

- Anti tuberculous drugs (Isoniazid, rifampicin, pyrazinamide)
- Anti convulsants (Sodium valproate, phenytoin, phenobarbitone, carbamazepine)
- Minocycline.
- Trovafloxacin.
- Halothane.
- Amitriptyline.

4.Biliary cirrhosis

Primary biliary cirrhosis.

Primary sclerosing cholangitis .

Autoimmune cholangiopathy.

5. Cardiac:

Right heart failure (CCF).

Tricuspid Regurgitation.

6. Cryptogenic

CLINICAL FEATURES:

Patient with cirrhosis may be identified in the following ways :

1. Patients may be identified on routine clinical examination.

2. They might have undergone laboratory/radiological imaging or some procedures which incidentally found out the presence of chronic liver disease.

3. They may present in a decompensated state.

4. Some patients may never come to clinical attention.

HISTORY:

This should include questions to identify risk factors for chronic liver disease like history of alcohol intake ,the dose, duration, calculation of alcohol intake in grams per day , jaundice, diabetes,tattooing, illicit drug use, blood transfusion, any surgery, family history of liver diseases and autoimmune conditions.

Questioning should also include those related to symptoms of chronic liver disease like fatigue, pedal edema, weight loss, confusion,hematemesis, malena, bleeding diathesis like epistaxis, ecchymotic spots, hematuria, bleeding gums, decreased urine output, fever, abdominal pain, altered sleep pattern.

Symptoms may vary from asymptomatic to overt features of decompensation. Patients with chronic liver disease may have generalised muscle wasting, large ascites and overt hepatic encephalopathy but only mild jaundice. Patients with primary biliary cirrhosis develops deep icterus but no muscle wasting. Patients may experience fatigue, anorexia, weight loss. Cutaneous manifestations may include jaundice, spider naevi, paper money skin, palmar erythema, dupuytrens contracture, white nails, disappearance of lunulae, terry nails, and finger clubbing.

Increased peripheral aromatisation that is conversion of androgens to estrogen occurs in adipose tissue, skeletal muscle and decreased metabolism of estrogens contributes to hyperestrogenemia which may be responsible for loss of axillary and pubic hair, gynaecomastia, impotence.

Anemia may be due to multiple causes like blood loss, folate deficiency, hemolysis, and hypersplenism. A unique form of hemolytic anemia can occur in severe alcoholic hepatitits called as Zieve's syndrome(13). Thrombocytopenia is usually the first sign of portal hypertension and hypersplenism.

Coagulopathy results from decreased production of coagulation factors and diminished absorption of Vitamin K from the gastrointestinal tract as the absorption of all the nutrients will be impaired due to gastro intestinal

congestion. Among the coagulation factors factor VII will be depleted first as it has the shortest halflife (6 hours).

SYMPTOMS:

- Fatigue.
- weakness .
- Poor appetite .
- Muscle wasting.
- Jaundice
- Breast enlargement in men
- Ascites
- Parotid gland enlargement.
- Altered sleep pattern.
- Somnolence.
- Pruritus.
- Blood vomiting .
- Redness of palms .
- Impotence,
- loss of libido.

SIGNS :

Signs may be classified according to the Etiology and those associated with decompensation.

SIGNS ASSOCIATED WITH ETIOLOGY:

Alcohol related:

- Parotid enlargement
- Gynecomastia
- Dupuytren's contracture
- Peripheral neuropathy
- Cerebellar signs
- Testicular atrophy- alcohol has a direct toxic effect over testis.

Wilson's disease:

- Kayer Fleischer ring- due to copper deposition in the descemet's membrane of the cornea.
- Hepatomegaly
- Dystonia, incoordination, tremors, dysarthria, involuntary movements

Hemochromatosis:

- Slate grey pigmentation of skin.
- Testicular atrophy.
- Diabetes mellitus.
- Congestive cardiac failure.
- Hepatomegaly.

NASH:

- Xanthomas, xanthelesma
- Corneal arcus

Viral hepatitis:

- Tattoo marks, injection marks

Right heart failure:

- Peripheral edema
- Elevated JVP

SIGNS OF DECOMPENSATION:

- Icterus
- Ascites

- Ecchymosis
- Asterixis
- Encephalopathy
- Bleeding varices
- Cruveilheir Baumgarten murmur
- Fetor hepaticus
- Caput medusae.

COMPLICATIONS :

- Portal hypertension
- Spontaneous bacterial peritonitis
- Hypersplenism
- Variceal bleeding
- Hepatorenal syndrome
- Portopulmonary hypertension
- Hepatic encephalopathy
- Hepatopulmonary syndrome
- Malignant transformation.

DIAGNOSIS:

Common laboratory investigations performed under the label LFT (liver function tests) are,

1) Enzyme tests:

- Serum aminotransferases (AST, ALT)
- Serum alkaline phosphatase(ALP)
- Gamma Glutamyl Transferase.

2) Serum bilirubin – Total , direct and indirect bilirubin.

3) Assessment of hepatic synthetic function:

- Serum albumin
- Prothrombin time and INR (for coagulation factors)

Aminotransferases:

Both aspartate transaminase and alanine transaminase may be elevated upto 2 – 7 fold(< 400 IU/L) , but can be normal in advanced stages of liver disease. AST/ALT ratio > 1 suggestive of alcoholic liver disease.

Alkaline phosphatase:

It is getting elevated in most forms of cirrhosis. But it will be less than three times the upper normal limit. High levels are noted in,

1) Primary biliary cirrhosis

2) Primary sclerosing cholangitis

Gamma Glutamyl Transferase:

- It is not a specific marker for alcoholic liver disease
- It is an easily inducible enzyme.
- Elevated in all forms of fatty liver.

Serum bilirubin:

- May be markedly increased in alcoholic hepatitis despite modest elevations in alkaline phosphatase.
- It may be normal in compensated state but elevated bilirubin indicates fairly advanced liver disease.

In primary biliary cirrhosis elevated bilirubin indicates poor prognosis.

Serum Albumin :

Albumin is solely synthesized by the liver .

In hepatitis albumin level < 3g/dl should raise the possibility of chronic liver disease. Hypoalbuminemia is not a specific marker for liver diseases. It can also occurs in protein losing enteropathy, nephrotic syndrome, protein energy malnutrition.

Prothrombin time:

It detects the abnormality in the coagulation pathway particularly extrinsic and common pathway.

It increases as liver disease progresses since coagulation factors are produced in liver.

Serum Globulin:

Elevated levels of globulin are seen in cirrhosis as various antigens are shunted away from liver, reach systemic circulation and elicit immunological response. Increased levels of IgM are seen in primary biliary cirrhosis, increased IgA is seen in alcoholic liver disease.

Serum Sodium:

Hyponatremia in chronic liver disease patients indicates poor prognosis.

It is due to high levels of ADH seen in cirrhotic patients and consequent dilutional hyponatremia. Only those who have serum levels of sodium less than 120-125 mmol/L needs water restriction(15).

Hematological investigations:

Anemia: May be due to

- Blood loss due to bleeding diathesis.
- Folate deficiency
- Direct toxicity of alcohol
- Hemolysis
- Anemia of chronic disease
- Hypersplenism

Thrombocytopenia:

Due to portal hypertension and hypersplenism, . It may cause bleeding if associated with coagulopathy.

Leucopenia, Neutropenia:

Due to hypersplenism and splenic margination of white bloodcells.

INVESTIGATIONS TO DETERMINE THE ETIOLOGY OF CHRONIC LIVER DISEASE:

Alcoholic liver disease (ALD) :

History of alcohol abuse.

AST/ALT ratio > 2 due to alcohol induced deficiency of pyridoxal phosphate(16).

Liver biopsy may show features typical of alcoholic hepatitis, Mallory's hyaline bodies, liver cell necrosis and fibrosis.

Chronic hepatitis C:

Anti HCV antibody

Quantitative PCR for HCV RNA

Liver biopsy to establish the severity of liver disease, macrovesicular steatosis.

Chronic hepatitis B:

- HBsAg
- HBeAg
- Quantitative PCR for HBV DNA.

NASH:

Associated features of metabolic syndrome like hyperglycemia, hyperlipidemia.

- ✓ Liver biopsy

Primary biliary cirrhosis:

- ✓ Elevated alkaline phosphatase

Anti-mitochondrial antibody directed against pyruvate dehydrogenase complex is considered to be specific for primary biliary cirrhosis.

Primary Sclerosing Cholangitis (PSC):

- ✓ Associated with inflammatory bowel disease(IBD).
- ✓ Contrast cholangiography shows diffuse, focal strictures and dilatation of bile ducts giving it a typical beaded appearance.

Autoimmune hepatitis:

- ✓ Increased gamma globulin levels
- ✓ Anti-LKM1 antibody
- ✓ Anti-smooth muscle antibody (ASMA)
- ✓ Anti-nuclear antibodies.

Hemochromatosis:

- ✓ Fasting transferrin saturation-More than 50% in men and women.
- ✓ Plasma ferritin
- ✓ Genetic testing
- ✓ Liver biopsy for measurement of liver iron (microgram/ G) and hepatic iron index.

Wilson's disease:

- ✓ Kayer Fleisher rings on slit lamp examination.
- ✓ Decreased serum ceruloplasmin.
- ✓ 24 hour urinary copper >100mg
- ✓ Copper content >200mg/g of liver tissue in liver biopsy.

Alpha 1 anti-trypsin deficiency:

- ✓ Decreased serum alpha1 anti-trypsin levels.
- ✓ Genetic testing

Right sided heart failure:

- ✓ Electrocardiogram
- ✓ Echocardiogram.

Imaging methods :

Ultrasound abdomen:

Provide useful information regarding liver size, echo texture. Useful screening to identify development of HCC (hepatocellular carcinoma) in a patient with preexisting chronic liver disease.

Doppler ultrasound:

Provides information regarding the blood flow in portal vein and hepatic veins.

Assess size of portal vein, splenic vein. Identify presence of collaterals. Portal venous pressure can be measured.

CT Abdomen with or without contrast:

- ✓ To assess liver size, shape.
- ✓ To identify liver nodule.
- ✓ To detect HCC.

MRI Abdomen:

- ✓ Most useful in the evaluation of intrahepatic and extrahepatic biliary tree.

- ✓ To detect malignancy.

Fibro scan :

It is a newer modality and gaining popularity nowadays. It is a noninvasive method to assess the stiffness of the liver and evaluate liver fibrosis and cirrhosis by using electromagnetic waves(17).

Liver biopsy:

It has proven value in the following situations.

1. Hepatocellular disease of uncertain cause.
2. Prolonged hepatitis with the possibility of chronic active hepatitis.
3. Unexplained hepatomegaly.
4. Unexplained splenomegaly.
5. Filling defects in the liver in imaging.
6. Staging of lymphoma.
7. Fever of unknown origin.

ASSESSMENT OF SEVERITY AND PROGNOSIS:

Severity may be assessed by

1) Child Pugh's scoring system.

2) MELD scoring system.

3) Liver biopsy

CHILD PUGH'S SCORING SYSTEM:

Clinical and Lab	**Points**		
	1	**2**	**3**
Ascites	None	Slight	Moderate
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dl)	<2	2-3	>3
Encephalopathy	None	Grade 1 and 2	Grade 3 and 4
PT/INR	<1.7	1.7-2.3	>2.3

Class A: Score 5-6

Survival at one and two year 100% and 65% respectively.

Class B: Score 7-9

Survival at one and two year 80% and 60% respectively.

Class C: Score 10-15

Survival at one and two years 45% and 35% respectively.

MELD SCORING SYSTEM:

MELD (model for end stage liver disease) was initially developed to assess short term prognosis in patients with chronic liver disease who undergo TIPS procedure(2,5) (Trans jugular intra-hepatic Porto systemic shunt). But its usefulness to assess the prognosis and severity of chronic liver disease has been well validated in several studies.It consists of three variables

1) Serum bilirubin

2) Serum creatinine

3) Prothrombin time INR(International Normalized Ratio).

SCORE	**THREE MONTH MORTALITY (%)**
>40	71.3
30-39	52.6
20-29	19.6
10-19	6
<9	5

MANAGEMENT OF CHRONIC LIVER DISEASE

MANAGEMENT IN A COMPENSATED STATE:

Adequate diet :

- ✓ 30-40 Kcal/kg body weight.
- ✓ 1.2-1.5 gram of protein per kg body weight per day(18).
- ✓ Abstinence from alcohol.
- ✓ Weight loss if obese.
- ✓ Early detection and treatment of complications.

Treatment of specific cause:

- ✓ Antiviral therapy for chronic hepatitis B and C
- ✓ Steroids and immunosuppressants for autoimmune hepatitis.
- ✓ Zinc, d-Penicillamine for Wilson's disease.
- ✓ Phlebotomy for hemochromatosis.
- ✓ Ursodeoxycholic acid for primary biliary cirrhosis.

DECOMPENSATED STATE:

Treatment is aimed at Identification and treatment of precipitating factors. Early detection and management of complications.

Hepatic encephalopathy :

- Avoidance of precipitating factors.
- Osmotic laxatives (lactulose and lactitol).
- Rifaxamin 400mg three times a day.
- Liver transplantation.

Portal hypertension:

- Propranolol 40-80 mg two times a day. Ascites and peripheral Ascites :
- Sodium restriction <2 g per day.
- Fluid restriction if there is Hyponatremia (< 120-125 mmol/L).
- Spironolactone starting dose 100 mg , maxi. dose 400mg per day
- Furosemide 40 mg per day, maximum 160 mg per day
- Large volume paracentesis with intravenous albumin.

Hepatorenal syndrome:

- Avoidance of nephrotoxins
- Intravenous albumin + Midodrine
- Octreotide

Spontaneous bacterial peritonitis

Cefotaxime 2 g IV tds or Ceftriaxone 1g iv BD for 7 days.

Norfloxacin 400 mg twice daily for 7 days.

The patient should be maintained on lifelong prophylaxis with Norfloxacin 400mg OD .

ROLE OF LIVER TRANSPLANTATION:

Liver transplantation is considered when liver no longer has its ability to do its various functions. The following are the most common indication for liver transplantation.

- Hepatitis C, B
- Alcoholic liver disease
- Autoimmune liver disease
- Primary biliary cirrhosis.

MALIGNANCY INDUCED ASCITES:

Malignant induced ascites is a marker of peritoneal carcinomatosis. The common etiologies for malignant induced ascites are carcinoma stomach, ovary, colorectum, lung, breast, pancreas, uterus, lymphoma. Malignant ascites accounts for 10% of the causes of ascites. The development of ascites is a worst prognostic sign in peritoneal carcinomatosis. The average life expectancy is approximately 20-24 weeks after the diagnosis of malignant ascites(18).

The formation of malignant ascites is multifactorial. The pathogenesis of malignant ascites is multifactorial. It is postulated that ascites formation is related to a combination of increased vascular permeability and impaired lymphatic drainage by the tumour burden. There are five microscopic barriers exists in the peritoneum. They prevents the shift of proteins away from the intravascular space. They are as follows:

1. Capillary endothelium,
2. Capillary basement membrane,
3. Interstitium,
4. Mesothelial basement membrane,
5. Mesothelial lining cells(19).

With the combination of tight junctions and anionic macromolecules, an effective barrier is maintained in the peritoneum. It prevents the leakage of protein molecules into the peritoneal cavity. In 1922, Putnam described the peritoneal membrane as a “living membrane”. He demonstrated that crystalloid solutions when they are instilled into the peritoneal cavity, they gets equilibrated between the peritoneal cavity and the serum. The movement of colloid was described as transmission in one direction into the serum from the peritoneal cavity,with the help of some “vital (membrane) activity”, probably by phagocytosis or mechanical filtration through intercellular spaces. The relative impermeability of the capillary membrane to plasma proteins forms the basic mechanism for osmotic gradients. It was initially described by Starling when he described about capillary forces. The starlings theory states that the exchange of fluid between the plasma and interstitium is dependingupon the hydrostatic and oncotic pressure in each compartment. Oncotic pressure differences forms the basis for fluid reabsorption from the interstitial space. It prevents edema formation(20) and it is mainly contributed by plasma proteins.

The macromolecules, proteins and cells do not preferentially leave the intravascular space. But they can accumulate in the peritoneal cavity and return to the systemic circulation with the help of the peritoneal lymphatic system. Recklinghausen is the one who first described the lymphatic stomata in the

body. He described that as small openings of lymphatics that connect the body cavity and lymphatic lumen which are responsible for movement of large particles into the vascular space. Several studies had demonstrated that there are three lymphatic pathways in the abdomen by using India ink injection and transmission electron microscopy. The principal pathway begins with the lymphatic stomata. It enters the peritoneal lymphatics *via* networks in the diaphragm and then undergoing filtration through regional lymph nodes of the diaphragm, and finally emptying into the thoracic duct(22). These different mechanisms of oncotic gradients and lymphatic drainage allows for a dynamic fluid balance created between the peritoneal cavity and the intravascular space.

During 1953, Holm-Nielson demonstrated another important mechanism in the malignant ascites. India ink was injected into the peritoneal cavity in malignant ascites. It was remained in the peritoneal cavity. It is suggesting that lymphatic obstruction plays a major role in pathogenesis of malignant ascites. Another scientist called Feldman later showed that in mice inoculated with tumor cells, radioactive labeled erythrocytes injected into the intra-peritoneal space failed to return to the intravascular space. It was due to tumor infiltrating the lymphatics. It is further confirmed by histological evaluation, and subsequent to these events was the formation of ascites. It was showed that

Radio-labeled red blood cells did not enter the intraperitoneal space at any increased rates until tumor burden had increased by 10 fold atleast. Development of ascites will not occur until late stages of tumor growth . The above mentioned studies demonstrated the vital role of lymphatic obstruction in the development of tumor related ascites. Several authors have offered theories regarding tumor metastasis. But it is still not clear why cancer cells preferentially localizes to the peritoneal cavity rather than other sites and cause malignant ascites(24) .

The mechanisms of ascitic fluid accummulation appears to be the combination of increased vascular permeability and impaired lymphatic drainage. Recent studies shows that vasculoendothelial growth factor (VEGF) appears to play an important role in increasing the vascular permeability. Tumour necrosis factor (TNF) also contributes to splanchnic hyperemia. So the cytokines which are released by the tumour cells plays an important role in the formation of malignant ascites.

In >50% of cases of peritoneal carcinomatosis, ascites is the first detected sign of intra-abdominal malignancy. The causes of intra-abdominal fluid production are many, including both benign and malignant causes like cirrhosis,

congestive heart failure, nephrosis, pancreatitis, peritonitis, primary malignancy or hepatic metastases. It is improbable to distinguish between benign ascites from malignant ascites by physical examination or radiographic techniques alone. So Invasive testing becomes necessary to differentiate the two types. Abdominal paracentesis with ascitic fluid analyses can diagnose malignant causes of ascites production in most cases, but laparoscopic tissue sampling may be necessary in some cases. Ascitic fluid analysis consists of microscopic, bio chemical and cytological evaluation to differentiate between infectious, inflammatory and malignancy induced ascites formation. In patients with peritoneal carcinomatosis, the ascites fluid has positive cytology, elevated protein concentrations and a low serum-ascites albumin gradient. While in some reports cytology is diagnostic in only 50%-60% of cases of malignant ascites, it has been demonstrated that up to 97% of patients with peritoneal carcinomatosis have positive cytology, indicating that the tumor is shedding cells into the peritoneal cavity, making it a highly sensitive test and the gold standard for diagnosing peritoneal carcinomatosis.

Before concluding that cytology is negative for malignant cells we should repeat it thrice with adequate amount of sample after centrifuging the sample. The sample should be analysed immediately after processing it. In patients with

peritoneal carcinomatosis and hepatic metastases, fluid cytology is positive and ascites protein concentrations are variable, but the serum-ascites albumin gradient remains elevated, with the addition of a markedly elevated serum alkaline phosphatase level (> 350 mg/dL). The usage of tumor markers, especially CEA, CA-125 and α fetoprotein, are not reliable in diagnosing malignancy but they can be of help in identifying the primary tumor causing malignant ascites(27).

The biochemical properties of ascites fluid, including fibronectin, cholesterol, lactate dehydrogenase, sialic acid, telomerase activity and proteases, have been studied and, while clinically helpful, they have not yet been found to be reliable in differentiating between malignant and benign ascites and they are not useful in routine analysis of ascitic fluid. So the combination of Tumor and biochemical markers along with the morphological features of the cytological smear, immunohistochemical staining and clinical history are important in determining both the presence of malignancy related ascites and the primary sites of metastatic carcinomas.

The quality of the ascitic fluid is distinctive in malignant ascites. It will have high ascitic fluid protein concentration, low SAAG, positive cytology.

If the diagnostic workup does not reveal the primary source of malignancy but confirms the presence of a malignancy, a search for the tumor of origin should be started. In male patients with positive cytology, whose diagnostic workup remains negative despite blood tests and radiological imaging, it may not be useful to pursue further investigations because knowing the tumor of origin may not affect management or outcome(29).

However, in female patients, if the conventional methods are failed to demonstrate the tumor of origin, laparoscopy or laparotomy should be done for tissue diagnosis, because patients with an ovarian malignancy will be responsive to tumor debulking and chemotherapy and their survival outcomes are better after treatment.

There are many studies which are trying to differentiate benign ascites from malignant ascites in a simple yet useful manner.Our study aim is to find out whether measuring gallbladder wall thickness by ultrasonography differentiates between portal hypertension induced ascites and malignant ascites.

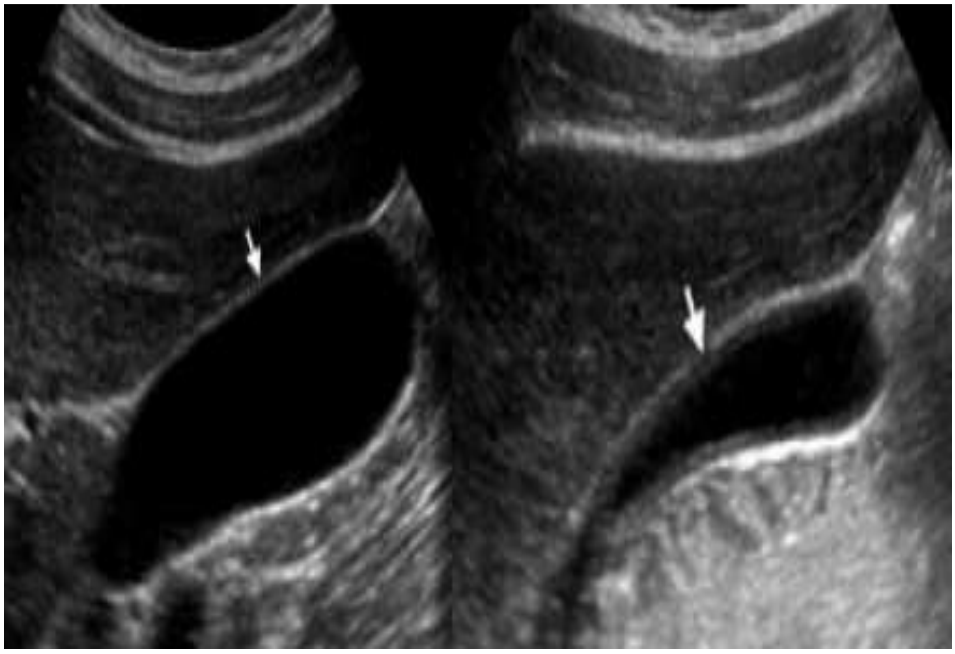
Ultrasonography has an accuracy of 93-95% in determination of gallbladder wall thickness if it is 1 mm. It is 100% sensitive when the thickness is > 1.5 mm. The normal gallbladder appears as a pencil thin line which is echogenic on ultrasonogram. The thickness of gallbladder depends on the degree of distension and pseudo thickening occurs in the post prandial state.

The gallbladder is a hollow pear shaped viscera with thin and regular walls. It is located in the gallbladder fossa between IV and V segments of the liver. This area is devoid of visceral peritoneum. The gallbladder is divided into infundibulum, body and fundus. Its walls comprised of four layers.

The innermost layer is mucosa which is formed by simple columnar epithelium and by a basal lamina. The second layer is made up of irregular muscular tissue. The third layer is by loose connective tissue and the last layer is formed by serosa. The function of the gallbladder is to store the bile and presents a volume of 30-50 ml bile(31).

The sonographic images provide a faithful representation of the gallbladder which can be correlated with its anatomical structure. By means of ultrasonography it is possible to identify three layers. The innermost layer that is mucosa represents the linear, echogenic layer with regular surface. The second

one corresponding to the muscular layer which is thin and slightly hypoechoic. The outermost layer is corresponding to serosa and it is echogenic, linear and regular.



LEFT: USG of a normal gallbladder after an overnight fast shows the wall as a pencil-thin echogenic line (arrow).RIGHT: US in the postprandial state shows pseudothickening of the gallbladder.

According to several authors, the upper limit of normality for gallbladder wall thickness is 3 mm. But in patients under inappropriate fasting ,the gallbladder wall thickness may exceed that limit due to gallbladder smooth muscle contraction. So 8 hours fasting before doing the ultrasound examination is recommended. Another cause of pseudo thickening is erroneous insonation by

the transducer. In this case, the performance of certain maneuvers such as changing the decubitus will be useful to correctly delineate the thickness of the gallbladder wall. Gallbladder thickening is classified as mild when it is 4-7 mm and marked when it is > 7 mm and also as focal or diffuse thickening(32). In cirrhosis patients the key sonographic finding is preservation of mucosal regularity and echogenicity.

The wall thickening occurs at the expense of hypoechoic layer corresponding to edema of the muscular layer and of the connective tissue.

There are multiple causes of gallbladder wall thickening. They are

1. Acute cholecystitis.
2. Chronic cholecystitis.
3. Acalculous cholecystitis.
4. Adenomyomatosis.
5. Gallbladder malignancy.
6. Congestive cardiac failure.
7. Cirrhosis of the liver.

8. Hypoalbuminemia.

9. Renal failure.

10. Pancreatitis

11. Sepsis.

We analyse the diagnostic usefulness of gallbladder wall thickness to differentiate between cirrhotic ascites with portal hypertension and malignant ascites. In this cross sectional study , we enrolled 30 patients of cirrhotic ascites and 30 patients with ascites due to known peritoneal carcinomatosis.

The inclusion criteria for diagnosis of cirrhosis includes spleenomegaly, spider angioma, palmar erythema and based on laboratory evaluation and liver biopsy. The abnormal sonographic findings of spleenomegaly, collateral veins in liver and splenic hilum, ascites, heterogenic liver echoes and irregular liver border were all defined as cirrhosis. Exclusion criteria includes acute and chronic renal insufficiency, heart failure, acute hepatitis, cholecystitis, sepsis.

All patients were examined after 8 hours of fasting and only those patients were included who had a fill gallbladder. Three measurements of gallbladder wall thickness were taken at each site and average measurement was used for analysis. A single operator performed all the ultrasound examinations both in cirrhotic patients and peritoneal carcinomatosis patients. Real time bidimensional and Doppler ultrasound examinations were performed by using 3.5 MHz transducer.

Gallbladder was examined by means of images obtained in both supine and left lateral decubitus positions in order to evaluate the wall thickness , longest axis, width & depth. Portal vein was studied in supine and suspended respiration. Gallbladder wall thickness was measured in the longitudinal scan with ultrasound beam orthogonally oriented at the level of gallbladder anterior wall.

Normal gallbladder wall should measure less than 3-4 mm. It is recommended that this measurement should be taken through the anterior wall of the gallbladder. Because the posterior acoustic shadowing will often make the posterior measurements inaccurate. The thickness was measured by vertical beam to the gallbladder wall and was measured from serosa to mucosa(34).

In liver cirrhosis gallbladder wall thickening is commoly observed. The thickening of gallbladder wall in cirrhosis is multifactorial. Portal hypertension leads to stasis of blood in the gallbladder veins and viscera. It leads to congestion and edema of the gallbladder wall , that is more in cirrhotics when comparing to non-cirrhotics.

The decreased intravascular osmotic pressure , hypoalbuminemia, decreased systemic vascular resistance are all contributing to the development of gallbladder wall thickening in cirrhosis patients. Diffuse gallbladder wall thickening is a non specific finding caused by several disorders. It includes both intrinsic (acute cholecystitis, adenomyomatosis, gallbladder malignancy) and extrinsic causes such as acute hepatititis, cirrhosis of liver, congestive cardiac failure, AIDS, hypoalbuminemia, pancreatitis(36).

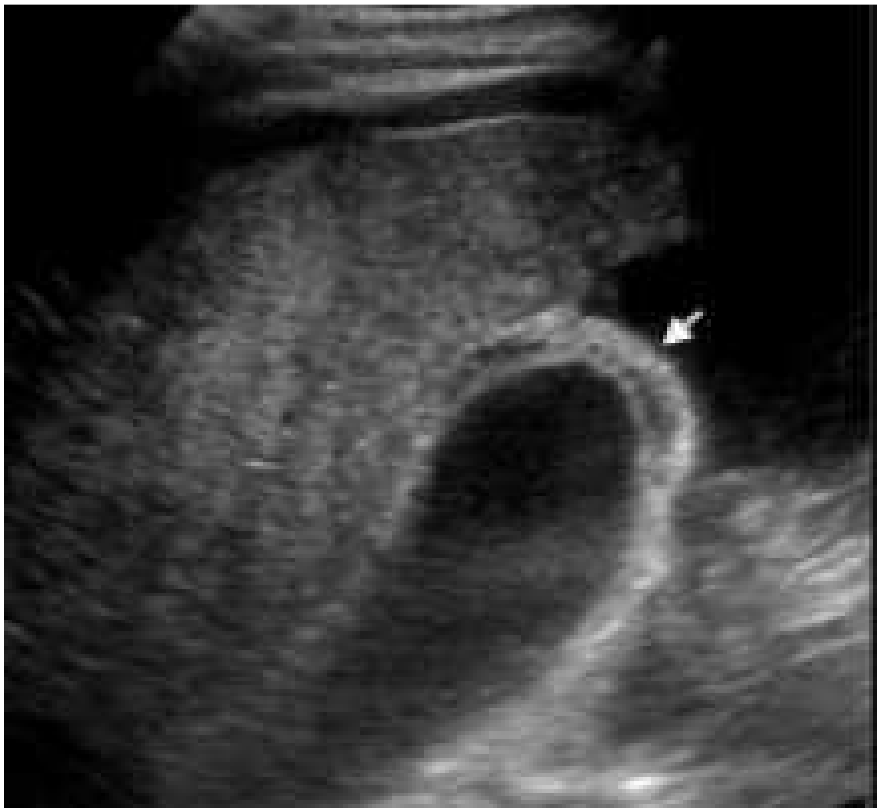
. 

Fig : USG Abdomen in a 56 yr old male with cirrhosis depicts gallbladder wall thickening (arrow), surrounded by ascites. Note the irregular cirrhotic liver parenchyma.

Gallbladder wall thickening is commonly reported in cirrhosis patients. It is often reported in association with portal hypertension. In a model of hamster cirrhosis , portal hypertension was associated with submucosal edema of the gallbladder and dilated vessels seen over the gallbladder wall. These histologic changes were related to gallbladder wall thickening which occurs in cirrhosis with portal hypertension. It is also associated with impaired contractility of the

gallbladder. It is well known that portal hypertension plays a crucial role in the transition of preclinical to clinical phase of cirrhosis of the liver. Portal hypertension also contributes to the development of hepatic encephalopathy, ascites.

It also directly causes the emergence of collateral circulation and variceal hemorrhage. Portal pressure can be measured by invasive methods and the calculation of hepatic venous pressure gradient (HVPP), with catheterisation of hepatic vein via the femoral or jugular route is most commonly used.

Several studies have reported that hypoalbuminemia is a major determining factor in the development of gallbladder wall thickening, where as other studies did not demonstrate such a correlation. Hypoalbuminemia causes edema and structural changes in the gallbladder wall. It leads to gallbladder wall thickening and also affect the gallbladder contractility. So the mechanisms which are responsible for gallbladder wall thickening seem to occur earlier and active in early stages of cirrhosis and precede the onset of portal hypertension(37).

In peritoneal carcinomatosis there is edema and inflammation of the peritoneum. This finding can be used a diagnostic sign for determining the etiology of the ascites in a case.

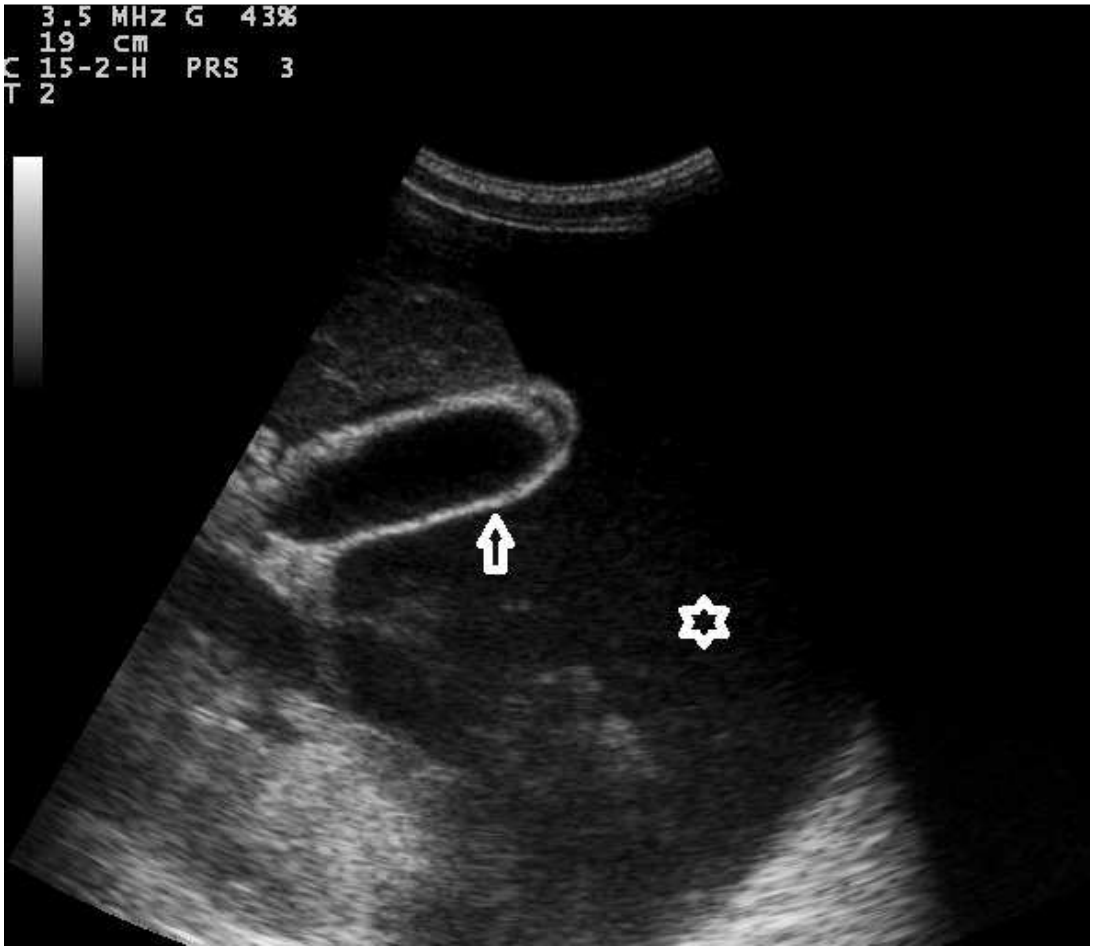


Fig: Abdominal ultrasonogram revealed (arrow) thin gall bladder wall (2 mm in a patients with malignant ascites (stellate) due to ovarian carcinoma**.**

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING:

This study was conducted at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, and Madras Medical College.

ETHICAL COMMITTEE APPROVAL:

Obtained.

STUDY DURATION:

This study was conducted over a period of six months.

STUDY POPULATION:

Patients admitted with chronic liver disease with ascites, malignant induced ascites at medical wards, Institute of Internal medicine.

SAMPLE SIZE:

Sixty patients.

TYPE OF STUDY

Cross sectional study.

INCLUSION CRITERIA:

- Known case of cirrhosis with ascites.
- Newly detected case of cirrhosis with ascites.
- Known case of peritoneal carcinomatosis with ascites.

EXCLUSION CRITERIA:

- Heart failure.
- Acute kidney injury.
- Chronic kidney disease.
- Acute cholecystitis.
- Acute hepatitis.
- Sepsis.

DATA COLLECTION AND METHODS

Informed consent will be obtained from each patient.

Patients have their history taken according to a Questionnaire and subjected to clinical examination.

Patients are subjected to routine blood investigations like complete blood count, renal function tests, liver function tests, PT-INR.

Chest X-ray, Echo cardiography and US Gabdomen will be done.

Patients Gallbladder wall thickness will be assessed by Ultrasonography after 8 hours of fasting with fill gallbladder. Three measurements of gallbladder wall thickness were taken at each site and average measurement was used for analysis.

A single operator performed all the ultrasound examinations both in cirrhotic patients and peritoneal carcinomatosis patients. Real time bidimensional and Doppler ultrasound examinations were performed by using

3.5 MHz transducer. Gallbladder was examined by means of images obtained in both supine and left lateral decubitus positions in order to evaluate the wall thickness. Thickness more than 3 mm was considered significant.

All the data will be entered in proforma (enclosed).

Data will be analyzed using SPSS package and ANOVA.

OBSERVATION

&

RESULTS

OBSERVATION AND RESULTS

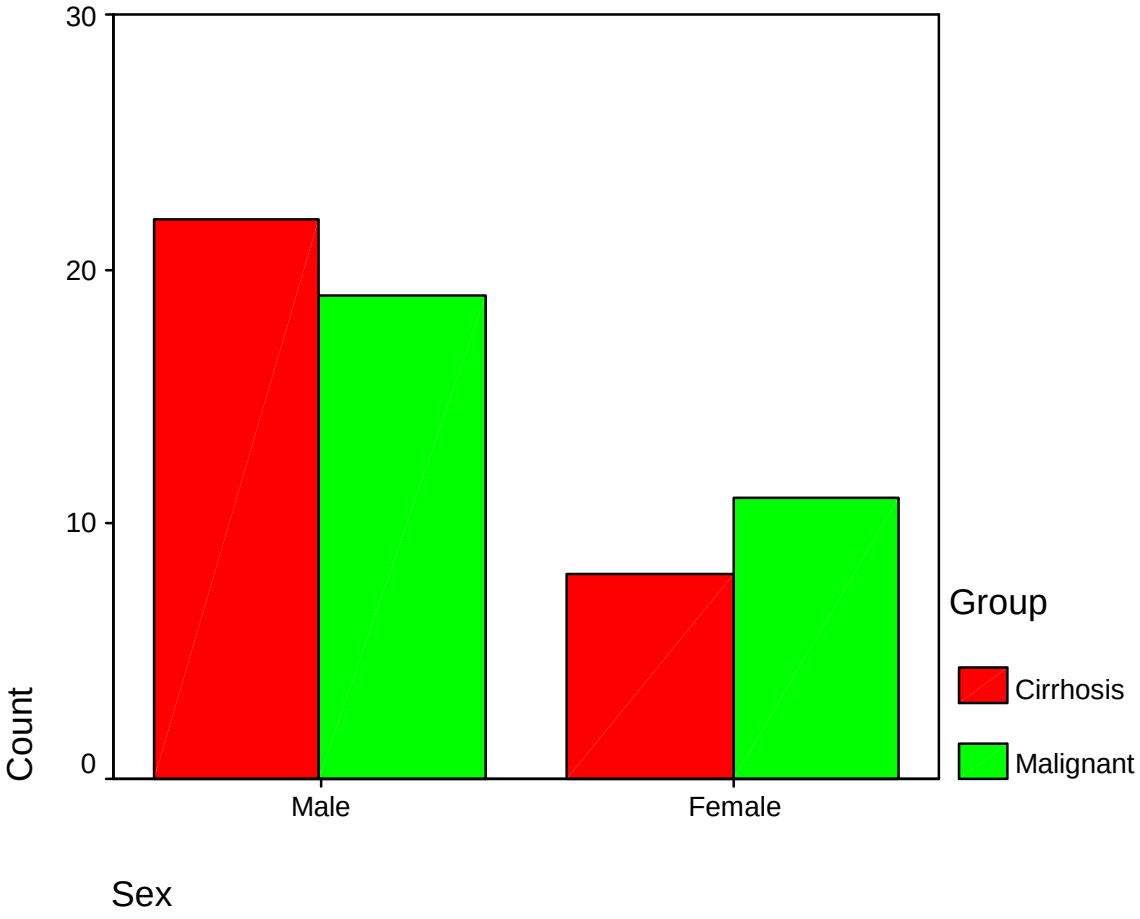
AGE VARIATION AMONG THE STUDY GROUPS:

Group	N	Mean	Std. Deviation	P value
Cirrhosis	30	51.03	10.08	0.58 Not significant
Malignant	30	53.47	11.057	

SEX DISTRIBUTION:

Sex		**Group**		**Total**	**P value**
		Cirrhosis	**Malignant**		
Males	Count	22	19	41	0.405 **NOT SIGNIFICANT**
	% within Sex	53.7%	46.3%	100.0%	
	% within Group	73.3%	63.3%	68.3%	
Females	Count	8	11	19	
	% within Sex	42.1%	57.9%	100.0%	
	% within Group	26.7%	36.7%	31.7%	
Total	Count	30	30	60	
	% within Sex	50.0%	50.0%	100.0%	
	% within Group	100.0%	100.0%	100.0%	

SEX DISTRIBUTION



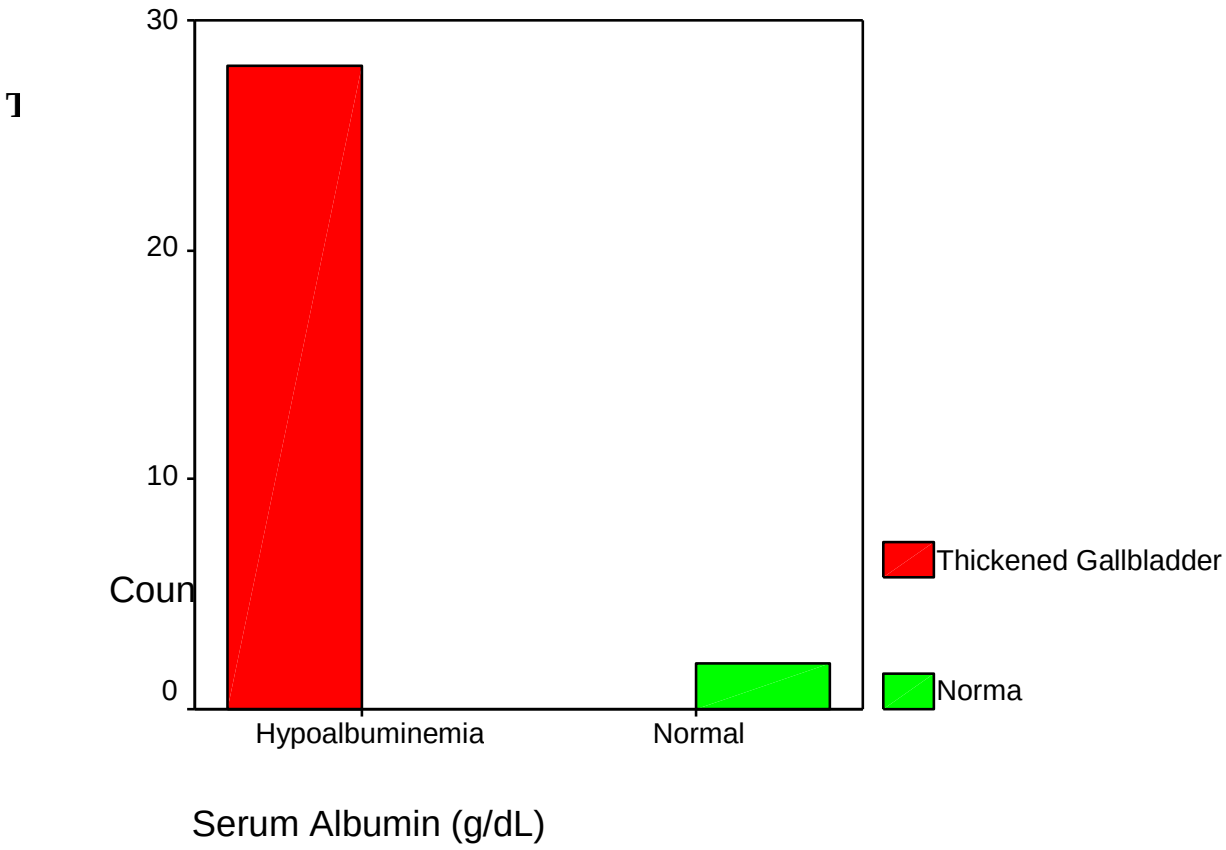
THICKENED GALLBLADDER IN CIRRHOSIS GROUP:

CIRRHOSIS		**Gallbladder wall thickness in mm**		**P value**
SERUM ALBUMIN (g/dl)		**Thickened gallbladder**	**Normal**	
Hypoalbuminemia	Count	28	0	<0.001 **SIGNIFICANT**
	%within serum albumin (g/dl)	100%	0%	
	%within gall bladder wall thickness (mm)	100%	0%	
Normal	Count	0	2	
	%within serum albumin (g/dl)	0%	100%	
	%within gall bladder wall thickness (mm)	0%	100%	
Total		28	2	

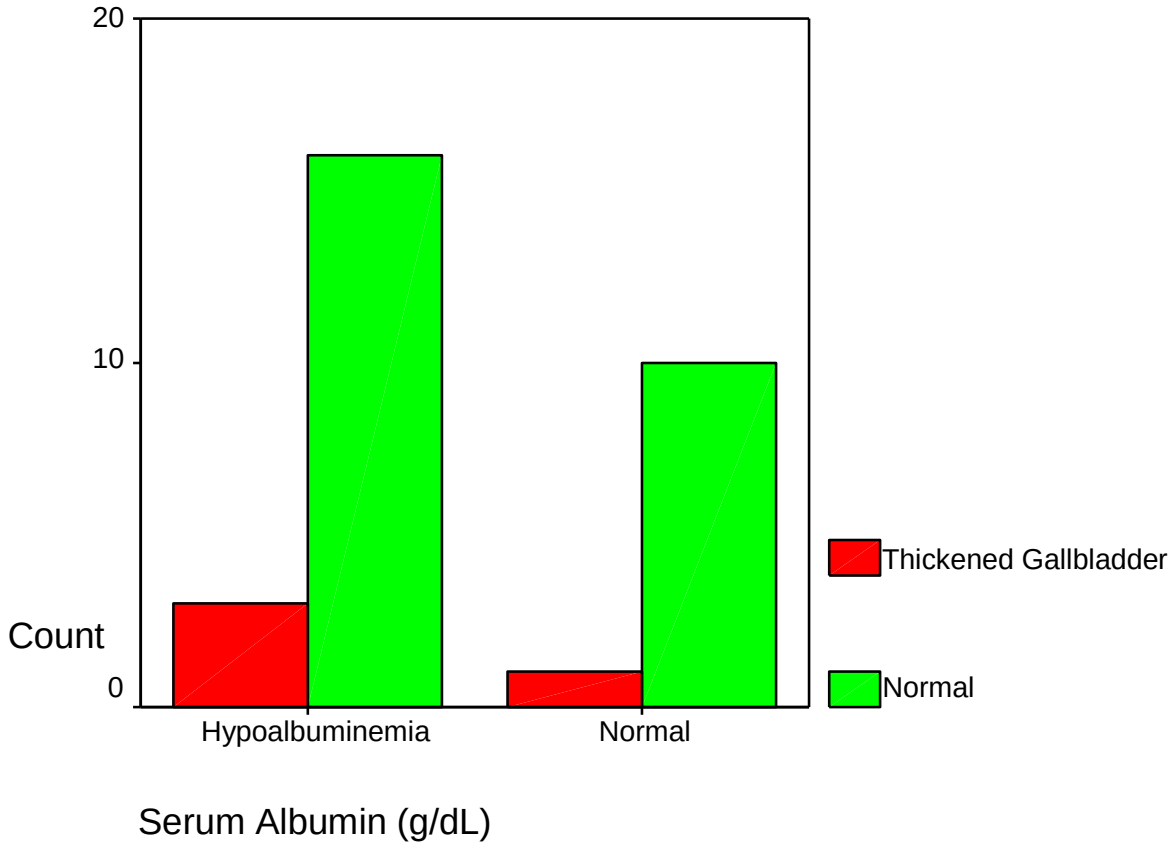
THICKENED GALLBLADDER IN MALIGNANT ASCITES GROUP:

MALIGNANT ASCITES		**Gallbladder wall thickness in mm**		**P value**
SERUM ALBUMIN (g/dl)		**Thickened gallbladder**	**Normal**	
Hypoalbuminemia	Count	3	16	<0.603 **NOT SIGNIFICANT**
	%within serum albumin (g/dl)	15.8%	84.2%	
	%within gall bladder wall thickness (mm)	75%	61.5%	
Normal	Count	1	10	
	%within serum albumin (g/dl)	9.1%	90.9%	
	%within gall bladder wall thickness (mm)	25%	38.5%	
Total		4	26	

THICKENED GALLBLADDER IN CIRRHOSIS GROUP:



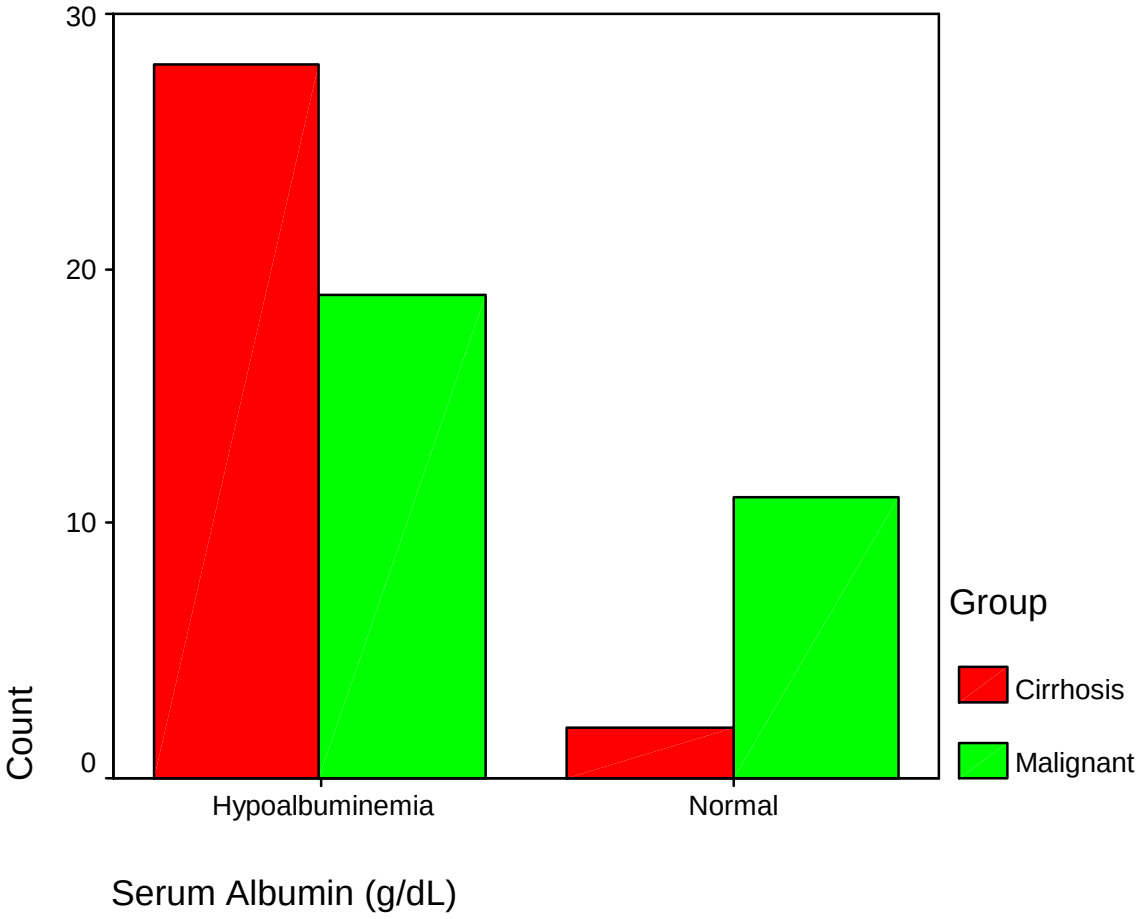
THICKENED GALLBLADDER IN MALIGNANT ASCITES GROUP



CORRELATION BETWEEN SERUM ALBUMIN AND GALLBLADDER WALL THICKNESS:

			Group		
			Cirrhosis	Malignant	P value
Serum Albumin (g/dL)	Hypoalbuminemia	Count	28	19	<0.001 **SIGNIFICANT**
		% within Serum Albumin (g/dL)	59.6%	40.4%	
		% within Group	93.3%	63.3%	
	Normal	Count	2	11	
		% within Serum Albumin (g/dL)	15.4%	84.6%	
		% within Group	6.7%	36.7%	
Total		Count	30	30	

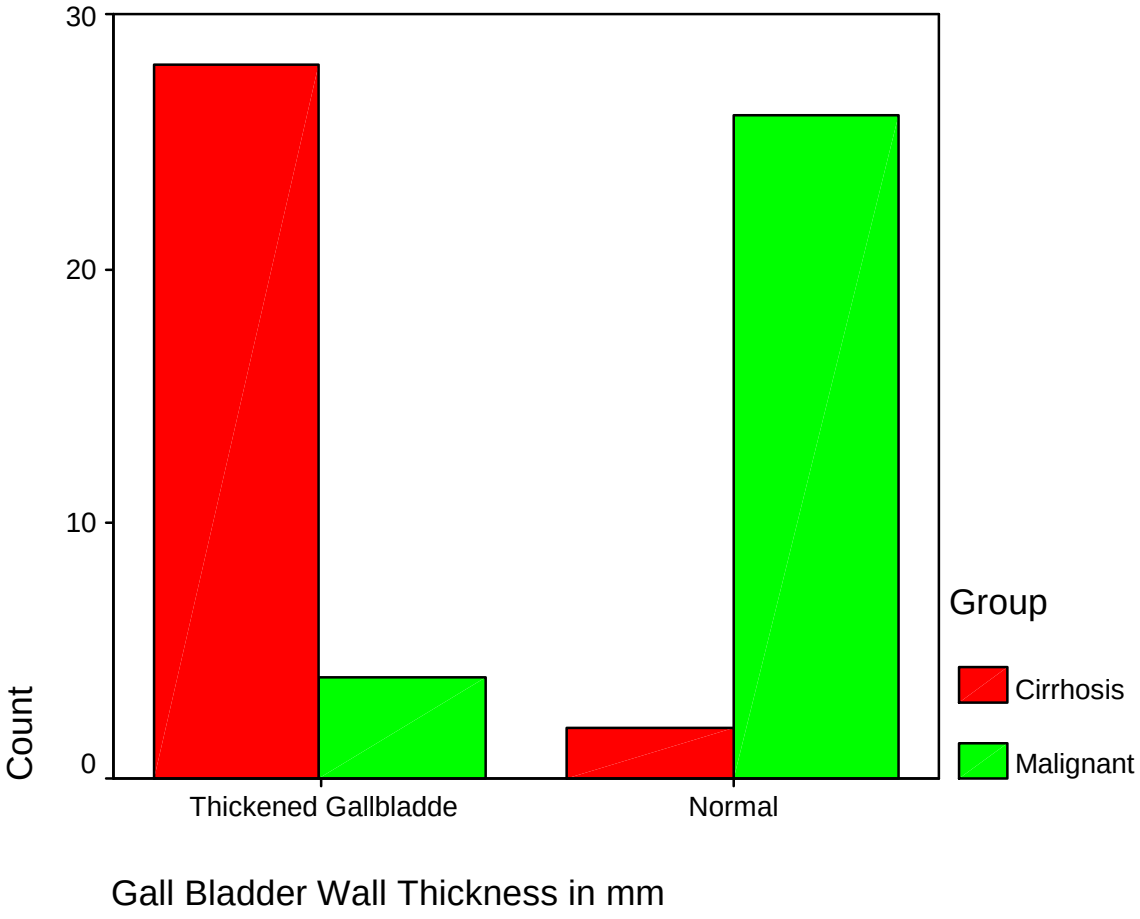
CORRELATION BETWEEN SERUM ALBUMIN AND GALLBLADDER WALL THICKNESS:



THICKENED GALLBLADDER IN CIRRHOSIS AND PERITONEAL CARCINOMATOSIS:

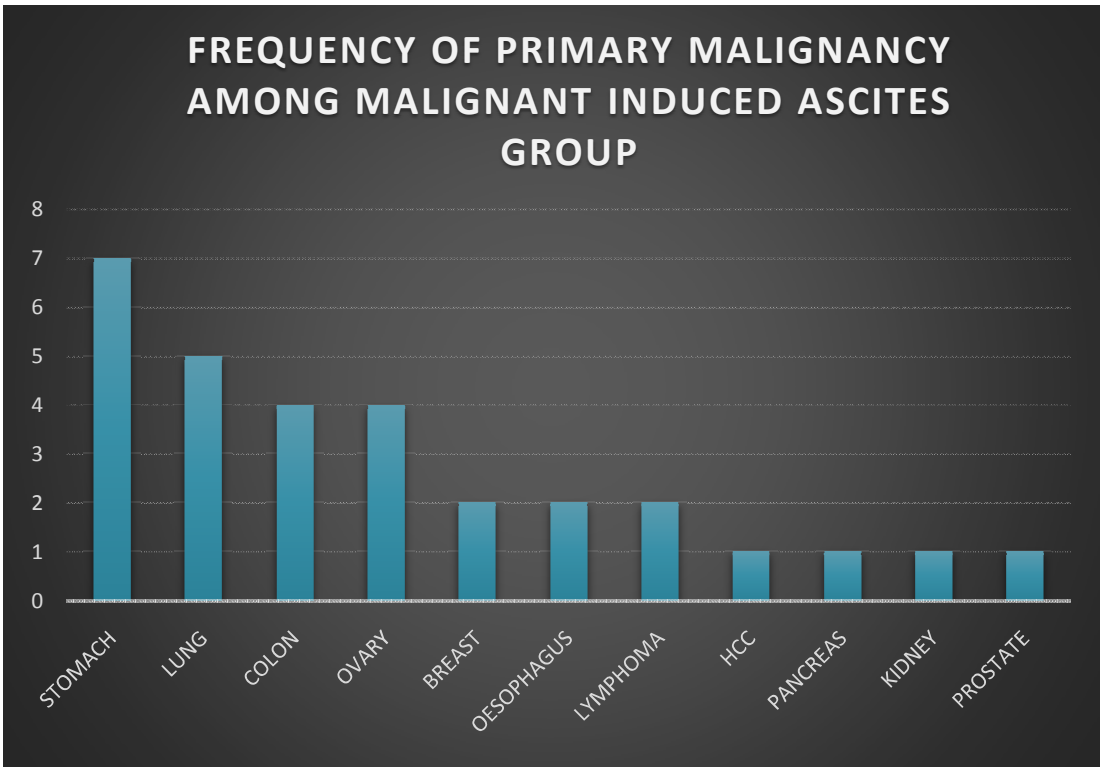
			Group	
			Cirrhosis	Malignant
Gall Bladder Wall Thickness in mm	Thickened Gallbladder	Count	28	4
		% within Gall Bladder Wall Thickness in mm	87.5%	12.5%
		% within Group	93.3%	13.3%
	Normal	Count	2	26
		% within Gall Bladder Wall Thickness in mm	7.1%	92.9%
		% within Group	6.7%	86.7%
Total		Count	30	30
		% within Gall Bladder Wall Thickness in mm	50.0%	50.0%
		% within Group	100.0%	100.0%

THICKENED GALLBLADDER IN CIRRHOSIS AND PERITONEAL CARCINOMATOSIS:



FREQUENCY OF PRIMARY MALIGNANCY AMONG THE PERITONEAL CARCINOMATOSIS GROUP:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		30	50.0	50.0	50.0
	BREAST	2	3.3	3.3	53.3
	COLON	4	6.7	6.7	60.0
	OESOPHAGUS	2	3.3	3.3	63.3
	HCC	1	1.7	1.7	65.0
	KIDNEY	1	1.7	1.7	66.7
	LUNG	5	8.3	8.3	75.0
	LYMPHOMA	2	3.3	3.3	78.3
	OVARY	4	6.7	6.7	85.0
	PANCREAS	1	1.7	1.7	86.7
	PROSTATE	1	1.7	1.7	88.3
	STOMACH	7	11.7	11.7	100.0
	Total	60	100.0	100.0	


FREQUENCY OF PRIMARY MALIGNANCY AMONG MALIGNANT INDUCED ASCITES GROUP
8
7
6
5
4
3
2
1
0
STOMACH
LUNG
COLON
OVARY
BREAST
OESOPHAGUS
LYMPHOMA
HCC
PANCREAS
KIDNEY
PROSTATE

RESULTS :

AGE DISTRIBUTION :

In our study among the cirrhosis group, 25% were in the age group of 30- 40years, 52% were in the age group of 41-50 years, 23% were in the age group of 51-60 years. The mean age is 51.03 yrs. Among the malignant induced ascites group, 8% were in the 30-40yrs, 12% were in the age group of 40-50 yrs, 55% were in 51-60 yrs, 25% were in the range of 61-70 yrs. The mean age in this group is 53.43 yrs.

SEX DISTRIBUTION:

In our study among the cirrhosis group, 73% were males and 27% were females. Among the malignant induced ascites group 63% were males and 37% were females. The correlation between sex distribution and gallbladder wall thickness was not significant.

THICKENED GALLBLADDER IN BOTH GROUPS:

Among the cirrhosis group, 28 patients had thickened gallbladder (>3 mm) and 2 patients had normal gallbladder wall thickness (<3 mm).

Among the malignant induced ascites group 26 patients had normal gallbladder wall thickness and 4 patients had thickened gallbladder.

The correlation of gallbladder wall thickness between these two groups is highly significant ($p < 0.001$).

CORRELATION BETWEEN SERUM ALBUMIN AND GALLBLADDER WALL THICKNESS:

Among the cirrhosis group, 28 patients had hypoalbuminemia (< 3.5 g/ dl) which were forming 93.3% of the group. 2 patients had normal albumin levels (3.5-5 g/dl) which formed 6.7% of the group.

Among the malignant induced ascites group 19 patients had hypoalbuminemia which were forming 63.3 % of the group. 11 patients had normal albumin levels which were forming 36.7 % of the group.

The correlation between hypoalbuminemia and thickening of gallbladder wall

is highly significant (< 0.001).

PRIMARY MALIGNANCY AMONG THE PERITONEAL CARCINOMATOSIS GROUP :

Among this group, the minimum and maximum age of patients with peritoneal carcinomatosis was 32 and 70 respectively. Peritoneal carcinomatosis was mostly in males, 19 patients (63%). The minimum and maximum gallbladder wall thickness was 1.3 mm and 3.70 mm respectively.

The most common etiology was cancer stomach (23%) followed by lung cancer (17%). Other common primary malignancies are ovarian and colon carcinomas, of each contributes about 13 % of the cases. Hepatocellular carcinoma, prostate, kidney , pancreatic malignancies were least common tumours in our study.

DISCUSSION

DISCUSSION

In a study by Hyang YS et al, gallbladder wall thickness had been measured in 31 peritoneal carcinomatosis patients and 49 cirrhotic ascites patients. There are three gallbladder patterns were recognized.

A – Single layered , non thickened wall.

B – Single layered and thickened wall.

C – Double layered and thickened wall.

Pattern A was frequently observed in malignant ascites patients.

Pattern B and C were very commonly detected in cirrhotic ascites.

If ‘ non thickened gallbladder wall’ is used as a criteria for the prediction of malignant ascites , the sensitivity is 80.6% and specificity is 93.9%. Our study is also in agreement with this previous study as the gallbladder was frequently thickened in cirrhosis induced ascites patients.

In a study by Wang et al, the mean age group of patients in cirrhosis induced ascites was 50-64 yrs. In our study the mean age group 46-52 yrs. Another study by Marti bonmarti et al , 54 patients with ascites were observed.They had found that gallbladder wall thickness was significantly increased in patients with liver cirrhosis.

But no correlation was found between serum albumin and gallbladder wall thickness which suggested that increased gallbladder wall thickness in a cirrhotic patient is mainly due to portal hypertension. In contrast to this study, our study showed that hypoalbuminemia is strongly correlated with thickened gallbladder wall in cirrhosis patients .

In a study by Georgiev P et al , 60 patients with cirrhosis and 39 patients with peritoneal carcinomatosis were compared for gallbladder wall thickness. Most of the cirrhotic patients have thickened gallbladder , often with three layered structure (7.7+ or – 3.4 mm). The gallbladders of peritoneal carcinomatosis patients were most often not thickened (2.5 + or – 1.6 mm) . The difference between the two groups were statistically significant in this regard. Thickening of the gallbladder was found in both groups of patients with decreased serum albumin level.

In a study by Afshin mohammadi et al, The minimum and maximum age of patients with peritoneal carcinomatosis was 25 and 80 respectively. The mean age was 54.9±11 years. Peritoneal carcinomatosis was mostly in males, 55 patients (55%). The minimum and maximum gallbladder wall thickness was 1.3 mm and 3.71 mm respectively. And mean GBWT was 2.2±0.6 mm. The least common etiologies for peritoneal carcinomatosis were hepatocellular carcinoma, lymphoma, ovarian and

prostate cancer, all together being only 2% of the cases. The most common etiology was gastric cancer (21%) followed by colon cancer (15%). In our study, the minimum and maximum age of patients with peritoneal carcinomatosis was 32 and 70 respectively. Peritoneal carcinomatosis was mostly in males, 19 patients (63%). The minimum and maximum gallbladder wall thickness was 1.3 mm and 3.70 mm respectively. The most common etiology was cancer stomach (23%) followed by lung cancer (17%).

The ascites induced by portal hypertension in our study was 73% in male patients and 23% in female patients. This reinforces the fact that the higher risk of hepatitis and cirrhosis in males due to involvement in high risk activities such as alcohol abuse, abnormal sexual behaviours, iv drug abuse.

In the peritoneal carcinomatosis group, 63% were males and 37 % were females. The absence of gender correlation is also in agreement with the previous studies.

CONCLUSION

CONCLUSION

- According to our study, the sonographic study of the gallbladder will be helpful as a simple and initial screening tool in differentiating between cirrhosis induced and peritoneal carcinomatosis induced ascites.

- Hypoalbuminemia is correlated well with the development of thickened gallbladder in cirrhosis induced ascites.

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LIMITATIONS OF STUDY

- One limitation of this study is low number of patients and the results should be confirmed in large number of patients.

- This is a cross sectional study. Randomized controlled trials should be done to confirm our results.

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ANNEXURE

‘‘ DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS’’.

PROFORMA:

Name : Patient ID

No: Age/Sex :

IP No :

Patientcharacteristics		**Drugs**
DurationofCLD		□Antibiotics
□Smoking		□Frusemide
□Alcoholism		□Spironolactone
		□Propranolol

CLINICALPARAMETERS			
Pulse		**BloodPressure**	
□Pallor		□Ascites	
□Icterus		□Dilatedveinsovertheabdomen	
□Edema		□Splenomegaly	
□Featuresofhypogonadism		□Hepaticflap	

Investigations:

RFT			**LFT**		
Glucose		mg/dl	Totalbilirubin		mg/dl
Urea		mg/dl	Directbilirubin		mg/dl
Creatinine		mg/dl	SGOT		U/l
Na+		mEq/l	SGPT		U/l
K+		mEq/l	ALP		U/l
HBsAg			Totalprotein		g/dl
Anti-HCV			Albumin		g/dl

ULTRASOUND ABDOMEN:

- Gallbladder wall thickness.
- Spleenomegaly.
- Ascites.
- Collateral veins in liver and spleenic hilum.
- Heterogenic liver echoes.
- Liver border irregularity.

PATIENTCONSENTFORM

StudyDetail	:	Differentiation of Benign from Malignant induced ascites by measuring Gallbladder wall thickness.
StudyCentre	:	RajivGandhiGovernmentGeneralHospital, Chennai.
Patient'sName	:	
Patient'sAge	:	
Identification	:	

Patient may check (□) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. □

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving reason, without my legal Rights being affected. □

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. □

However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I here by consent to participate in this study. ☐

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

Signature/thumb impression

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name:

Dr.S.MUTHUKANI

MASTER CHART :

S.NO.	AGE (YR)	SEX	PRIMARY MALIGNANCY	SERUM ALBUMIN (g/dL)	PLATELETS PER cumm.	SGOT (Iu/L)	SGPT (Iu/L)	GALL BLADDER WALL THICKNESS (GBWT) mm
1	36	M	NA	2.1	60000	46	48	4.5
2	38	M	NA	1.4	43000	62	64	4.7
3	42	M	NA	1.3	41000	40	84	5.2
4	45	M	NA	1.5	15000	41	97	5.6
5	47	M	NA	2.4	26000	72	43	4.8
6	43	M	NA	2.5	100000	74	24	4.6
7	52	M	NA	1.7	86000	102	43	5.3
8	44	M	NA	1.2	76000	108	64	5.4
9	41	M	NA	1.3	54000	137	78	5.6
10	36	M	NA	1.1	48000	32	28	6.1
11	49	M	NA	2.1	42000	28	27	6.3
12	38	M	NA	2.7	30000	40	16	7.2
13	45	M	NA	2.4	20000	18	19	4.7
14	44	M	NA	3.1	78000	30	28	4.9
15	50	M	NA	3	112000	28	42	6.5
16	43	M	NA	2.7	112000	28	42	6.5
17	48	M	NA	1.8	67000	41	26	5.3
18	51	M	NA	1.4	43000	38	28	4.8
19	52	M	NA	1.2	49000	39	27	4.6
20	41	M	NA	1.3	29000	22	20	4.4
21	47	M	NA	2.2	34000	24	40	6.8
22	49	M	NA	2.6	19000	26	21	7.4
23	38	F	NA	1.7	62000	28	26	7.3
24	42	F	NA	2.6	77000	18	24	6.5
25	45	F	NA	1.4	68000	43	26	5.2
26	47	F	NA	1.7	43000	28	42	5.4
27	46	F	NA	1.6	32000	40	44	5.8
28	43	F	NA	1.2	41000	33	38	5.2
29	52	F	NA	1.4	49000	46	42	4.6
30	51	F	NA	2.3	68000	48	52	7.1

31	57	M	STOMACH	3.8	NA	NA	NA	1.3
32	40	M	HCC	3.1	NA	NA	NA	1.5
33	46	M	STOMACH	2.7	NA	NA	NA	1.7
34	64	M	LUNG	3.2	NA	NA	NA	2
35	62	M	COLON	3.4	NA	NA	NA	1.8
36	34	M	LYMPHOMA	3.5	NA	NA	NA	1.6
37	46	M	LUNG	3.2	NA	NA	NA	1.5
38	48	M	ESOPHAGUS	3	NA	NA	NA	2.1
39	52	M	PROSTATE	2.5	NA	NA	NA	1.7
40	61	M	COLON	3.5	NA	NA	NA	1.6
41	68	M	STOMACH	3.7	NA	NA	NA	1.9
42	70	M	PANCREAS	3.1	NA	NA	NA	2.5
43	32	M	LYMPHOMA	3.6	NA	NA	NA	2.1
44	64	M	STOMACH	3.2	NA	NA	NA	1.8
45	62	M	COLON	3.3	NA	NA	NA	1.9
46	49	M	ESOPHAGUS	1.2	NA	NA	NA	3.1
47	53	M	LUNG	3.5	NA	NA	NA	2.6
48	58	M	COLON	3.6	NA	NA	NA	3.7
49	51	M	STOMACH	3	NA	NA	NA	1.8
50	54	F	STOMACH	1.4	NA	NA	NA	3.2
51	65	F	KIDNEY	3.2	NA	NA	NA	1.6
52	48	F	OVARY	3.6	NA	NA	NA	1.7
53	47	F	LUNG	1.5	NA	NA	NA	3.1
54	56	F	BREAST	3.8	NA	NA	NA	2.8
55	54	F	OVARY	3.9	NA	NA	NA	1.5
56	49	F	BREAST	4	NA	NA	NA	1.4
57	47	F	LUNG	3.2	NA	NA	NA	2.1
58	52	F	OVARY	3.6	NA	NA	NA	2.4
59	62	F	STOMACH	3.8	NA	NA	NA	1.8
60	58	F	OVARY	4.2	NA	NA	NA	1.7

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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

CERTIFICATE OF APPROVAL

To
Dr.S.Muthukani,
PG in MD General medicine
Madras Medical College, Chennai-3.

Dear Dr. S.Muthukani

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Differentiation of Benign from malignant induced Ascites by measuring Gall bladder wall thickness" No.22072013.

The following members of Ethics Committee were present in the meeting held on 02.07.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.G.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali, MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. Kalai Selvi -- Member
   Prof of Pharmacology, MMC, Ch-3
6. Prof. Siva Subramanian, -- Member
   Director, Instt. of Internal Medicine, MMC, Ch-3
7. Thiru. S. Govindsamy, BABL -- Lawyer
8. 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.

R Nandhini 12/7/13
Member Secretary, Ethics Committee

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DISSERTATION TITLED "DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS" Submitted in partial fulfilment of Requirements for M.D.DEGREE EXAMINATION BRANCH-I GENERAL MEDICINE THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY CHENNAI INSTITUTE OF INTERNAL MEDICINE MADRAS MEDICAL COLLEGE CHENNAI - 600003. APRIL 2014 CERTIFICATE This is to certify that the dissertation entitled A STUDY ON "DIFFERENTIATION OF BENIGN FROM MALIGNANT INDUCED ASCITES BY MEASURING GALLBLADDER WALL THICKNESS" is a bonafide work done by DR.S . M U T H U K A N I , Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai-3, in partial fulfillment of the...