"APO A1 AND LIPID PROFILE IN CIRRHOTIC PATIENTS AND ITS CORRELATION WITH PROGNOSTIC SCORES: A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI"

By

REG NO. BG0116011

Dissertation

Submitted to the
KLE Academy of Higher Education and Research,
Belagavi, Karnataka.

In partial fulfillment
of the requirements for the degree of

M.D.
in
GENERAL MEDICINE

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

APRIL - 2019

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA

Endorsement

This is to certify that the dissertation entitled **"APO A1 AND LIPID PROFILE IN CIRRHOTIC PATIENTS AND ITS CORRELATION WITH PROGNOSTIC SCORES: A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI"** is a bonafide research work done by **(REG NO. BG0116011).**

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

Date:
Place: Belagavi

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

Date:
Place: Belagavi

LIST OF ABBREVIATIONS

ALT	–	Alanine Amino Transferase
ANA	–	Anti Nuclear Antibodies
Apo A1	–	Apolipoprotein A1
APTT	–	Activated Partial Thromboplastin Time
AST	–	Aspartate Amino Transferase
BMI	–	Body Mass Index
BUN	–	Blood Urea Nitrogen
cAMP	–	Cyclic Adenosine Mono Phosphate
cGMP	–	Cyclic Guanosine Mono Phosphate
HCC	–	Hepato Cellular Carcinoma
HCV	–	Hepatitis C Virus
HDL	–	High density lipoproteins
HE	–	Hepatic Encephalopathy
HSC	–	Hepatic Stellate Cells
INR	–	International Normalized Rate
KC	–	Kupffer Cells
LDL	–	low density lipoproteins

LSEC	–	Liver Sinusoidal Endothelial Cells
MELD	–	Model for End stage Liver Disease
PT	–	Prothrombin Time
RES	–	Reticulo Endothelial System
TG	–	Triglycerides
TIPS	–	Trans Jugular Intrahepatic Porto systemic Shunt
TB	–	Total Bilirubin
VLDL	–	Very Low Density Lipoprotein

ABSTRACT

APO A1 AND LIPID PROFILE IN CIRRHOTIC PATIENTS AND ITS CORRELATION WITH PROGNOSTIC SCORES: A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI

BACKGROUND AND OBJECTIVES

Liver is considered the primary site for cholesterol and lipoprotein synthesis. In cirrhosis, glycogen reserves are substantially reduced, inducing lipolysis and malnutrition and thereby altering the lipid metabolism. Such modifications evolve along with liver disease progression and can be used as a prognostic indicator for decompensated disease. This study was done to evaluate the lipid profile and levels of Apo A1 in patients with cirrhosis and to determine its association with Child-Pugh and MELD scores.

MATERIALS AND METHODS

A total of 106 subjects with liver cirrhosis as evidenced by clinical, biochemical or ultrasonographical features of cirrhosis were included and were classified as per different prognostic scores like Child-Pugh score and MELD score. Lipid profile and Apo A1 measurements were done. The correlation between the Child Pugh score and MELD score with levels of Apo A1 and lipid profile was analyzed.

RESULTS -

All components of the lipid profile were found to be low in patients diagnosed with cirrhosis. Low Apolipoprotein A1 levels (< 1.2 g/L) was seen in 71.64% of the patients. Correlation of MELD score with different components of the lipid profile revealed that there is negative correlation of MELD score with all components of the lipid profile like total cholesterol, LDL, HDL, VLDL, triglycerides and Apo A1. However, statistically significant negative correlation of MELD score was seen only with Apo A1 levels ($p < 0.0001$) and HDL levels ($p < 0.0001$). ANOVA test applied to study variation of means of different components of lipid profile in the different classes of Child Pugh classification revealed that there was statistically significant variance in the means of Apo A1, total cholesterol and HDL levels between the 3 classes of Child Pugh scoring classification.

INTERPRETATION AND CONCLUSION –

A reduction in the lipid profile and Apo A1 in cirrhotics was significantly associated with the severity of liver disease as determined by Child-Pugh and MELD prognostic scores. Evaluation of lipid profile and Apo A1 may be used to determine the synthetic function of liver.

KEY WORDS – Liver cirrhosis, Apolipoprotein A1, MELD score , Child Pugh Score , Lipid Profile .

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INTRODUCTION

Cirrhosis is a common hepatological disorder seen in clinical practice. Cirrhosis is a pathologically defined entity that is associated with a spectrum of characteristic clinical manifestations.

This peculiar transformation of the liver was identified by the first anatomic pathologist, Gianbattista Morgagni in his 500 autopsies published in 1761 but the name of "cirrhosis" (‘cirr’ is orange colour in greek) was given by Laennec in 1826 because of the yellowish-tan colour of the cirrhotic liver. In the present era of modern medicine, cirrhosis of liver has been studied in depth.

The liver plays a key role in the metabolism of plasma lipids and lipoproteins[1]. The liver is considered the primary site for cholesterol and lipoprotein synthesis.

In healthy organisms, a complex balance is maintained between the biosynthesis, utilization and transport of lipid fractions. However, in cirrhosis, the lipid metabolism is altered such that glycogen reserves are substantially reduced, inducing lipolysis and malnutrition[2]

As majority of endogenous cholesterol is synthesized in the hepatic microsomes, synthesis and metabolism of cholesterol is impaired in chronic liver disease resulting in a decrease in plasma level[3].

Severe metabolic impairment in cirrhosis can produce a worsening of the serum lipoprotein pattern. HDL cholesterol and its apolipoproteins have been shown to be reduced in cirrhosis, as also the serum levels of low density lipoprotein (LDL) cholesterol[4].

Previous studies have shown that patients with cirrhosis have an altered lipid metabolism, in particular hypocholesterolemia and hypobetalipoproteinemia[5, 6]. Such modifications evolve along with liver disease progression and can be used as a prognostic indicator for decompensated disease[7, 8, 9]. The mechanisms involved in the reduction of lipid fractions in cirrhotic patients are complex and will still require many studies to be fully understood. Enzymatic (acylCoA: cholesterol acyltransferase - ACAT), protein (microsomal triglyceride transfer protein - MTP) and apoprotein (Apo AI) reductions are thought to be related to such changes[10, 11, 12]

This study aims to determine the alteration in the lipid profile, each of its components like total cholesterol, Low density Lipoprotein (LDL), high density lipoprotein (HDL) , triglycerides (TG) , very low density lipoproteins (VLDL) and in particular Apolipoprotein A1 in patients with liver cirrhosis due to any etiology. We also aim to correlate these values with the worsening in cirrhosis which is determined by Child Pugh Score and MELD score.

OBJECTIVES

1. To evaluate the lipid profile and levels of Apo A1 in patients with cirrhosis

2. To determine the association of lipid profile and level of Apo A1 with MELD score and Child Pugh score in cirrhotic patients.

REVIEW OF LITERATURE

Hepatocytes play a critical role in regulating lipid metabolism. The liver is considered the primary site for cholesterol and lipoprotein synthesis.[13]

HISTORY

Laennec gave cirrhosis its name from the Greek word kirrhos, meaning tawny yellow. According to most medical history textbooks this baptism was first published in a footnote commenting on the incidental finding of yellow nodules in the liver of Jean Edme, a patient described in the first and second editions of Laennec's treatise De J'auscultation mediate[14].

The earliest concepts of cirrhosis dates back to 3500 BC with the Babylonian divination and inspection of the liver , and around 3000 BC to Egyptian , Chinese and Peruvian knowledge of the liver , jaundice, hepatitis and ascites .

Hippocrates (460- 377 BC) described the disease and paracentesis in Corpus Hippocraticum .Diocles of Crystos described hepatic ascites , and Erasistratos of Alexandria described the hard liver and ascites in the year 350 BC .Works in clinical medicine including description of ascites , obstructive jaundice and treatment of liver disease were recorded between AD 25- 200 in Roman medicine. In the literature of Byzantine medicine in the 5^{th} and 6^{th} century, physical findings of hepatic ascites and its treatment by biliary purgatives, dehydration and paracentesis were described. Liver diseases and cirrhosis were also described in Arabian medicine in the 10^{th} and 11^{th} century.

Certain ancient Egyptian scrolls mention the aspiration of clear straw coloured fluid from the abdomen when punctured using needles, before the embalmment process.

The sentiment towards moderation in drinking was documented in a Chinese imperial edict in 12th century BC.

By the 2nd century AD, during the Hung's dynasty rule in china, Chinese medical practitioners had clearly warned public about excessive consumption of wine, which leads to liver damage and eventually insanity, which in modern times is referred to as hepatic encephalopathy.

Buddhist monasteries wrote texts about the severity of the disease and the yellowish discolouration of the eyes along with distension of the abdomen.

In ancient India, the references to alcoholic liver disease and cirrhosis, appear in the rig Veda and Atharva Veda, where they mention the condition associated to excessive consumption of wine and called it abdominal droopsy.

However, it was only in 1930, that the first theory of pathogenesis of liver cirrhosis was put forward by Roessle.

DEFINITION

Cirrhosis, a final pathway for a wide variety of chronic liver diseases, is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules[15,16]

EPIDEMIOLOGY

Irrespective of age, sex, region or race, chronic liver disease occurs throughout the world. According to WHO, about 46% of global diseases and 59% of the mortality is because of chronic diseases and almost 35 million people in the world die of chronic diseases [17]

Liver disease rates are steadily increasing over the years. Liver diseases are recognized as the second leading cause of mortality amongst all digestive diseases in the US[18]

The global prevalence of cirrhosis from autopsy studies ranges from 4.5% to 9.5% in the general population [19.] Hence, it is estimated that more than around fifty million people in the world, taking the adult population, would be affected with chronic liver disease.

Non-invasive tests like transient elastography, which give a more realistic picture could emerge in the near future.

During 2001, the estimated worldwide mortality from cirrhosis was 771,000 people. It ranked 14th and 10th as the leading cause of death in the world and in developed countries, respectively[20]. Deaths from cirrhosis have been estimated to increase and would make it as the 12th leading cause of death in 2020[21].

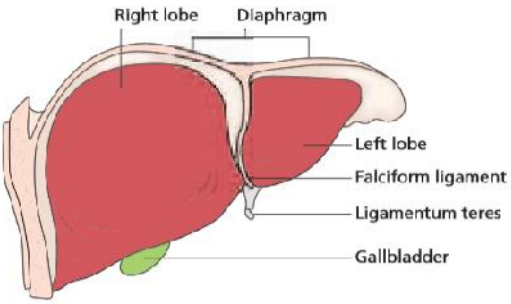
LIVER ANATOMY – IN HEALTH

Liver is the largest organ in the body and it weighs around 1200–1500g.It comprises one-fiftieth of the total adult body weight. The liver is relatively larger in infancy, comprising one-eighteenth of the birth weight. This is mainly due to a large left lobe[22].

Traditionally, liver is divided into 4 lobes based on its external appearance: right, left, caudate, and quadrate.

On the anterior surface, the falciform ligament divides it into the right and left anatomic lobes. The inferior surface has the quadrate lobe, which is defined by the gallbladder fossa, porta hepatis, and ligamentum teres hepatis. The caudate lobe is delineated by the inferior vena cava groove, porta hepatis, and the fissure of ligamentum venosum. Although these lobes are convenient and well known, they are not true functional lobes[15].

Anatomical lobes are two, the right being about six times the size of the left. Lesser segments of the right lobe are the caudate lobe (on the posterior surface) and the quadrate lobe (on the inferior surface). The right and left lobes are separated anteriorly by a fold of peritoneum which is called the falciform ligament, posteriorly by the fissure for the ligamentum venosum and inferiorly by the fissure for the ligamentum teres[22].



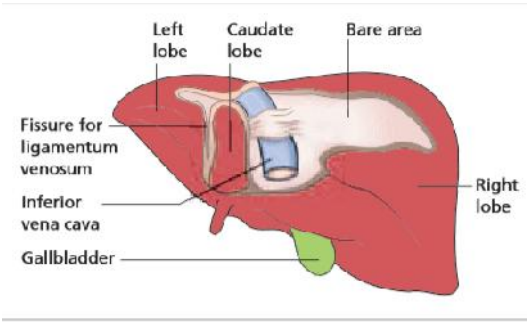


Figure 3.1- Anterior View Of Liver **Figure 3.2- Posterior View Of Liver**

The true right and left lobes of the liver are of roughly equal size and are divided by a plane passing through the bed of the gallbladder and the notch of the inferior vena cava. This plane, which has no external indications, is called the Cantlie line[15,23].

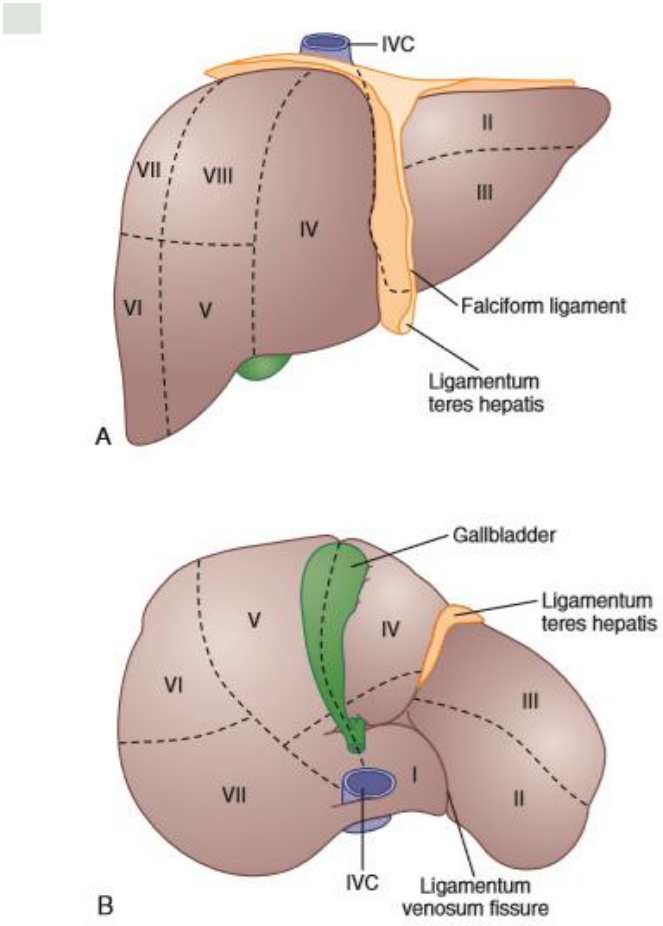


Figure 3.3- Segmental anatomy of liver based on Couinaud terminology

Based on arterial blood supply, portal venous blood supply, biliary drainage, and hepatic venous drainage, the liver is further divided into right and left functional lobes. Each of these is divided into 2 segments, and these are further subdivided into 2 sub segments. Several systems of subdivision have been proposed, but the most widely used systems are those of Couinaud, which follows the distribution of the portal and hepatic veins[24], and Healey and Schroy, which is based on the distribution of bile ducts[25]. In these systems, the sub segments are assigned numbers from 1 to 8, with the caudate lobe being sub segment 1 and the others following in a clockwise pattern.

The liver has dual blood supply. It receives approximately 70% of its blood supply and 40% of its oxygen from the portal vein and 30% of its blood supply and 60% of its oxygen from the hepatic artery[26]. Portal vein is formed from the confluence of the superior mesenteric vein and the splenic vein. At the hilum, the portal vein divides into right and left branches, on which the right and left lobes of the liver are based[27]. The hepatic artery commonly arises from the celiac trunk of the abdominal aorta, although occasionally it arises from the superior mesenteric artery. There exists a common variant, that is a left hepatic artery that branches from the left gastric artery and a right hepatic artery branch that arises from the superior mesenteric artery[27]

In the hilum, the hepatic artery lies anterior to the portal vein and to the left of the bile duct. In the liver, the arteries, portal veins, and bile ducts are surrounded by a fibrous sheath, the Glissonian sheath, whereas the hepatic veins lack this structure[28]. Three major hepatic veins drain into the inferior vena cava, although in 60% to 85% of persons, the left and middle veins unite to enter the inferior vena cava as a single vein[15]

The vessels enter the liver through a fissure, which is called the porta hepatis, which lies far back on the inferior surface of the right lobe. Inside the porta, the portal vein and hepatic artery further divide into branches to the right and left lobes, and the right and left hepatic bile ducts join to form the common hepatic duct[22]

The extrahepatic biliary tract is composed of the common hepatic duct, cystic duct, gallbladder, and right and left hepatic ducts. The right and left hepatic ducts drain the right and left lobes of the liver, respectively. The right and left hepatic ducts together give rise to the common hepatic duct. The caudate lobe drains into the origin of the left hepatic duct or to the right hepatic duct. The cystic duct usually drains into the lateral aspect of the common hepatic duct below its origin to form the bile duct[29].

The hepatic nerve plexus contains fibres from the sympathetic ganglia from T7 to T10, which synapse in the coeliac plexus, the right and left vagi and the right phrenic nerve. It accompanies the hepatic artery and bile ducts into their finest ramifications, even to the portal tracts and hepatic parenchyma[30]

The ligamentum venosum, which is a slender remnant of the ductus venosus of the fetus, arises from the left branch of the portal vein and fuses with the inferior vena cava at the entrance of the left hepatic vein. The ligamentum teres, which is a remnant of the umbilical vein of the fetus, runs in the free edge of the falciform ligament from the umbilicus to the inferior border of the liver and joins the left branch of the portal vein. Small veins accompanying it, function by connecting the portal vein with veins around the umbilicus. These veins become prominent when the portal venous system is obstructed inside the liver. The venous drainage from the liver is into the right and left hepatic veins and these emerge from the back of the liver and at once enter the inferior vena cava very near its point of entry into the right atrium[22].

Lymphatic vessels end in small groups of glands around the porta hepatis. Efferent vessels drain into glands around the coeliac axis. Some superficial lymphatics pass through the diaphragm in the falciform ligament and finally reach the mediastinal glands. Another group accompanies the inferior vena cava into the thorax and they end in a few small glands around the intrathoracic portion of the inferior vena cava.

The liver is completely covered with peritoneum, except in three places. It comes into direct contact with the diaphragm at the bare area of liver, which lies to the right of the fossa for the inferior vena cava. The other areas without peritoneal covering over the liver surface are the fossae for the inferior vena cava and gallbladder. The liver is kept in position by peritoneal ligaments and by the intra-abdominal pressure transmitted by the tone of the muscles of the abdominal wall[22].

HEPATIC MORPHOLOGY/HISTOLOGY

In 1833, Kiernan introduced the concept of hepatic lobules as the basic architecture. He described it as circumscribed pyramidal lobules consisting of a central tributary of the hepatic vein and at the periphery a portal tract containing the bile duct, portal vein radicle and hepatic artery branch. Columns of liver cells and blood-containing sinusoids extend between these two systems[22].

Stereoscopic reconstructions and scanning electron microscopy have shown the human liver as columns of liver cells radiating from a central vein, and interlaced in orderly fashion by sinusoids

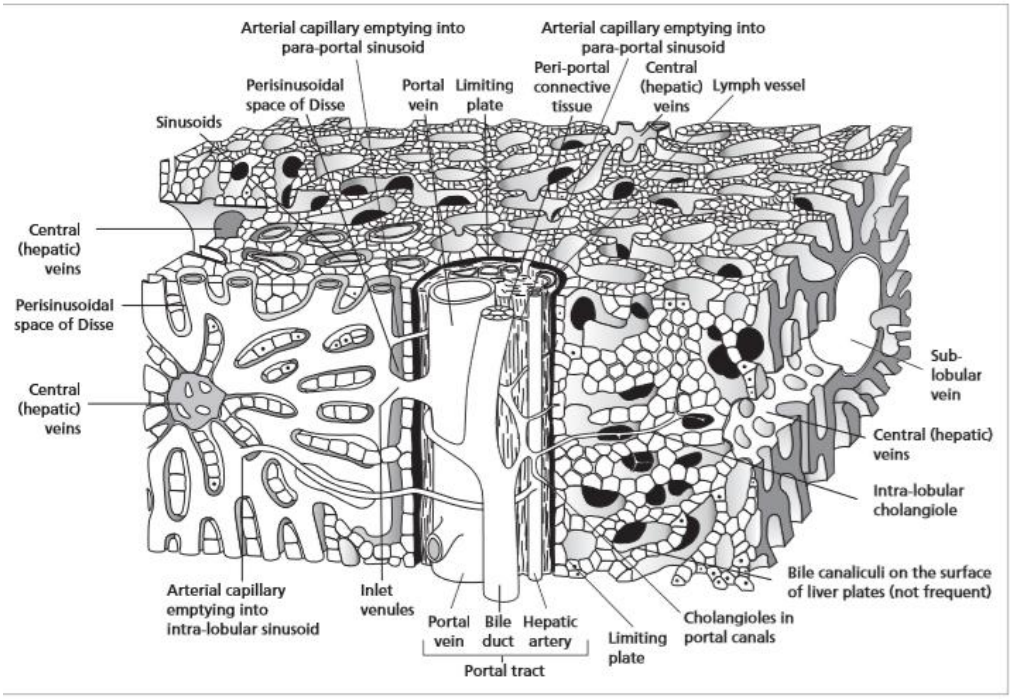


Figure 3.4 – Structure of normal liver

The liver tissue is pervaded by two systems of tunnels, the portal tracts and the hepatic central canals which dovetail in such a way that they never touch each other; the terminal tunnels of the two systems are separated by about 0.5mm. As far as possible the two systems of tunnels run in planes perpendicular to each other. The sinusoids are irregularly disposed, normally in a direction perpendicular to the lines connecting the central veins. The terminal branches of the portal vein discharge their blood into the sinusoids and the direction of flow is determined by the higher pressure in the portal vein than in the central vein.

The central hepatic canals contain radicles of the hepatic vein and their adventitia. They are surrounded by a limiting plate of liver cells. The portal triads contain the portal vein radicle, the hepatic arteriole and bile duct with a few round cells and a little connective tissue. They are surrounded by a limiting plate of liver cells. Portal dyads are as frequent as triads, with the portal vein being the most

frequently absent element. Within each linear centimetre of liver tissue obtained at biopsy there are usually two interlobular bile ducts, two hepatic arteries and one portal vein per portal tract, with six full portal triads[31].

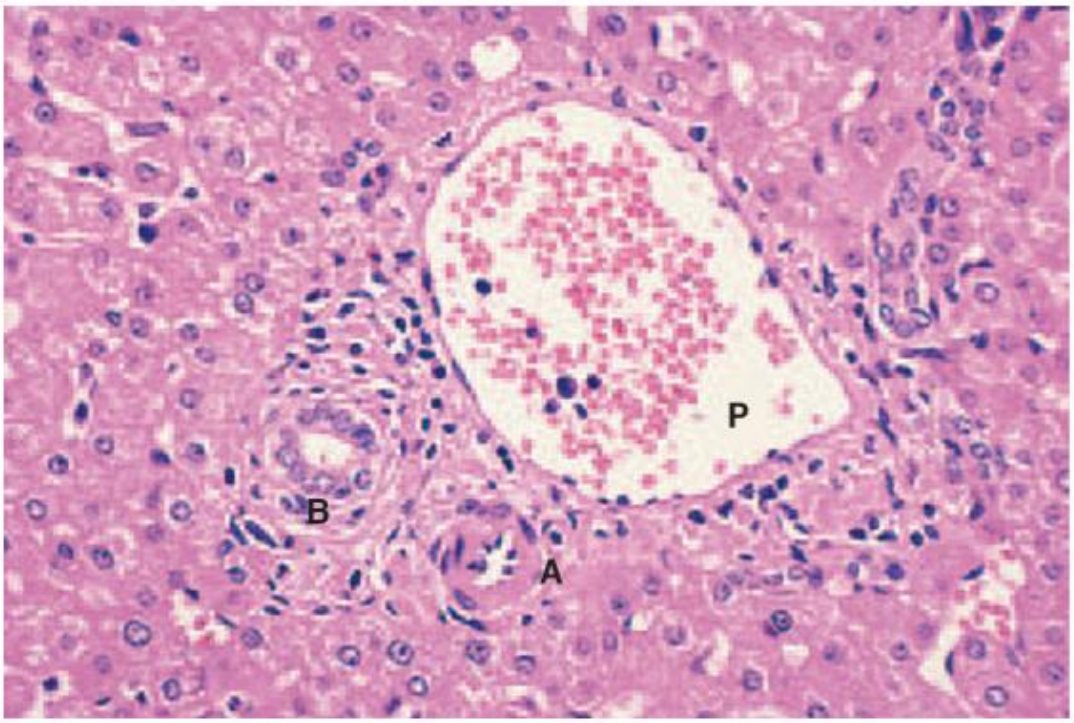


Fig. 1.11. Normal portal tract. A, hepatic artery; B, bile duct; P, portal vein. (H & E.)

Figure 3.5- Normal portal tract- histology

The liver has to be divided functionally. Traditionally, the unit is based on a central hepatic vein and its surrounding liver cells. However, Rappaport envisages a series of functional acini, each centered on the portal triad with its terminal branch of portal vein, hepatic artery and bile duct (zone 1). These interdigitate, mainly perpendicularly, with terminal hepatic veins of adjacent acini. The circulatory peripheries of acini (adjacent to terminal hepatic veins) (zone 3) suffer most from injury whether viral, toxic or anoxic. Bridging necrosis is located in this area.

The regions closer to the axis formed by afferent vessels and bile ducts survive longer and may later form the core from which regeneration will proceed. The contribution of each acinar zone to liver cell regeneration depends on the acinar location of damage[32]

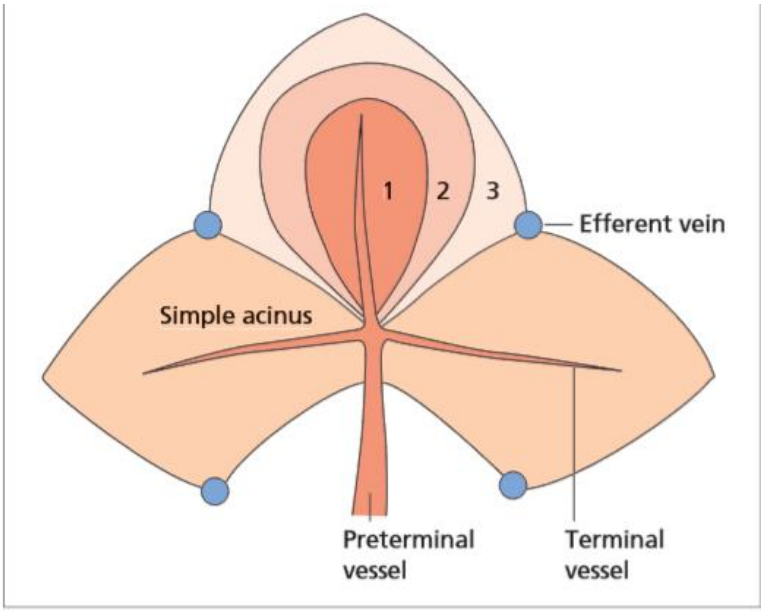


Fig. 1.12. The complex acinus according to Rappaport. Zone 1 is adjacent to the entry (portal venous) system. Zone 3 is adjacent to the exit (hepatic venous) system.

Figure 3.6 – The complex acinus according to Rappaport

The liver cells (hepatocytes) comprise about 60% of the liver. They are polygonal and approximately 30mm in diameter. The nucleus is single, and it divides by mitosis.

The lifespan of liver cells is around 150 days in experimental animals. The sinusoids are lined by endothelial cells. Associated with the sinusoids are the phagocytic cells of the reticulo-endothelial system (Kupffer cells), and the hepatic stellate cells, which have also been called fat storing cells, Ito cells and lipocytes.

The space of Disse is a tissue space between hepatocytes and sinusoidal endothelial cells. The hepatic lymphatics are found in the peri-portal connective tissue and are lined throughout by endothelium. Tissue fluid seeps through the endothelium into the lymph vessels. The branch of the hepatic arteriole forms a plexus around the bile ducts and supplies the structures in the portal tracts. It empties into the sinusoidal network at different levels. There is no direct hepatic arteriolar–portal venous anastomoses. The excretory system of the liver begins with the bile canaliculi. The intralobular canalicular network drains into thin-walled terminal bile ducts or ductules (cholangioles, canals of Hering) lined with cuboidal epithelium. These terminate in larger (interlobular) bile ducts in the portal canals.

METABOLIC FUNCTIONS OF THE LIVER

The liver cells are all together a large chemically reactant pool having a very high rate of metabolism, sharing substrates and energy from one metabolic system to another, processing and synthesizing multiple substance that are transported to other areas of the body and performing a myriad of other metabolic functions.

I. Carbohydrate Metabolism:

In carbohydrate metabolism, the liver performs the following specific functions:

1. Storage of glycogen
2. Conversion of galactose and fructose into glucose
3. Gluconeogenesis
4. Formation of many important chemical compounds form the intermediate products of carbohydrate metabolism.

II. Fat Metabolism:

Although some fat metabolism takes place in all cells of the body, certain aspects of fat metabolism occur mainly in the liver. Specific functions of the liver in fat metabolism are:

1. A very high rate of oxidation of fatty acids to supply energy to other bodily functions.
2. Formation of most of the lipoproteins
3. Synthesis of large quantities of cholesterol and proteins to fat
4. Conversion of large quantities of carbohydrates and protein to fat.

III. Protein Metabolism:

Even though a large proportion of the processes for carbohydrate and fat metabolism occurs in the liver, the body could probably dispense with many of these functions of the liver and still survive. On the other hand, the body cannot dispense with the services of the liver in protein metabolism for more than a few days without death ensuing. The most important function of the liver in protein metabolism are.

1. Deamination of amino acids
2. Formation of urea for the removal of ammonia from the body fluids
3. Formation of plasma proteins, and
4. Interconversions among the different amino acids and other compounds important to the metabolic process of the body.

IV. Miscellaneous Metabolic Functions of the Liver Storage of Vitamins:

The liver has a propensity for storing vitamins and has long been known as an excellent source of certain vitamins in treating patients. The single vitamin stored in greatest quantity in the liver is the vitamin A, but large quantities of vitamin D and B12 are normally stored as well. Sufficient quantities of vitamin A can be stored to prevent the deficiency of vitamin A for as long as 10 months. Sufficient vitamin D can be stored to prevent deficiency for as long as 3 to 4 months, and vitamin B12 can be stored for at least a year and may be several years.

V. Relationship of the Liver to Blood Coagulation:

The liver forms a large proportion of the blood substances used in the coagulation process. These are fibrinogen, prothrombin, accelerator, globulin, factor VII, and several other important coagulation factors. Vitamin K is required for the metabolic processes of the liver for the formation of prothrombin and factors VII, IX, and X. In the absence of vitamin K, the concentrations of these substances fall very low, and this almost prevents blood coagulation.

VI. Storage of iron:

Except for iron in the haemoglobin of the blood, by far the greater proportion of the iron in the body is usually stored in the liver in the form of ferritin. The hepatic cells contain large amounts of a protein called apoferritin, which can combine with either small or large quantities of iron. Therefore, when iron is available in the body in extra quantities, it combines with apoferritin to form ferritin and is stored in this form in the hepatic cells until needed elsewhere

PATHOGENESIS OF CIRRHOSIS

Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases. Even though the causes of liver cirrhosis are multifactorial, there are a few pathological characteristics that are common to all cases of liver cirrhosis- these include degeneration and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissues and regenerative nodules, and loss of liver function[16,33-35]. Fibrosis is a precursor of cirrhosis and this is a pivotal pathological process in the evolution of all chronic liver diseases to cirrhosis[36.37].

The liver is formed by parenchymal cells and other cells commonly known as nonparenchymal cells. The hepatic sinusoids are lined by three different nonparenchymal cells: liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs). Both hepatic parenchymal and nonparenchymal cells are involved in the initiation and progression of liver fibrosis and cirrhosis[15].

The liver cell type most implicated in the pathogenesis of liver fibrosis is the hepatic stellate cell. In normal liver, the hepatic stellate cell is viewed as a pericyte that lies albuminal to the sinusoidal endothelial cell in the space of Disse[38]. On activation, a hepatic stellate cell transforms into a myofibroblast[39]. Activation is characterized by increase in the expression of smooth muscle actin, motility, and contractility.

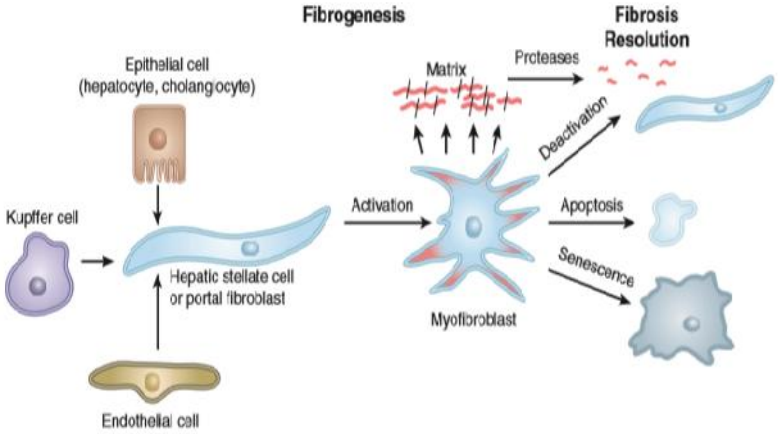


FIGURE 74-1. Schematic overview of the pathogenesis of fibrosis and reversal of fibrosis in cirrhosis. Epithelial cell injury in combination with cytokine release by Kupffer cells and paracrine molecule release by sinusoidal endothelial cells leads to activation of hepatic stellate cells (or portal fibroblasts) into myofibroblasts. Reversal of fibrosis results from myofibroblast deactivation, apoptosis, or senescence. Matrix proteases can also achieve fibrosis resolution (see text for details).

Figure 3.7 – Pathogenesis of cirrhosis

HSCs (Hepatic Stellate Cells) are also known as Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells, and their main function is storage of vitamin A and other retinoids[35,37,40].

Multiple injurious insults and/or exposure to inflammatory cytokines such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and interleukin (IL)-1, lead to transition of hepatic stellate cells from a quiescent to activated state. HSC activation is a pivotal event in initiation and progression of hepatic fibrosis and a major contributor to collagen deposition[40,41].

This activation of HSCs is characterized by cell proliferation and migration, contraction after transforming into myofibroblasts, generation of a large amount of collagen and other extracellular matrix (ECM), finally leading to fibrosis of the liver parenchyma[42].

LSECs (liver sinusoidal endothelial cells) constitute the sinusoidal wall and it is also called the endothelium. The structural characteristic of LSECs is the fenestrae on the surface of the endothelium[43]. LSECs have high endocytotic capacity[44]. Chronic alcohol abuse could result in defenestration, and a decrease in the number of fenestrae[44,45]. In cirrhotic liver, defenestration of sinusoidal endothelium and the presence of a subendothelial basement membrane are frequently present[46].

Defenestration and capillarization of the hepatic endothelium are believed to be important in the initiation of perisinusoidal fibrosis by altering retinol metabolism. It has been shown that LSECs can secrete the cytokine IL-33 to activate HSCs and promote fibrosis[47]. Defenestration and capillarization of LSECs lead to impaired substrate exchange and are considered major contributing factors for hepatic dysfunction in liver cirrhosis[48]. However, differentiated LSECs can promote reversion of activated HSCs to quiescence and thereby accelerate regression and prevent progression of fibrosis through vascular endothelial growth factor (VEGF)-stimulated NO production[49,50]

Kupffer Cells are also known as Browicz-Kupffer cells and stellate macrophages. They are specialized macrophages located in the lining walls of the sinusoids of the liver that form part of the reticuloendothelial system (RES)[51]. These Kupffer Cells are activated by many injurious factors such as viral infection, alcohol, high-fat diet, and iron deposition. Activated KCs destroy hepatocytes by producing harmful soluble mediators and serving as antigen-presenting cells during viral infection[52]. KC-mediated hepatic inflammation is considered to aggravate liver injury and fibrosis[53,54].

KCs are involved in the activation of HSCs and formation of fibrosis. Alcohol can induce the circulating level of Gram-negative bacterial lipopolysaccharide (LPS), these lipopolysaccharides are strong activators of KCs[55]. In cases of genetic hemochromatosis, iron overload in KCs induces the expression of intercellular adhesion molecule (ICAM)-1 on hepatocytes, thereby facilitating activation of HSCs and collagen deposition in the hepatic tissues[56]. Gelatinase secreted by activated KCs triggers the phenotypic change in HSCs by degrading collagen type IV[57]. KCs engulf apoptotic bodies and produce death ligands, including Fas ligand and TNF-α, thereby promotes inflammation and fibrogenesis[58]. In addition, KCs activated by β-glucans increase portal pressure through the release of thromboxane A2 in normal and fibrotic liver[59].

Hepatocytes are the primary liver parenchymal cells, and they play complicated roles in fibrosis and cirrhosis. Hepatocytes are targets for most hepatotoxic agents, including hepatitis viruses, alcohol metabolites, and bile acids. Chronic liver diseases either promotes apoptosis or trigger compensatory regeneration of hepatocytes[60]. Damaged hepatocytes release reactive oxygen species and fibrogenic mediators, they also induce activation of HSCs, and stimulate the fibrogenic actions of myofibroblasts[61]. Apoptosis of hepatocytes is a common event in liver injury and contributes to tissue inflammation, fibrogenesis, and development of cirrhosis. Both HCV infection and ethanol consumption induce hepatocyte apoptosis in animal models and humans, and induction may be related to downregulation of Bcl-2 signalling[62]. Chronic HCV infection can induce hepatocyte G1 arrest and impair hepatocellular function and limit hepatic regeneration[63]. In CCl_4-induced liver injury, hepatocyte apoptosis is induced at the early phase, which is followed by constant proliferation and if it persists, liver cirrhosis ensues at a later stage.

Hepatocytes are the major sources of matrix metalloproteinases (MMP-2, MMP-3 and MMP-13) and tissue inhibitors of matrix metalloproteinases (TIMP-1 and TIMP-2); all of which are involved in the pathogenesis of liver cirrhosis in CCl_4-induced liver cirrhosis in rats[64]. In the last fibrotic stage or cirrhosis, hypoxic hepatocytes become a predominant source of TGF-β1, further exacerbating hepatic fibrogenesis[65]. Recently, it has been shown that hepatocyte telomere shortening, and senescence can result in fibrotic scarring at the cirrhosis stage, presenting a novel explanation for the pathophysiology of cirrhosis[66].

Therefore, multiple cell types in the liver participate in fibrogenesis, although the hepatic stellate cell is most directly implicated in this process because of its abundant capacity to produce matrix.

ETIOLOGY

Table 3.1-Common causes of cirrhosis[15]

Viral	Hepatitis B Virus Hepatitis C Virus Hepatitis D Virus
Autoimmune	Autoimmune hepatitis Primary Biliary Cirrhosis Primary Sclerosing Cholangitis
Toxic	Alcohol Arsenic
Metabolic	α1-Antitrypsin deficiency Galactosemia Glycogen storage disease Hemochromatosis Nonalcoholic fatty liver disease Wilson disease
Biliary	Atresia Stone Tumor
Vascular	Budd-Chiari syndrome Cardiac fibrosis
Genetic	Cystic Fibrosis Lysosomal acid lipase deficiency
Iatrogenic	Biliary injury Drugs: high-dose vitamin A, methotrexate

Alcoholic liver disease and cirrhosis –

Three principle alcohol induced lesions are –

- Alcoholic fatty liver
- Alcoholic hepatitis
- Alcoholic cirrhosis

Although chronic alcoholism is the most common cause of cirrhosis, the quantity and duration of drinking necessary to cause cirrhosis remains unclear. The typical alcoholic patient with cirrhosis has had a daily consumption of a pint or more of whisky, several quarts wine, or an equivalent amount of beer or another kind of spirit for at least 10 years. The amount and duration of ethanol ingestion, rather than the type of alcoholic beverage or the pattern of ingestion, appear to be the important determinants of liver injury. In general, the latent period preceding the development of cirrhosis is inversely related to the level of daily alcohol intake. In alcoholic fatty liver, the organ is enlarged, yellow greasy and firm. Hepatocytes are distended by large cytoplasmic fat vaculoes which push the hepatocyte nucleus against the cell membrane.

In alcoholic hepatitis, morphologic features include hepatocyte degeneration and necrosis, often with ballooned cells and an infiltrate of polymorphonuclear leukocytes and lymphocytes. The polymorphonuclear cells may encircle damaged hepatocytes which contain Mallory bodies or alcoholic hyaline, which are clumps of perinuclear, deeply eosinophilic material believed to represent aggregated intermediate filaments. With continued intake of alcohol and destruction of hepatocytes, fibroblasts appear at the site of injury and stimulate collagen formation.

The fine connective tissue network surrounds small masses of remaining liver cells which regenerate and form nodules. With continued hepatocyte destruction and collagen deposition, the liver shrinks in size, acquires a nodular appearance and becomes hard as "end-stage" cirrhosis develops.

Post necrotic cirrhosis/post viral cirrhosis

Post necrotic cirrhosis represents the final common pathway of many types advanced liver injury. Post necrotic cirrhosis is characterized morphologically by

1. Extensive confluent loss of liver cells
2. Stromal collapse and fibrosis and
3. Irregular nodules of regenerating hepatocytes, varying in size from microscopic to several centimeters in diameter.

Post necrotic cirrhosis is a morphologic term referring to a defined stage of advanced chronic liver injury of both specific and unknown causes. The known causes include viral hepatitis, drugs and toxins.

Biliary cirrhosis

Biliary cirrhosis results from injury to or prolonged obstruction of either the intrahepatic or extrahepatic biliary system. Primary biliary cirrhosis, the cause of which is unknown, is characterized by chronic inflammation and fibrous obliteration of intrahepatic bile ductules. It is frequently associated with a variety of disorders presumed to be autoimmune in nature, such as the CREST syndrome, the sicca syndrome, autoimmune thyroiditis and renal tubular acidosis, and therefore, a disordered immune response may be involved. Secondary biliary cirrhosis is the result

of long-standing obstruction of the larger extra-hepatic ducts. Causes include post-operative strictures or gallstones, chronic pancreatitis leading to biliary stricture, idiopathic sclerosing cholangitis, congenital biliary atresia and cystic fibrosis.

Cardiac cirrhosis

Prolonged, severe right-sided congestive heart failure may lead to chronic liver injury and cardiac cirrhosis. With prolonged passive congestion and ischemia from poor perfusion secondary to reduced cardiac output, necrosis of centrilobular hepatocytes ensues and leads to fibrosis in these central areas. Gross examination of the liver shows alternating red (congested) and pale (fibrotic) areas, a pattern often referred to as "nutmeg liver". Improvement in management of cardiac disorders, particularly advances in surgical treatment, has reduced the frequency of cardiac cirrhosis.

Cryptogenic cirrhosis

The etiology is unknown and this is clearly a heterogeneous group. The advent of HbsAg transferred many previously designated cryptogenic cirrhotics to the post-necrotic group. Estimations of serum smooth muscle and mitochondrial antibodies and better interpretation of liver histology separate others into the chronic active hepatitis primary biliary cirrhosis group. There remains a hard core of patients in whom the cirrhosis remains cryptogenic.

CLASSIFICATION OF CIRRHOSIS

Cirrhosis was classified morphologically as micronodular, macronodular, or mixed. Micronodular cirrhosis, which is characterized by nodules less than 3 mm in diameter, was believed to be caused by alcohol, hemochromatosis, cholestatic causes of cirrhosis, and hepatic venous outflow obstruction. However, macronodular cirrhosis, characterized by various sized nodules larger than 3 mm, and was believed to be secondary to chronic viral hepatitis.

Although it is important from a historic perspective, the morphological classification system has a number of limitations and has therefore largely been abandoned. Firstly, it is relatively nonspecific with regard to etiology. Second, the morphologic appearance of the liver may change as the liver disease progresses; micronodular cirrhosis usually progresses to macronodular cirrhosis[67]. Third, is that the serological markers available today are more specific than morphological appearance of the liver for determining the etiology of cirrhosis. As an example, antimitochondrial antibodies have a specificity of 98 percent for primary biliary cholangitis[68]. Finally, accurate assessment of liver morphology can only be achieved at surgery, laparoscopy, or autopsy, while in today's clinical practice there are less invasive means to make an etiologic diagnosis.

Cirrhosis may be classified either anatomically or etiologically

1) MORPHOLOGIC CLASSIFICATION

a) MICRONDULAR CIRRHOSIS

Histologically has small rather uniform 3mm nodules separated by thin fibrous septa usually due to a chemical agent as alcohol which diffuse uniformly throughout the liver[3]

b) MACRONODULAR CIRRHOSIS

Histologically has larger nodules separated by wider scars and irregularly distributed throughout the liver usually due to an infectious agent such as viral hepatitis which does not diffuse uniformly throughout the liver.

c) MIXED

Having both micronodular and macronodular features.

2) ETIOLOGICAL CLASSIFICATION

1. Alcoholic.
2. Cryptogenic and post necrotic.
3. Biliary.
4. Cardiac
5. Metabolic, inherited, and drug-related.

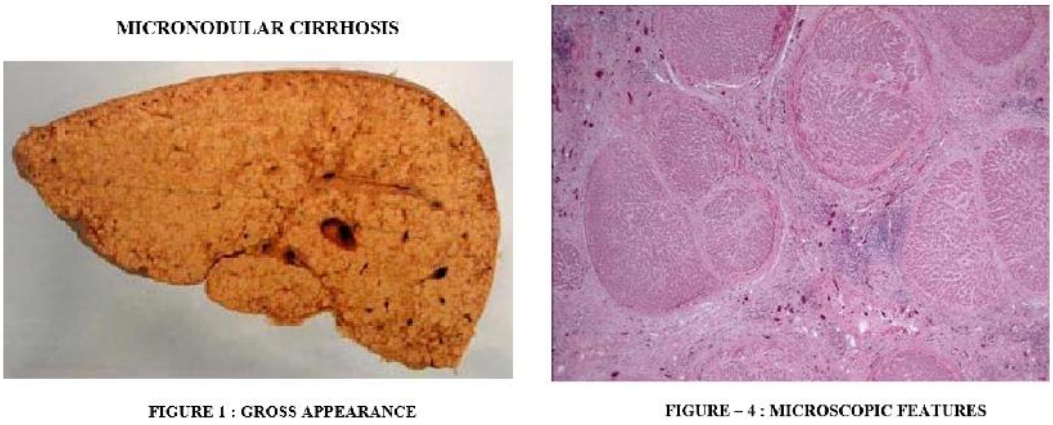


Figure 3.8 – Micronodular cirrhosis – gross and microscopy

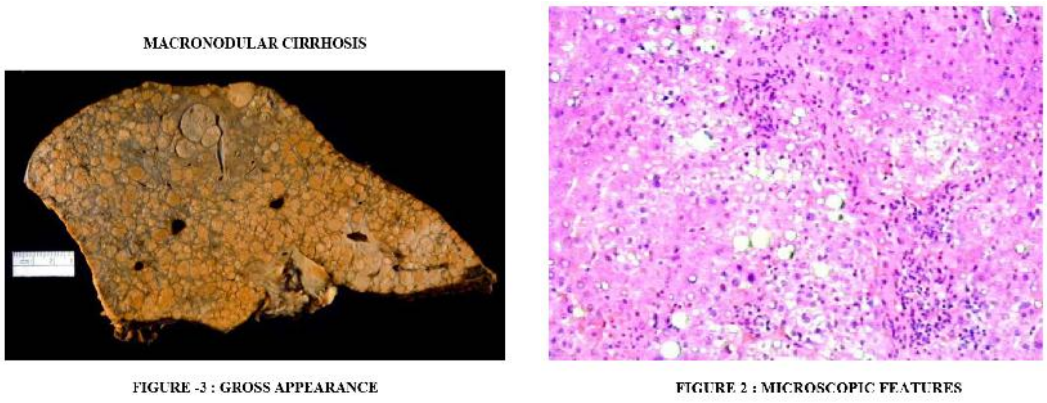


Figure 3.9 – Macronodular cirrhosis – gross appearance and microscopy

CLINICAL FEATURES

The clinical manifestations of cirrhosis include nonspecific symptoms (eg, anorexia, weight loss, weakness, fatigue) or signs and symptoms of overt hepatic decompensation (jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension from ascites, confusion due to hepatic encephalopathy). Physical examination findings include jaundice, spider angiomata, gynecomastia, ascites, splenomegaly, palmar erythema, digital clubbing, and asterixis.

Symptoms —

Patients with compensated cirrhosis will mostly be asymptomatic or they may report nonspecific symptoms, such as anorexia, weight loss, weakness, and fatigue. However, patients with decompensated cirrhosis usually present with jaundice, pruritus, signs of upper gastrointestinal bleeding (hematemesis, melena, hematochezia), abdominal distension due to ascites, or confusion due to hepatic encephalopathy. Patients with cirrhosis may sometimes experience muscle cramps, which can be severe [69]. The cause is not completely understood, although it may be related to a reduction in effective circulating plasma volume. The cause of diarrhoea in patients with cirrhosis may be multifactorial (eg, alterations in small bowel motility, small bowel bacterial overgrowth, changes in intestinal permeability and bile acid deficiency)[70]. In women, chronic anovulation is common, which may manifest as amenorrhea or irregular menstrual bleeding[71]. Some of the abnormalities may be due to variations in testosterone, estradiol, prolactin, and luteinizing hormone levels in patients with cirrhosis compared with normal controls[72]. Men with cirrhosis may develop hypogonadism. It is manifested by impotence, infertility, loss of sexual drive, and testicular atrophy. This is mostly seen predominantly in patients with alcoholic

cirrhosis and hemochromatosis. More than one mechanism appears to be involved. In some cases, primary gonadal injury appears to be more prominent, as suggested by increased serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations, whereas in others, suppression of hypothalamic or pituitary function may have a primary role, as suggested by serum LH concentrations that are not elevated.

In addition, they may have features related to the underlying cause of cirrhosis such as cryoglobulinemia from hepatitis C, diabetes mellitus and arthropathy in patients with hemochromatosis, or extrahepatic autoimmune diseases (such as hemolytic anemia or thyroiditis) in patients with autoimmune hepatitis.

Signs -

A number of physical findings have been described in patients with cirrhosis, including jaundice, spider angiomata, gynecomastia, ascites, splenomegaly, palmar erythema, digital clubbing, and asterixis.

Skin findings -

Patients with cirrhosis frequently develop jaundice and spider angiomata.

Jaundice is a yellow colouring of the skin and mucous membranes that results from increased serum bilirubin. It is usually not detectable until the bilirubin is greater than 2 to 3 mg/dL. Hyperbilirubinemia may also cause the urine to appear dark or "cola" coloured.

Patients with cirrhosis also develop spider angiomata. Spiderangiomata (also referred to as spider telangiectasia) are vascular lesions consisting of a central

arteriole surrounded by many smaller vessels. They are frequently found on the trunk, face, and upper limbs. The body of the lesion (which is the central arteriole) will be seen pulsating when it is compressed with a glass slide. Blood fills the central arteriole first before filling the peripheral tips of each "leg" after blanching. There are usually multiple radiating legs and surrounding erythema that may encompass the entire lesion or only its central portion.

The pathogenesis of spider angiomata is not completely understood, but they are believed to result from alterations in sex hormone metabolism. One study suggested that the presence of spider angiomata in men was associated with an increase in the estradiol to free testosterone ratio[73]. As a general rule, the number and size of spider angiomata correlate with the severity of liver disease[73,74]. Patients with numerous and large spider angiomata are at an increased risk for variceal hemorrhage.

Head and neck findings -

Head and neck findings in patients with cirrhosis may include parotid gland enlargement and fetor hepaticus.

Parotid gland enlargement is usually seen in patients with alcoholic liver disease and is probably due to alcohol, not cirrhosis per se. Enlargement is usually secondary to fatty infiltration, fibrosis, and edema rather than a hyperfunctioning gland[75].

Fetor hepaticus describes a sweet, pungent smell to the breath of a patient with cirrhosis. It is caused by increased concentrations of dimethyl sulfide, the presence of which suggests underlying severe portal-systemic shunting[76].

Chest findings –

Gynecomastia is found in up to two-thirds of patients with cirrhosis. It is possibly caused by increased production of androstenedione from the adrenals, enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol[77]. Men may also develop other features like loss of chest or axillary hair and inversion of the normal male pubic hair pattern.

Abdominal findings -

Findings on abdominal examination include hepatomegaly, splenomegaly, ascites, caput medusae, and a Cruveilhier-Baumgarten murmur.

Ascites -

Ascites is the accumulation of fluid in the peritoneal cavity. Physical findings in patients with ascites include abdominal distension, a fluid wave, and flank dullness to percussion. In one study, the absence of flank dullness was an accurate predictor against the presence of ascites; the probability of ascites being present was less than 10 percent in such patients[78]. However, approximately 1500 mL of fluid had to be present for flank dullness to be detected.

Hepatomegaly —

In cirrhotics liver may be enlarged, normal sized, or small. When palpable, the cirrhotic liver has a firm and nodular consistency.

Splenomegaly —

Splenomegaly is common, especially in patients with cirrhosis from nonalcoholic etiologies[79]. It is believed to be caused primarily by congestion of the red pulp due to from portal hypertension. However, splenic size does not correlate well with portal pressures, suggesting that other factors may be contributing

Caput medusae —

The veins of the lower abdominal wall normally drain inferiorly into the iliofemoral system, while the veins of the upper abdominal wall drain superiorly into the veins of the thoracic wall and axilla. When portal hypertension occurs due to cirrhosis, the umbilical vein, normally obliterated in early life, may open. Blood from the portal venous system is shunted through the periumbilical veins into the umbilical vein and ultimately to the abdominal wall veins, causing them to become prominent. This appearance has been said to resemble the head (caput) of the mythical Gorgon Medusa. One method that has been proposed to distinguish vena caval obstruction from portal hypertension is to pass a finger along dilated veins located below the umbilicus to strip them of blood and determine the direction of blood flow during refilling. In portosystemic collateral veins, the blood flow should be directed inferiorly, away from the umbilicus, whereas vena caval collateral vein flow should be cephalad. However, the actual ability of this maneuver to discriminate between the two is poor, since in both conditions the dilated veins may lack valves and thus have bidirectional blood flow[80].

Cruveilhier-Baumgarten murmur —

The Cruveilhier-Baumgarten murmur is a venous hum that can be auscultated in patients with portal hypertension. It results from collateral connections between the portal system and the remnant of the umbilical vein. It is best appreciated when the stethoscope is placed over the epigastrium. The murmur is increased by maneuvers that increase intraabdominal pressure, such as the Valsalva maneuver, and diminished by applying pressure on the skin above the umbilicus.

Genitourinary findings —

Men with cirrhosis may have testicular atrophy

Extremity findings —

Findings on examination of the extremities of a patient with cirrhosis may include palmar erythema, nail changes, clubbing, hypertrophic osteoarthropathy, and Dupuytren's contracture.

Palmar erythema is an exaggeration of the normal speckled mottling of the palm and is believed to be due to altered sex hormone metabolism. It is most frequently found on the thenar and hypothenar eminences, while sparing the central portions of the palm. However, palmar erythema is not specific for liver disease and can be seen in association with pregnancy, rheumatoid arthritis, hyperthyroidism, and hematological malignancies.

Nail changes seen in cirrhosis are Muehrcke nails and Terry nails. Muehrcke nails are paired horizontal white bands separated by normal colour. The exact pathogenesis is not completely understood, but it is believed to be caused by

hypoalbuminemia. They are not specific for cirrhosis and they may also be seen in other conditions associated with a low serum albumin, such as the nephrotic syndrome. In patients with Terry nails, the proximal two-thirds of the nail plate appears white, whereas the distal one-third is red. This finding is also believed to be secondary to a low serum albumin.

Clubbing and hypertrophic osteoarthropathy are two additional findings in patients with cirrhosis. Hypertrophic osteoarthropathy (HOA) is a chronic proliferative periostitis of the long bones that can cause considerable pain. Clubbing is more common in biliary causes of cirrhosis (particularly primary biliary cirrhosis), while hypertrophic osteoarthropathy can be seen with various causes of liver disease. Neither feature is specific for liver disease.

Dupuytren's contracture occurs due to the thickening and shortening of the palmar fascia, which causes flexion deformities of the fingers. Pathologically, it is characterized by fibroblastic proliferation and disorderly collagen deposition with fascial thickening. The pathogenesis is unknown, but it may be related to free radical formation generated by the oxidative metabolism of hypoxanthine[81,82]. It is relatively common in patients with alcoholic cirrhosis, in whom it may be found in as many as one third of the patients.

Neurologic findings-

Asterixis (bilateral but asynchronous flapping motions of outstretched, dorsiflexed hands) is seen in patients with grade 2 and grade 3 hepatic encephalopathy. Asterixis, also called flapping tremors may also be seen in patients with uremia and severe heart failure.

NATURAL HISTORY OF DISEASE

Cirrhosis may be classified broadly as compensated or decompensated. The development of complications of variceal hemorrhage, ascites, encephalopathy, jaundice, or hepatocellular carcinoma characterizes decompensated cirrhosis. In compensated cirrhosis, these complications are absent. Four clinical stages of cirrhosis have been proposed, with stages 1 and 2 representing compensated cirrhosis, and stages 3 and 4 representing decompensated cirrhosis. Stage 1 cirrhosis is characterized by absence of both ascites and varices; stage 2 cirrhosis is characterized by the presence of varices without bleeding and the absence of ascites; stage 3 cirrhosis is characterized by ascites with or without esophageal varices; and stage 4 cirrhosis is characterized by variceal bleeding with or without ascites. In the future, it is possible that staging of cirrhosis will consider not only clinical and histologic parameters, but also hemodynamic and biological data[83].

Most deaths in patients with cirrhosis occur due to hepatic decompensation; however, in the compensated stages, the most common cause of death is cardiovascular disease, followed by stroke, malignancy, and renal disease[84]. Complications of portal hypertension, hepatocellular carcinoma (HCC), and sepsis are the usual causes of mortality in patients with decompensated cirrhosis.

DIAGNOSIS

Laboratory tests —

Several noninvasive tests for the diagnosis of cirrhosis have been proposed, but none has yet emerged as a standard. Examples include the AST to platelet ratio index and Fibro Test/ Fibro Sure. However, they can provide adjunctive information to conventional laboratory testing.

Anatomical diagnosis-

The diagnosis of cirrhosis depends on demonstrating widespread nodules in the liver combined with fibrosis. This may be done by direct visualization, for instance at laparotomy or laparoscopy. However, laparotomy should never be used to diagnose cirrhosis because it may precipitate liver failure even in those with very well-compensated disease. Laparoscopy visualizes the nodular liver and allows directed liver biopsy[22].

Radio-isotope scanning may show decreased hepatic uptake, an irregular pattern and uptake by spleen and bone marrow. Nodules are not identified. Using ultrasound, cirrhosis is suggested by liver surface nodularity and portal vein mean flow velocity [85]. The caudate lobe is enlarged relative to the right lobe. However, ultrasound is not reliable for the diagnosis of cirrhosis.

Regenerating nodules may be shown as focal lesions. These should be considered malignant unless proved otherwise by serial imaging and alpha-fetoprotein levels. CT scan is cost-effective for the diagnosis of cirrhosis and its complications. Liver size can be assessed, and the irregular nodular surface seen. Benign regenerative nodules are not visualized by CT. Fatty change, increased density due to iron and a space occupying lesion can be recognized. After intravenous contrast, the portal vein and hepatic veins can be identified in the liver, and a collateral circulation with splenomegaly may give confirmation to the diagnosis of portal hypertension. Large collateral vessels, usually peri-splenic or para-oesophageal, may add confirmation to a clinical diagnosis of chronic porto-systemic encephalopathy. Ascites can be seen. The CT scan provides an objective record useful for following the course. Directed biopsy of a selected area can be performed safely.

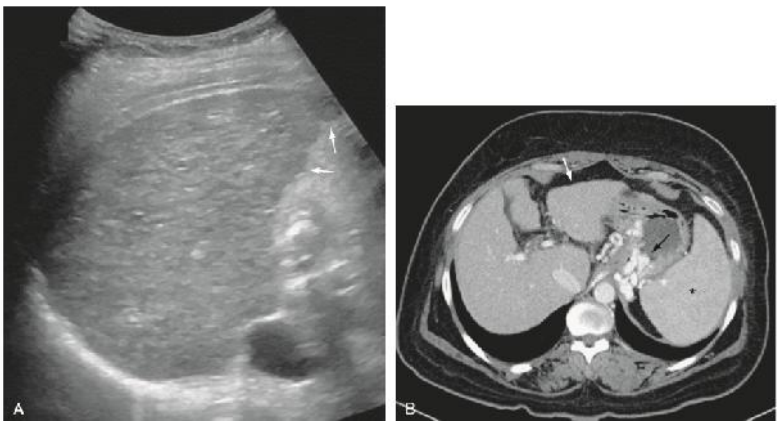


Figure 3.10-A) USG showing heterogenous parenchyma with nodularity B) CT scan showing nodular left lobe of liver Biopsy diagnosis of cirrhosis may be difficult. Reticulin and collagen stains are essential for the demonstration of a rim of fibrosis around the nodule.

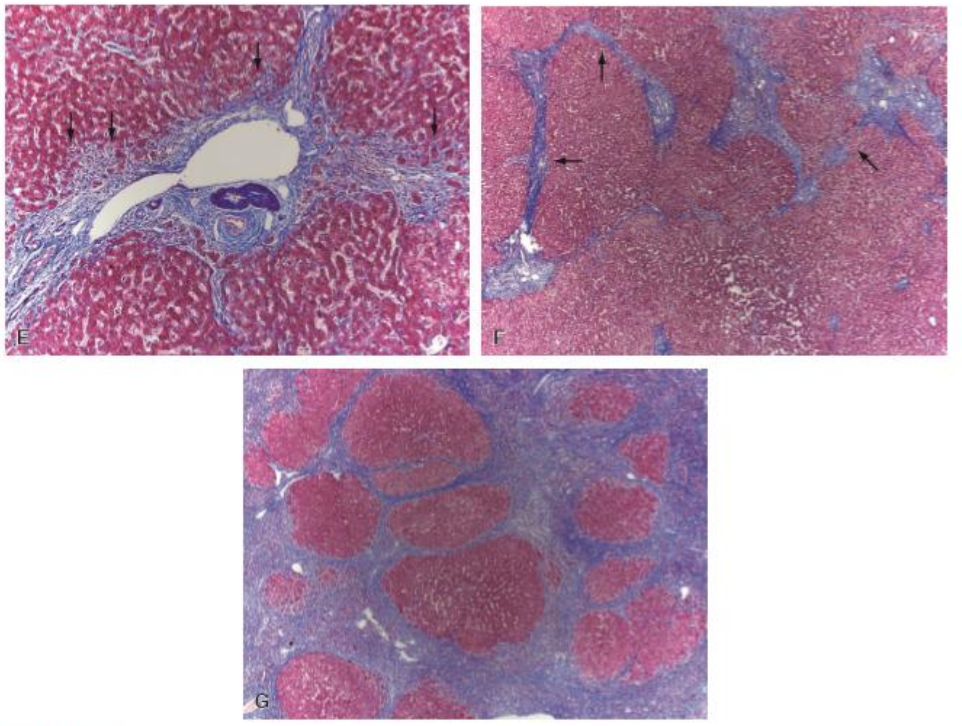


FIGURE 74-2, cont'd *E*, Periportal fibrosis characterizes stage 2. Expansion of the portal tract by fibrosis in blue is seen. The collagen is not confined to the portal tract but also extends to involve the surrounding periportal acinar parenchyma *(arrows)*. (Masson's trichrome stain.) *F*, In stage 3, bridging fibrosis is seen. Multiple portal tracts demonstrate increased fibrosis in blue and connect with one another, forming fibrous bridges *(arrows)*. (Masson's trichrome stain.) *G*, In cirrhosis (stage 4), the normal liver architecture is completely distorted and replaced by regenerative nodules that are separated by fibrous septa in blue. (Masson's trichrome stain.) *(Images courtesy Taofic Mounajjed, MD, Rochester, Minn.)*

Figure 3.11- Periportal fibrosis – Histology

Helpful diagnostic points include absence of portal tracts, abnormal vascular arrangements, hepatic arterioles not accompanied by portal veins, the presence of nodules with fibrous septa, variability in liver cell size and appearance in different areas, and thickened liver cell plates[86]. Since neither liver biopsy nor scanning have a diagnostic sensitivity greater than 90% (ultrasound, 87%; liver biopsy, 62%)[85], it has been proposed that ultrasound be done before liver biopsy is performed [87]. If cirrhosis is suspected on ultrasound (or clinical findings) at least two separate liver biopsy specimens should be taken for histology. If histology does not show cirrhosis but the specimen shows fragmentation, fibrosis or architectural disruption, this together with the ultrasound result should allow a diagnosis of cirrhosis to be made[87].

Elastography – Increasing scarring of the liver is associated with increasing "stiffness" of the tissue. This is one of the methods that have been developed to assess liver stiffness.

PROGNOSIS

Liver-related mortality is the eighth leading disease cause of death in the United States. Among persons 45 to 64 years of age, cirrhosis is the third leading cause of death. As compared with the general population, persons with compensated cirrhosis have a 5-fold increased risk of death, whereas patients with decompensated cirrhosis have a 10-fold increased risk. The median survival in patients with compensated cirrhosis is 9 to 12 years, compared with 2 years in those with decompensated cirrhosis.

Prognosis depends not only on the clinical stage of the disease but also on the presence of comorbidities. Generic scores to determine mortality risk include the

Child-Turcotte Pugh score (Child-Pugh class) and the MELD score and its modifications as well as von Willebrand factor levels. Measuring the hepatic vein pressure gradient (HVPG) is a useful tool to assess prognosis but is invasive and expensive, making repeated measurements impractical.

Infection and renal failure are commonly associated with mortality in patients with cirrhosis. Patients with an infection have a 4-fold increase in mortality compared with cirrhotic patients without an infection[88].Patients with renal failure have a 7- to 8-fold increased risk of death compared with patients without renal failure[89].

CHILD PUGH SCORE

Child–Pugh score was initially proposed by Child and Turcotte to predict the operative risk in patients undergoing portosystemic shunt surgery for variceal bleeding. The primary version of Child–Pugh score included ascites, hepatic encephalopathy (HE), nutritional status, total bilirubin, and albumin. Pugh et al modified the Child–Pugh classification by adding prothrombin time or international normalized ratio (INR) and removing nutritional status[90].

Child and Turcotte first described their classification of the "hepatic functional reserve" of patients with cirrhosis in 1964. Child-Turcotte criteria (CTC) classified patients as Groups A, B, and C, in descending order of prognosis. Group A, were described as having good hepatic function, i.e., they ". . . may well be unaware of their disease, are not jaundiced, have never had ascites or nutritional or neuropsychiatric disturbances. . . " and have normal serum albumin and bilirubin concentrations. At the opposite end of the spectrum, patients in Group C ". . . are jaundiced, have ascites, which is uncontrolled or controlled only by the most stringent

of medical programs. . . have been in hepatic coma. . . whose general nutrition is poor. . . " and who have abnormally low serum albumin and abnormally high bilirubin levels. "They are 'dead end' cirrhotics, familiar sights on Skid Row or in large charity clinics." Group B was defined as being in between A and C. The authors presented a tabular summary of these criteria[91,92].

TABLE 1. CRITERIA FOR CHILD-TURCOTTE CLASSIFICATION

Group designation	A	B	C
Serum bilirubin[a] (mg·%)	Below 2.0	2.0–3.0	Over 3.0
Serum albumin (gm·%)	Over 3.5	3.0–3.5	Under 3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced "coma"
Nutrition	Excellent	Good	Poor, "wasting"

Table 3.2- Original Child – Turcotte classification

The Child-Turcotte classification, as modified by Pugh et al., was recorded on diagnosis in 598 completely followed patients with cirrhosis of the liver. The variables that comprise the Pugh classification are ascites, encephalopathy, serum albumin, serum total bilirubin, and prothrombin time. The Pugh score categorized in three classes (class A = score 5 or 6, class B = score 7 to 11, class C = score 12 to 15) separates the series into three groups of approximately equal size with significant differences in median survivals (p less than 0.005) and in survival curves (p less than 0.0001). The characteristics of simplicity, availability, low cost and good discrimination power make the Pugh classification a very useful method to estimate prognosis in patients with cirrhosis of the liver[93].

The following table of modified Child Pugh Classification was used in our study

Parameters	Value	Point
Encephalopathy	none Grade I-II Grade III-IV	1 2 3
Ascites	none mild uncontrolled	1 2 3
Bilirubin (mg/dL)	< 2 2-3 >3	1 2 3
Albumin(g/dL)	> 3.5 2.8-3.5 < 2.8	1 2 3
Prothrombin time (INR)	< 1.7 1.7-2.3 >2.3	1 2 3

Group A= 5–6 points; Group B= 7–9 points; Group C=10–15 points

Table 3.3-Modified Child- Pugh classification

The grading of encephalopathy used in the above table is as follows

Encephalopathy Grades (from the FDA)

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

- Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Grading of ascites is as follows

None – no detectable ascites

Moderate – diuretic responsive

Severe – unresponsive to diuretics

MELD SCORE

The original MELD score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict three-month survival. In patients with cirrhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction and increased three-month mortality risk[94].

MELD was originally developed to predict three-month mortality following transjugular intrahepatic portosystemic shunt (TIPS) placement and was derived using data from a population of 231 patients with cirrhosis who underwent elective TIPS placement. The model was subsequently validated in an independent cohort of patients from the Netherlands undergoing TIPS placement[95]. The original model included serum bilirubin, serum creatinine, INR, and etiology of the liver disease (cholestatic or alcoholic versus other etiologies). The etiology of liver disease was subsequently removed from the model because it posed difficulties, such as how to categorize patients with multiple causes of liver disease.

In January 2016, Organ Procurement and Transplantation Network Policy 9.1 (MELD Score) was updated to include serum sodium as a factor in the calculation of the MELD score. The MELD-Na score is used by UNOS, for deceased donor liver allocation.

MELD-Na = MELD + 1.32 * (137-Na) - [0.033*MELD* (137-Na)]

Serum sodium is a reflection of the vasodilatory state in cirrhosis and predicts waitlist mortality independent of the MELD score[96]. There is a linear increase in mortality by 5 percent for each mEq decrease in serum sodium between 125 and 140 mEq/L[97]. Addition of serum sodium to the MELD model elevates the transplant priority for about 12 percent of listed patients[96]. A limitation of the MELD-Na score is that serum sodium levels may be vulnerable to alterations by diuretic use and intravenous fluid administration.

The primary use of the MELD and MELD-Na scores is in prioritizing patients on the waitlist for deceased donor liver transplantation based on liver disease severity and short-term mortality risk. However, as described above, the MELD score also predicts mortality following TIPS placement and has been demonstrated to have predictive value for outcomes in patients with cirrhosis undergoing non-transplantation surgical procedures. Several other applications of the MELD score have been demonstrated and include, but are not limited to, predicting mortality in acute alcoholic hepatitis and in acute variceal hemorrhage[98,99]

UNOS (United Network for Organ Sharing) initially adopted the Child-Turcotte-Pugh (CTP) scoring system for its liver transplantation prioritization system. However, it soon became apparent that the CTP score was not sufficient to resolve the

dominance of waiting time as a deciding factor. The failure of the CTP score was due to several factors. The CTP score includes subjective parameters such as the degree of ascites and encephalopathy. The quantification of the degree of abnormality in these two findings may vary based on the observer and the method of detection used. In addition, the findings may be altered substantially by medical interventions (eg, the use of diuretics for ascites, or lactulose and rifaximin for encephalopathy).

The CTP score is limited in its discriminatory capacity due to both a "ceiling" and a "floor" effect. A patient with a serum bilirubin level of 4 mg/dL, for example, is assigned the same number of points as a patient with a bilirubin of 15 mg/dL, even though the degree of elevation in serum bilirubin level is known to be an important prognostic indicator in patients with cirrhosis.

During the liver transplant community's search for a more equitable allocation system, the MELD score emerged as a more objective model for prioritizing patients based on liver disease severity. The MELD score was initially adopted by UNOS in 2002 for use in deceased donor liver allocation for adults with cirrhosis. MELDNa was added into the deceased donor liver allocation system in 2016.

Child–Pugh and MELD scores have been widely used to predict the outcomes of cirrhotic patients. However, they have some drawbacks. First, 2 variables (i.e., ascites and HE) included in Child–Pugh score are subjective and may be variable according to the physicians' judgment and the use of diuretics and lactulose. Second, INR, which is one component of both Child-Pugh and MELD scores, does not sufficiently reflect coagulopathy and consequently liver function in liver cirrhosis. Third, there is an interlaboratory variation in INR value.

LIPIDS AND LIVER

The liver is central to lipid metabolism and lipoprotein metabolism. Cholesterol is found in cell membranes and is a precursor of bile acids and steroid hormones. It is synthesized in the liver, small intestine and in other tissues. Some is derived from intestinal absorption, reaching the liver in chylomicron remnants[22].

Cholesterol synthesis mainly takes place from acetyl coenzyme A (CoA) in the microsomal fraction and in cytosol.

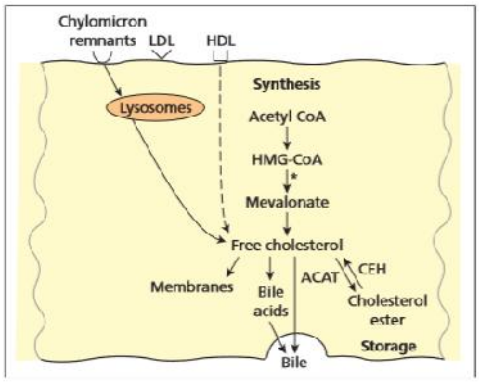


Fig. 2.6. Hepatic cholesterol balance. Free cholesterol is derived from intra-cellular synthesis, and from the uptake of chylomicron remnants and lipoproteins from the circulation. Storage is as cholesterol ester: ACAT (acyl CoA-cholesterol ester transferase, which esterifies free cholesterol to fatty acids) and CEH (cholesteryl ester hydrolase, which hydrolyses the ester linkage). Bile acids are synthesized from free cholesterol, and both are secreted into bile. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting step. HDL, high density lipoprotein; LDL, low density lipoprotein.

Figure 3.12 – Lipid metabolism

The rate-limiting step is the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonate by the enzyme HMG-CoA reductase. Cholesterol that is found in membranes and in bile is present almost exclusively as free cholesterol. Bile is the only significant route for cholesterol excretion. In plasma and in certain tissues such as liver, adrenal and skin, cholesterol esters (cholesterol esterified with long-chain fatty acids) are also found. Cholesterol esters are more nonpolar than free

cholesterol and therefore are even less soluble in water. Esterification is carried out in plasma by the enzyme lecithin cholesterol acyl transferase (LCAT) which is synthesized in the liver

Triglycerides are simpler compounds than the phospholipids. They have a backbone of glycerol, the hydroxy groups of which have been esterified with fatty acids. Naturally occurring triglycerides contain a variety of fatty acids; they act as a store of energy and also a method of transport of energy from the gut and liver to peripheral tissues.

LIPOPROTEINS

Lipids, like cholesterol and triglycerides, are insoluble in plasma. Circulating lipid is carried in lipoproteins that transport the lipid to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation. The lipoproteins consist of esterified and unesterified cholesterol, triglycerides, phospholipids, and protein. Based on the physicochemical characteristics of lipoproteins, these particles have been classified by their lipoprotein subclass size and concentrations.

CLASSIFICATION — the five major lipoproteins are presented below.

Chylomicrons — they are very large particles that carry dietary lipid. They are associated with a variety of apolipoproteins, including A-I, A-II, A-IV, B-48, C-I, C-II, C-III, and E.

Very low-density lipoprotein — Very low density lipoprotein (VLDL) particles carry endogenous triglycerides and to a lesser degree cholesterol. The major apolipoproteins associated with VLDL are B-100, C-I, C-II, C-III, and E.

Intermediate density lipoprotein — Intermediate density lipoprotein (IDL) particles carry cholesterol esters and triglycerides. It is associated with apolipoproteins B-100, C-III, and E.

Low density lipoprotein — Low density lipoprotein (LDL) particles carry cholesterol esters and are associated with apolipoproteins B-100 and C-III.

High density lipoprotein — High density lipoprotein (HDL) particles carry cholesterol esters. These particles are associated with apolipoproteins (apo) A-I, A-II, C-I, C-II, C-III, D, and E.

APOLIPOPROTEINS-

A-I – Structural protein for HDL; ligand for ABCA1 (ATP Binding Cassette) transporter, activator of lecithin-cholesterol acyltransferase (LCAT).

A-II – Structural protein for HDL; activator of hepatic lipase.

A-IV – Activator of lipoprotein lipase (LPL) and LCAT.

B-100 – It is the structural protein for VLDL, IDL, LDL, and Lp(a); ligand for the LDL receptor; required for assembly and secretion of VLDL.

B-48 – It contains 48 percent of B-100; required for assembly and secretion of chylomicrons; does not bind to LDL receptor.

C-I – Activator of LCAT.

C-II – Essential cofactor for LPL.

C-III – Interferes with apo-E-mediated clearance of triglyceride-enriched lipoproteins and remnants by cellular receptors, particularly in the liver; inhibits triglyceride

hydrolysis by lipoprotein lipase and hepatic lipase; and has multiple proatherogenic effects on the arterial wall, including interfering with normal endothelial function.

D – May be a cofactor for cholesteryl ester transfer protein.

E – Ligand for hepatic chylomicron and VLDL remnant receptor, leading to clearance of these lipoproteins from the circulation; ligand for LDL receptor.

There are several metabolic cycles for lipoprotein, of which two are prominent: one is involved in fat absorbed from the intestine (exogenous pathway), and the other is responsible for the handling of endogenously synthesized lipid (endogenous pathway). There is overlap between the two.

Dietary fat is absorbed from the small intestine, and incorporated into chylomicrons. These enter the circulation (via the thoracic duct) where the triglyceride is removed by the action of lipoprotein lipases. The triglyceride is utilized or stored in tissue. The chylomicron remnant is taken up by the liver by the LDL receptor related protein. The cholesterol enters metabolic pathways or plasma membranes or is excreted in bile.

In the endogenous pathway, cholesterol and triglyceride leave the liver in VLDL. In the circulation the triglyceride is removed by the action of lipoprotein lipases. As a result, VLDL particles become smaller, forming intermediate density lipoprotein (IDL), and then LDL, the major carrier for cholesterol. The predominant route for removal of LDL is by LDL receptors on the liver surface, but there are receptors on other cells which become important in the formation of atheromatous plaques.

HDL is the particle facilitating cholesterol removal from peripheral tissues. Cholesterol is transported out of the cell by the cholesterol-efflux regulatory protein, expressed from the adenosine triphosphate (ATP) binding cassette transporter 1 gene (ABC1). The HDL cholesterol is either taken up by the liver or is incorporated into IDL resulting in the mature LDL. This removal of peripheral cholesterol is an important pathway, as reflected in the protective effect of a high HDL–cholesterol level against coronary artery disease. The metabolism of the HDL particle is still unclear. Most apolipoproteins are made by the liver, some by the intestines. Apart from being components of lipoproteins, some have other functions: Apo A-1 activates plasma LCAT; C-11 activates lipoprotein lipase.

As majority of endogenous cholesterol is synthesized in the hepatic microsomes, synthesis and metabolism of cholesterol is impaired I chronic liver disease resulting in decreased plasma levels. Severe metabolic impairment that is associated with cirrhosis produces a worsening of lipoprotein pattern. HDL cholesterol and the apolipoproteins associated with it have been shown to be reduced in cirrhosis.

In India, there are very few studies on lipid profile is patients with cirrhosis. Hence, this study was undertaken to study the effect of cirrhosis on lipid profile and to study these values in correlation with the already existing prognostic indices like MELD score and Child – Pugh score

METHODOLOGY

SOURCE OF DATA –

The study was conducted among patients admitted with cirrhosis of liver, in Department of Medicine at KLES Dr Prabhakar Kore Hospital & MRC, Belgaum

STUDY DESIGN

It was a cross sectional study conducted over a duration of one year, from January 2017 to December 2017

INCLUSION CRITERIA-

Subjects with liver cirrhosis as evidenced by clinical, biochemical or ultrasonographical features of cirrhosis, irrespective of etiology of cirrhosis

EXCLUSION CRITERIA-

Conditions that could interfere with the lipid metabolism –

- primary dyslipidaemia
- hypothyroidism
- chronic renal failure
- patients on statins.

METHODOLOGY-

The patients admitted in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre with cirrhosis of liver as evidenced clinically, biochemically and ultrasonographically were considered for the study .A total of 106 patients were taken up for the study .The patients underwent clinical

examination and were classified as per different prognostic scores (MELD and Child Pugh Score) and also underwent blood investigations like Liver function tests, PT/INR , renal function tests , lipid profile and Apo A1 levels .

INVESTIGATIONS-

Ultrasonography of abdomen

Liver function tests

Renal function tests

PT/INR

Lipid Profile

Apo A1

SAMPLE SIZE CALCULATION-

According to formula: $n=4\times pq/ d^2$

Where n= sample number

p=prevalence

q= 100-p

d= 10

Hence n= 4×79×21/7.9×7.9

n=106

SAMPLING METHOD -

Random sampling

STATISTICAL ANALYSIS

Mean, standard deviation and range were used to describe demographics, levels of Apo A1 and lipid profile.

Frequency / percentage used to describe gender distribution and distribution of subjects as per etiology and class of Child –Pugh score.

Pearson’s correlation co-efficient was used to determine association between Apo A1 level and MELD score.

ANOVA was used to describe relation between Apo A1 level and Child-Pugh score. Scheffe's Post-hoc test was used to describe differences in means of lipid profile and Apo A1 values between the different groups as classified by Child Pugh score.

RESULTS

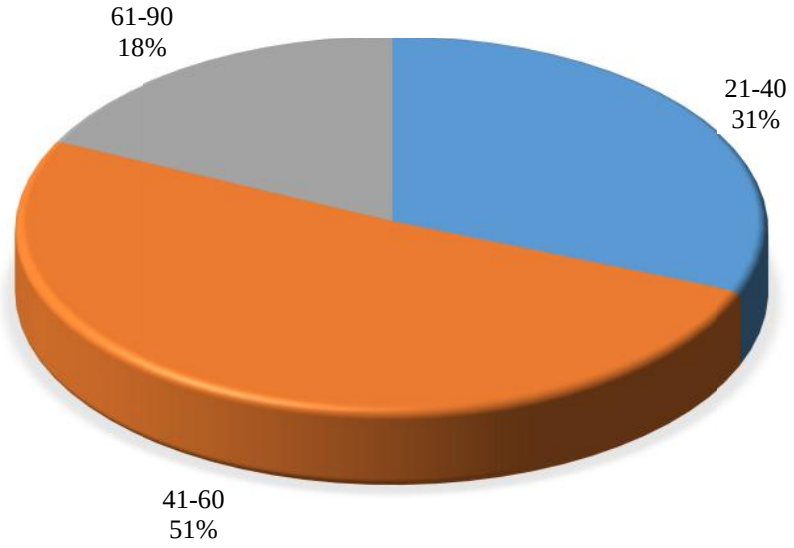
A total of 106 patients aged >18 years, diagnosed as cirrhosis of liver clinically, biochemically and radiologically formed part of the study population.

The results obtained were as follows -

TABLE 5.1 – AGE DISTRIBUTION

AGE IN YEARS	NUMBER	PERCENTAGE
21- 40	33	31.13
41-60	54	50.94
61-90	19	17.92
TOTAL	106	100
MEAN ± SD = 48.96 ±13.29		

GRAPH 5.1- AGE DISTRIBUTION

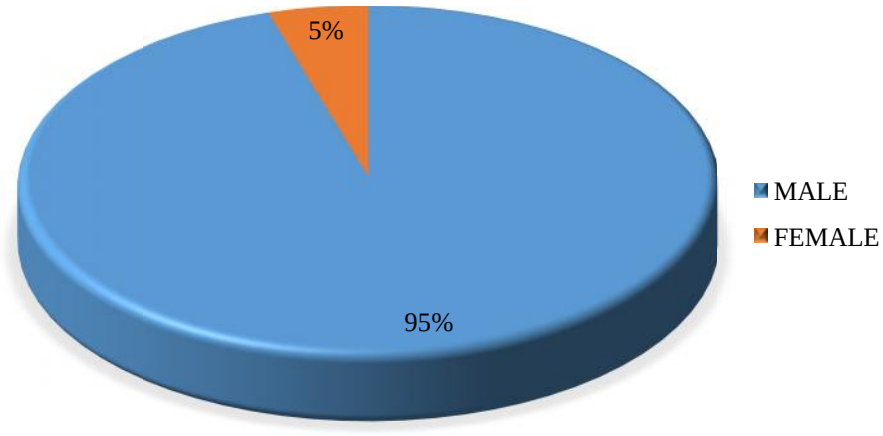


The mean age of the study population was 48.96 ±13.29 years and ranged from 21 years to 90 years. Table 1 depicts the age distribution of the patients with cirrhosis of liver and from the table it can be concluded that majority of the cirrhotic patients were in the age group of 41- 60 years.

TABLE 5.2 – GENDER DISTRIBUTION

GENDER	NUMBER	PERCENTAGE
SFEMALE	5	4.72
MALE	101	95.28
TOTAL	106	100.00

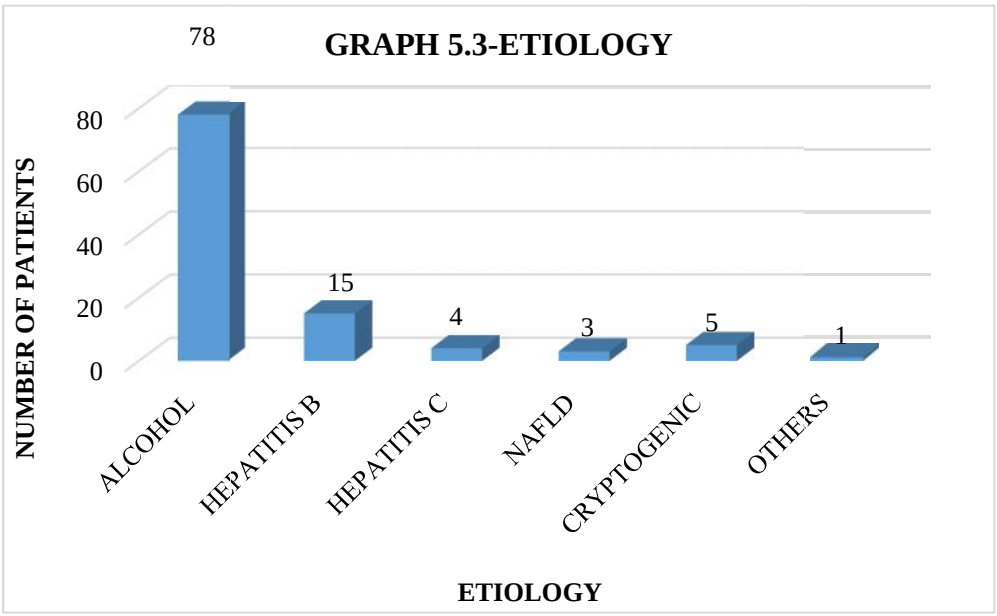
GRAPH 5.2-GENDER DISTRIBUTION



Males formed majority of the study population. Table 2 depicts that 95.28 % of the population were males as compared to only 4.72 % females

TABLE 5.3 - ETIOLOGY OF CIRRHOSIS

ETIOLOGY	NUMBER	PERCENTAGE
ALCOHOL	78	73.58
HEPATITIS B	15	14.15
HEPATITIS C	4	3.77
NAFLD	3	2.83
CRYPTOGENIC	5	4.72
OTHERS	1	0.94
TOTAL	106	100.00

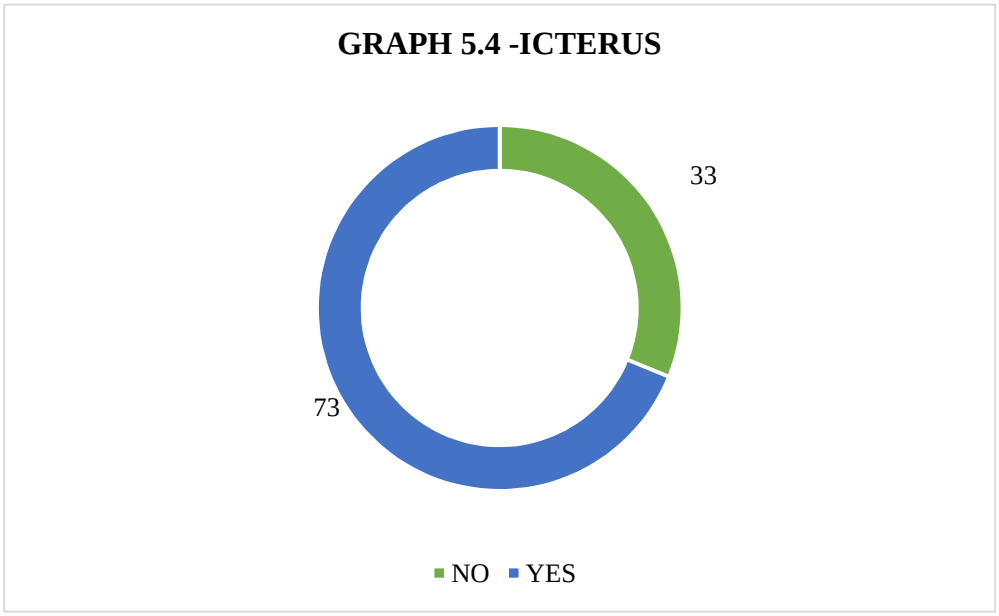


Alcohol was found to be the major cause for cirrhosis of liver, 73.58 % of cirrhotics were alcoholics. Other causes of cirrhosis included chronic hepatitis B, chronic hepatitis C and NAFLD.

TABLE 5.4 –ICTERUS

ICTERUS	NUMBER	PERCENTAGE
ABSENCE	33	31.13
PRESENCE	73	68.87
TOTAL	106	100

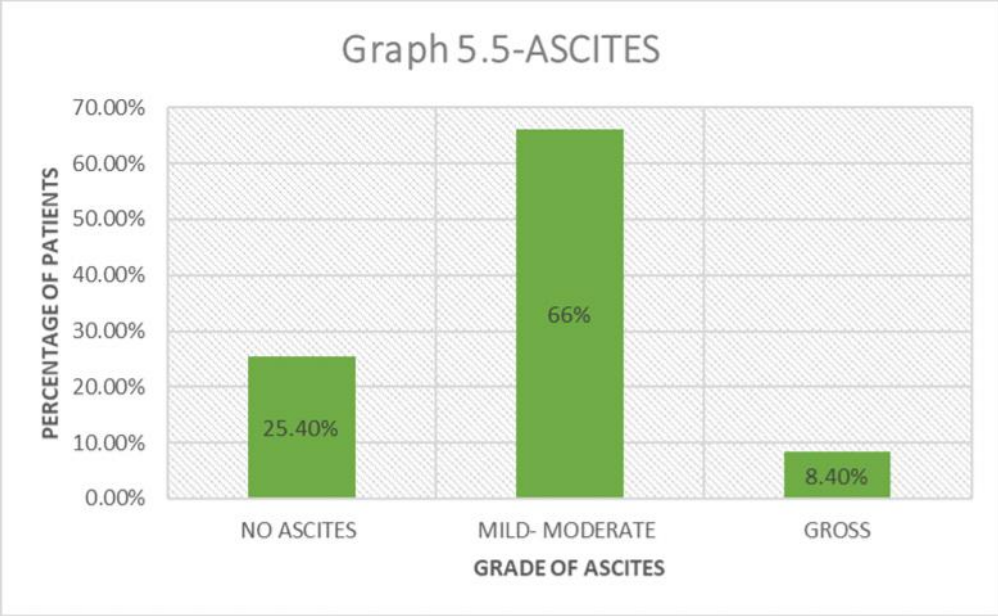
GRAPH 5.4 -ICTERUS



The above table depicts that among the 106 patients, 73 of them (68.87 %) had jaundice clinically.

TABLE 5.5– GRADE OF ASCITES

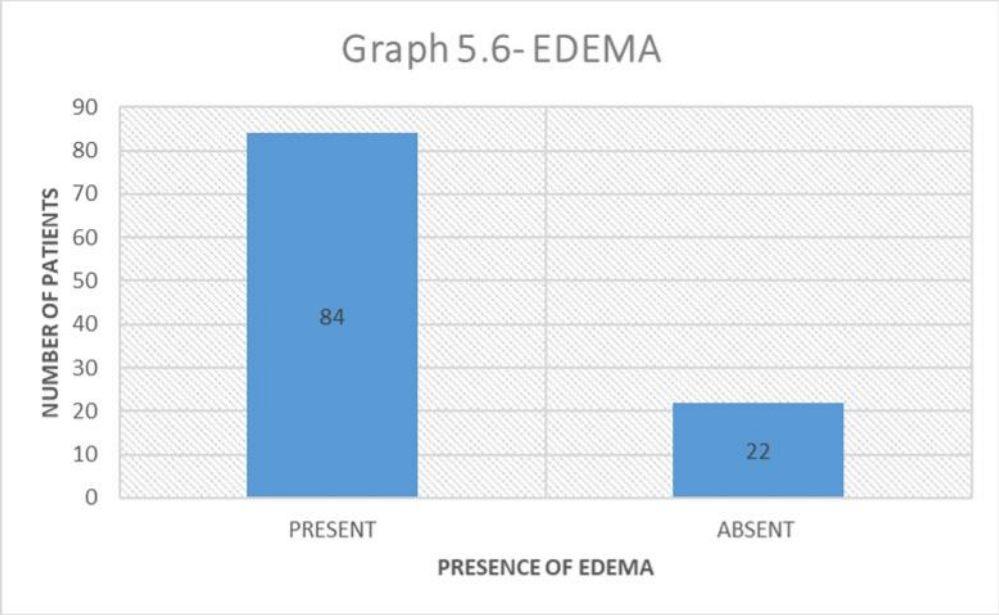
ASCITES	NUMBER	PERCENTAGE
NO ASCITES	27	25.47
MILD -MODERATE	70	66.04
GROSS	9	8.49
TOTAL	106	100.00



As seen in the above table,66 % of the patients had mild to moderate ascites and 8.4 % had gross ascites. Around 25 % of the patients did not present with ascites.

TABLE 5.6- EDEMA

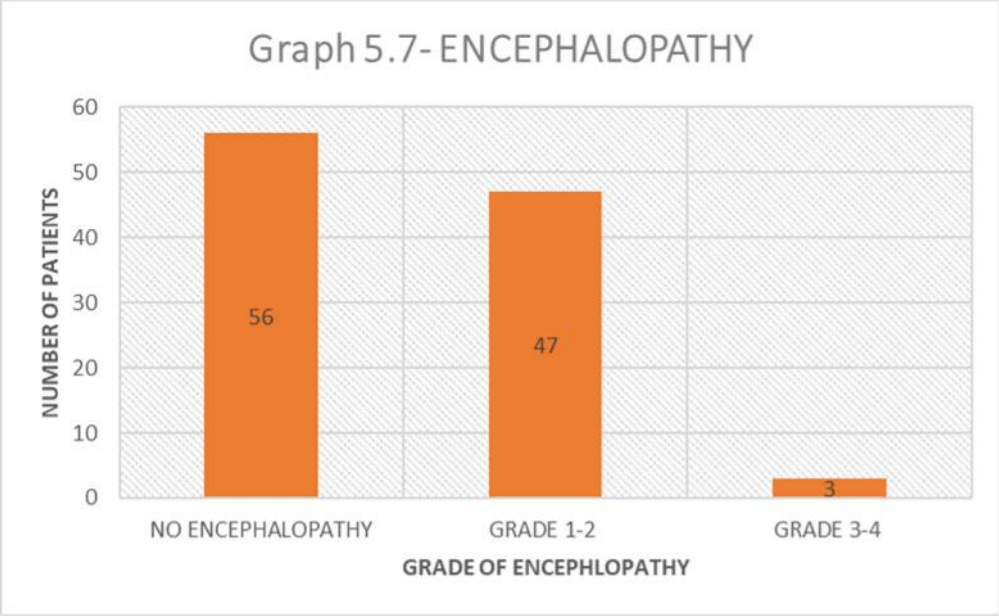
EDEMA	NUMBER	PERCENTAGE
NO	22	20.75
YES	84	79.25
TOTAL	106	100.00



Above tabledepicts that majority of the patients with cirrhosis of liver, that is 79.25 % (84 out of 106) patients presented to the hospital with edema.

TABLE 5.7 – GRADE OF ENCEPHALOPATHY

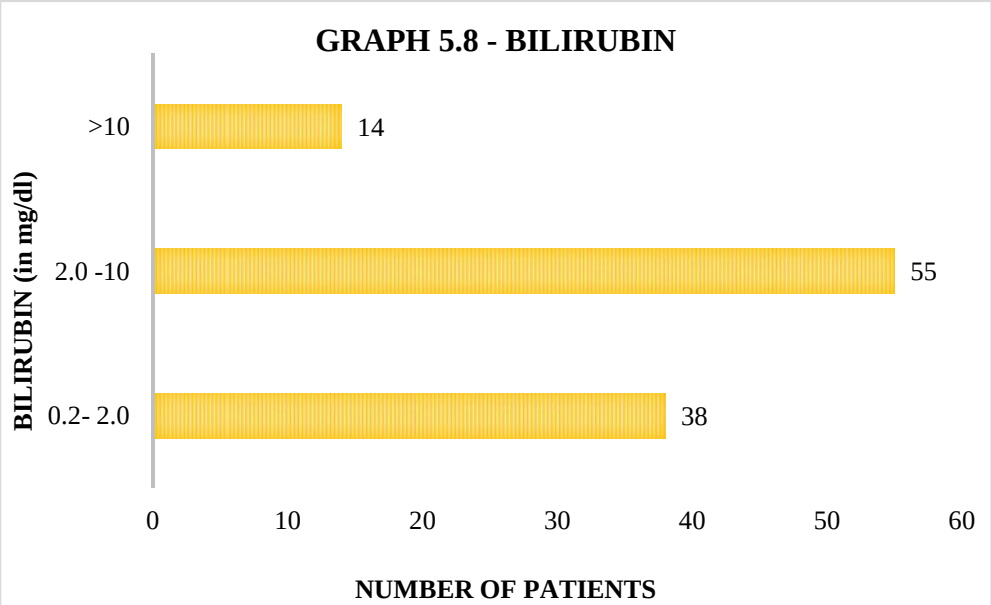
ENCEPHALOPATHY	**NUMBER**	**PERCENTAGE**
NO ENCEPHALOPATHY	56	52.83
GRADE 1 – 2	47	44.34
GRADE 3-4	3	2.83
TOTAL	106	100.00



As per the above graph, 47 out of 106 patients (44.3 % of the patients) had grade 1 to grade 2 encephalopathy and only 3 patients (2.83 %) had grade 3 to grade 4 encephalopathy.

TABLE 5.8 – VALUE OF TOTAL BILIRUBIN

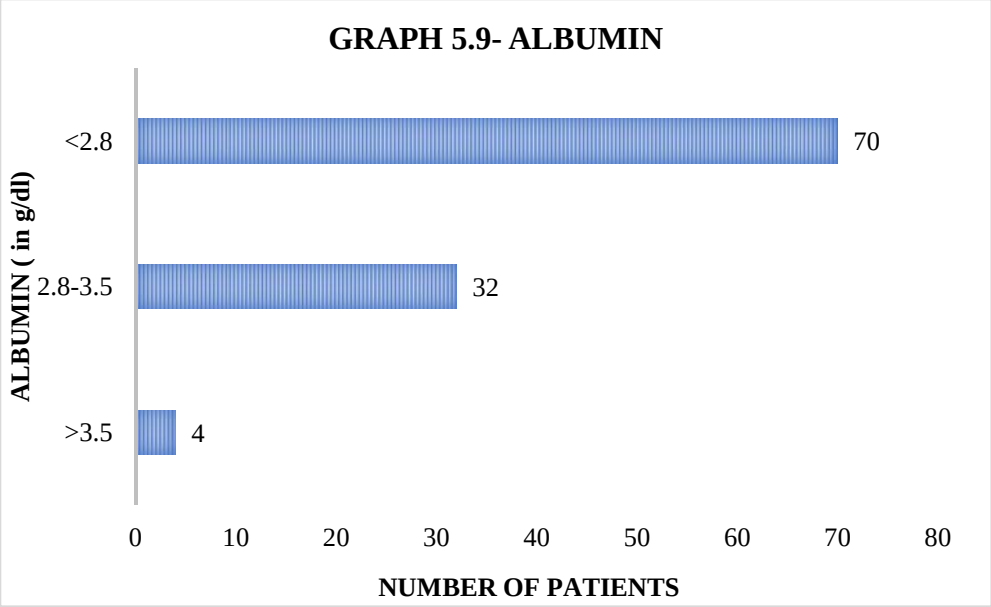
BILIRUBIN(in mg/dl)	NUMBER	PERCENTAGE
0.2-2	38	35.8
2-10	55	51.8
>10	14	13.2
TOTAL	106	100
MEAN ±SD= 5.62 ± 7.68		



The above table shows that among the 106 patients in our study , majority of them , that is 51.8 % of them had a total bilirubin value in the range of 2 mg/dl to 10 mg/dl and only 13.2 % of them had a bilirubin value of more than 10 mg/dl . The mean value of total bilirubin was 5.62 ± 7.68 mg/dl.

TABLE 5.9- SERUM ALBUMIN CONCENTRATION

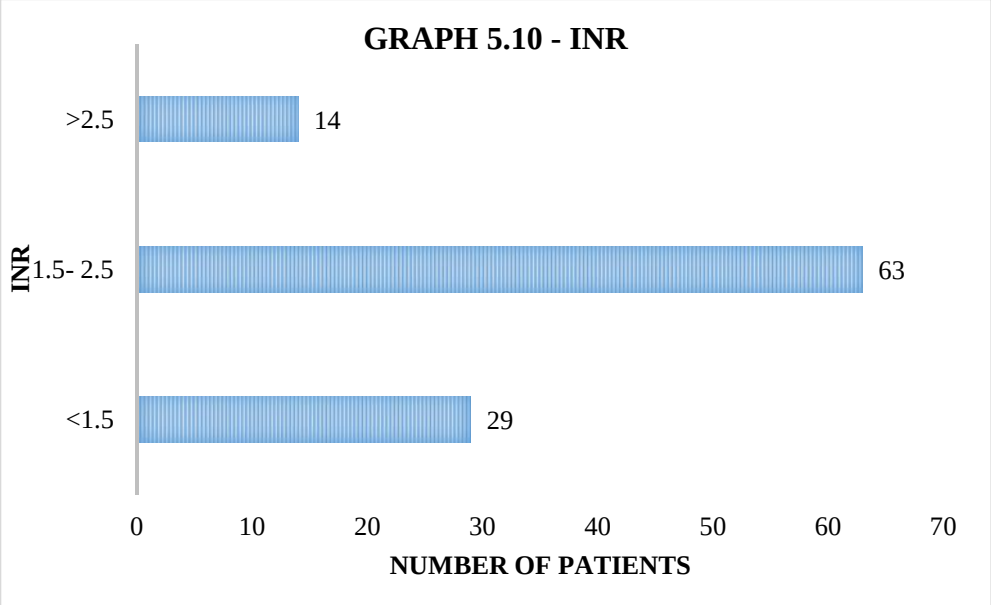
ALBUMIN (in g/dl)	NUMBER	PERCENTAGE
>3.5	4	3.77
2.8-3.5	32	30.1
<2.8	70	66.03
TOTAL	106	100
MEAN ±SD= 2.56± 0.53		



As per the above table, 70 out of 106 patients had an albumin value of <2.8g/dl and 32 of them had albumin value between 2.8g/dl and 3.5g/dl.

TABLE 5.10– VALUE OF INR

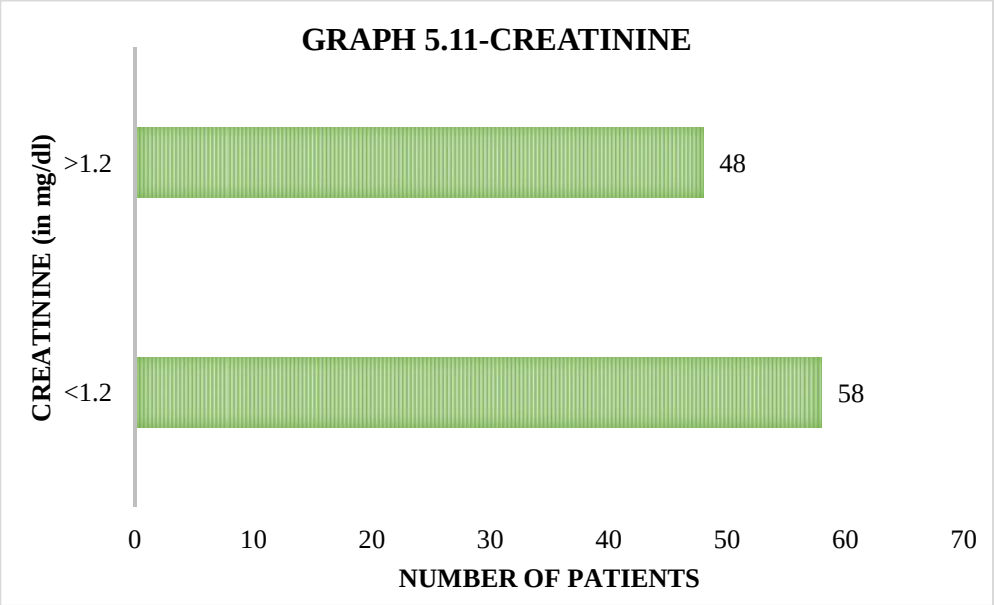
INR	NUMBER	PERCENTAGE
<1.5	29	27.3
1.5- 2.5	63	59.43
>2.5	14	13.20
TOTAL	106	100
MEAN ±SD =1.91±0.65		



Among our study subjects the values of INR ranged from 0.99 to 5.36 with a mean of 1.91±0.65. INR of 1.5 to 2.5 was found in 63 out of 106 (59.43%) of the subjects and an INR of >2.5 was seen in 14 (13.2 %) of the patients.

TABLE 5.11 – VALUE OF CREATININE

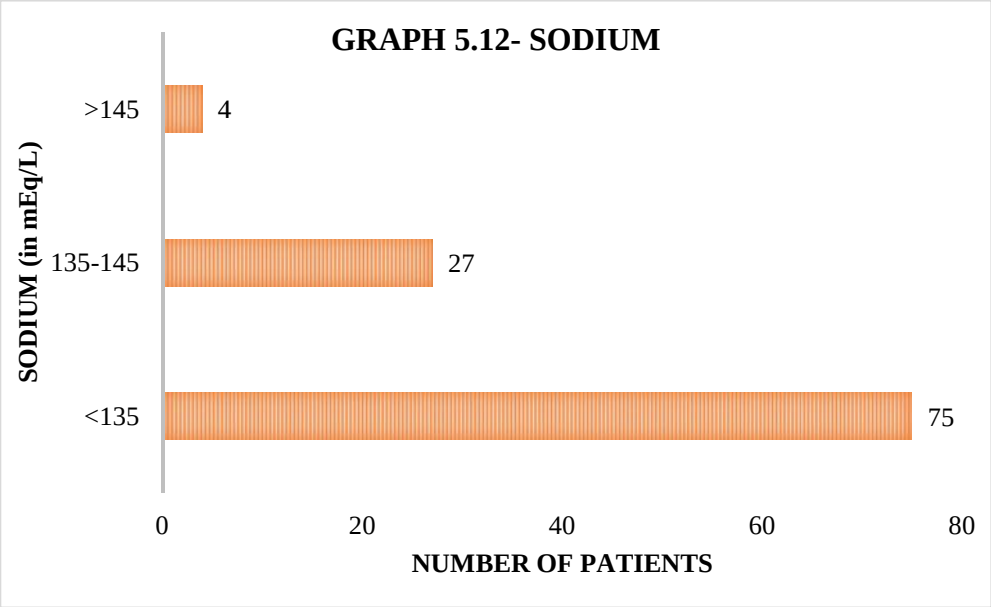
CREATININE (in mg/dl)	NUMBER	PERCENTAGE
<1.2	58	54.71
>1.2	48	45.28
TOTAL	106	100
MEAN ±SD=1.41±0.92		



45.28 % of the patients had deranged renal function in the form of raised serum creatinine of >1.2mg/dl, as depicted in the above table.

TABLE 5.12 – PRESENCE OF HYPONATREMIA

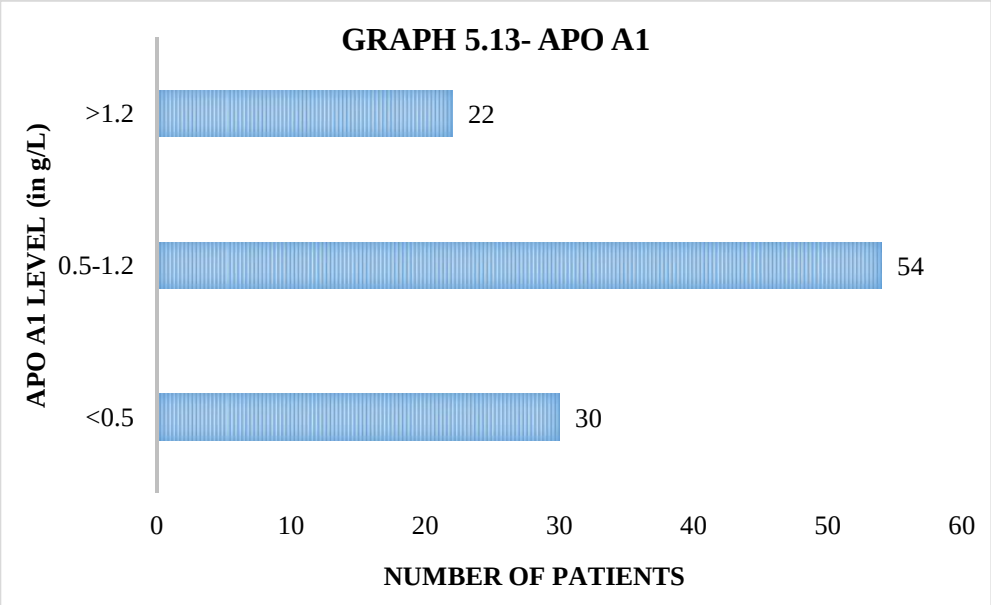
SODIUM (in mEq/L)	NUMBER	PERCENTAGE
<135	75	70.7
135-145	27	25.47
>145	4	3.77
TOTAL	106	100



The above table depicts that around70 % of the patients had hyponatremia (sodium< 135 mEq/L) wherea sonly 3.77 % of them had hypernatremia (sodium> 145 mEq/L).

TABLE 5.13- APOLIPOPROTEIN A1 LEVEL

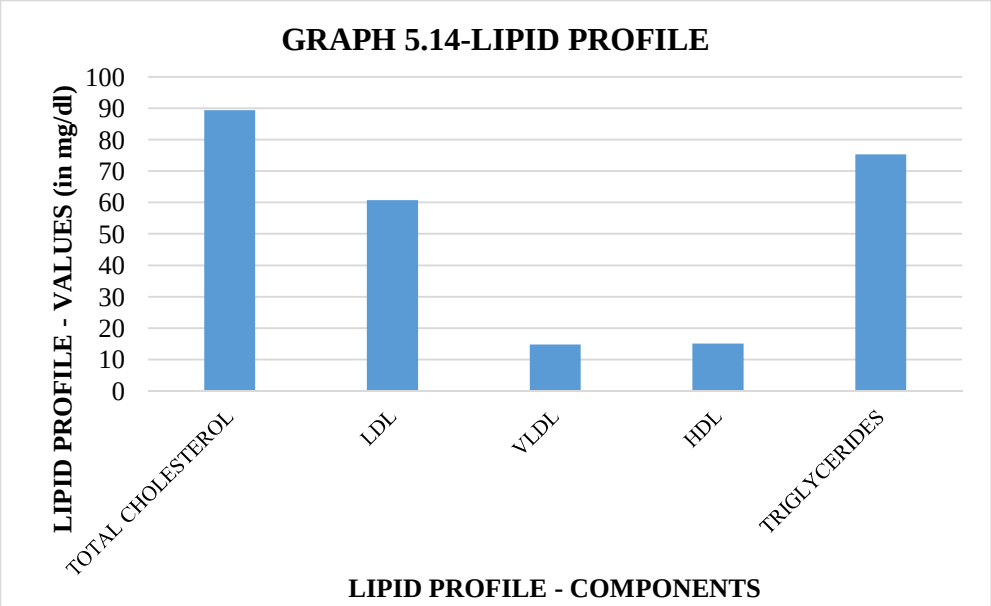
APO A1 (g/L)	NUMBER	PERCENTAGE
<0.5	30	28.3
0.5-1.2	54	50.94
>1.2	22	20.7
TOTAL	106	100
MEAN±SD=0.79±0.44		



The mean level of Apolipoprotein A1 in the studied cirrhotic patients was 0.79±0.44g/L. Only 35.8 % of the patients had an Apo A1 level of more than 1g/L and the rest 64.5 % had a very low level of <1g/L, with 30 out of the 106 patients having value less than 0.5g/L. The range of Apo A1 levels among cirrhotic patients was between 0.01g/L to 1.93g/L.

TABLE 5.14– LIPID PROFILE

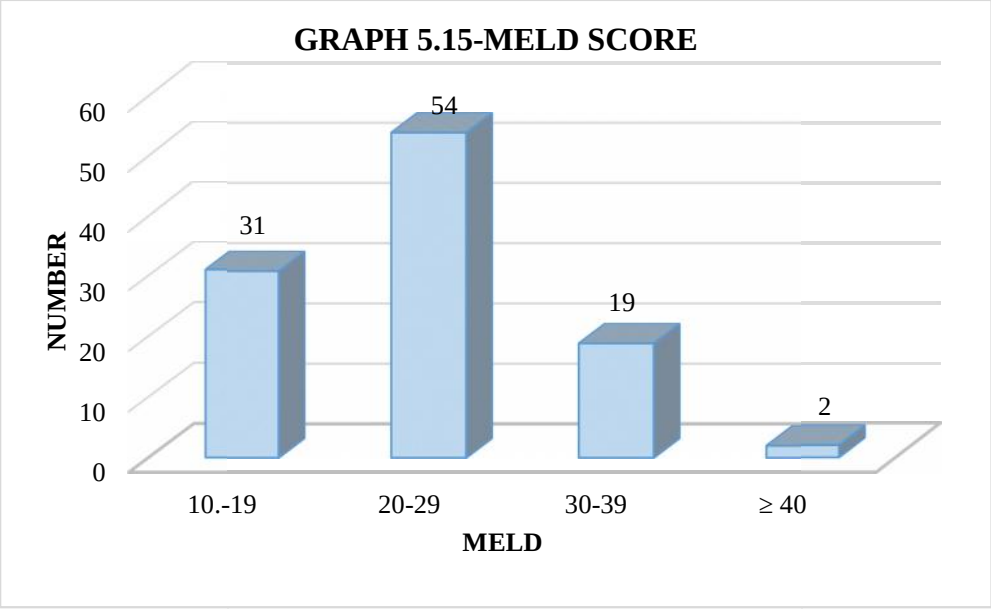
LIPID PROFILE	MEAN (mg/dl)	SD	MIN	MAX
TOTAL CHOLESTEROL	89.38	34.49	28	220
LDL	60.74	26.69	9	151
HDL	15.06	9.67	5	50
TRIGLYCERIDES	75.33	33.41	22	211
VLDL	14.78	6.72	4.4	42



The above table shows that the mean, of the different components of the lipid profile was low, that of total cholesterol being 89.38±34.49 mg/dl, LDL being 60.74±26.69mg/dl, VLDL being 14.78±6.72mg/dl, HDL 15.06±9.67 mg/dl and Triglycerides of 75.33±33.41mg/dl.

TABLE 5.15 – MELD SCORE DISTRIBUTION

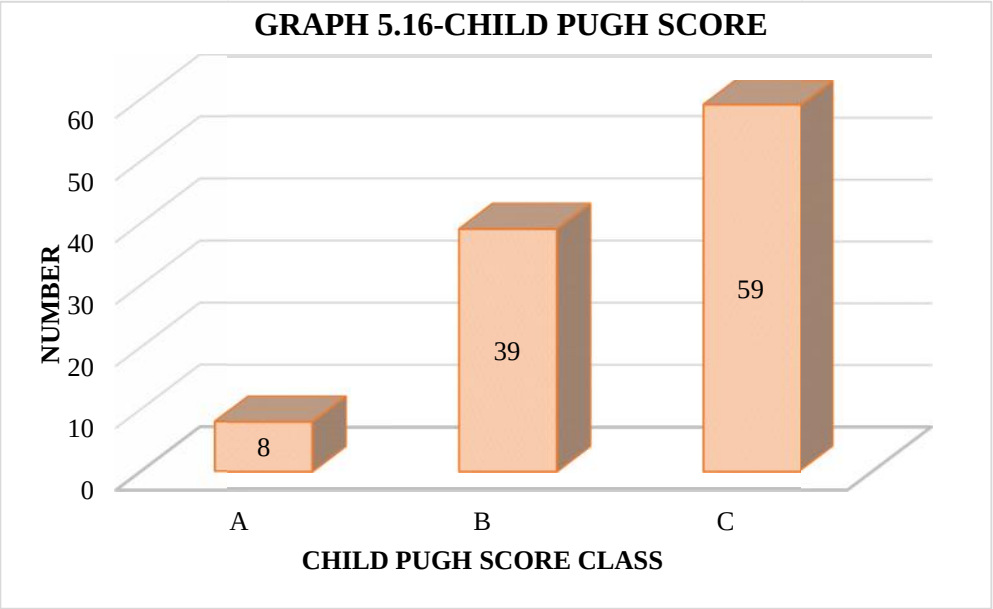
MELD	NUMBER	PERCENTAGE
10-19	31	29.25
20-29	54	50.94
30-39	19	17.92
≥ 40	2	1.89
TOTAL	106	100.00



The above table depicts that 54 out of 106 patients (50.94%) belonged to a MELD score range of 20- 29 and only 2 patients had a MELD score of > 40 .

Table 5.16 – CHILD PUGH SCORE

CHILD PUGH	NUMBER	PERCENTAGE
A	8	7.55
B	39	36.79
C	59	55.66
TOTAL	106	100.00

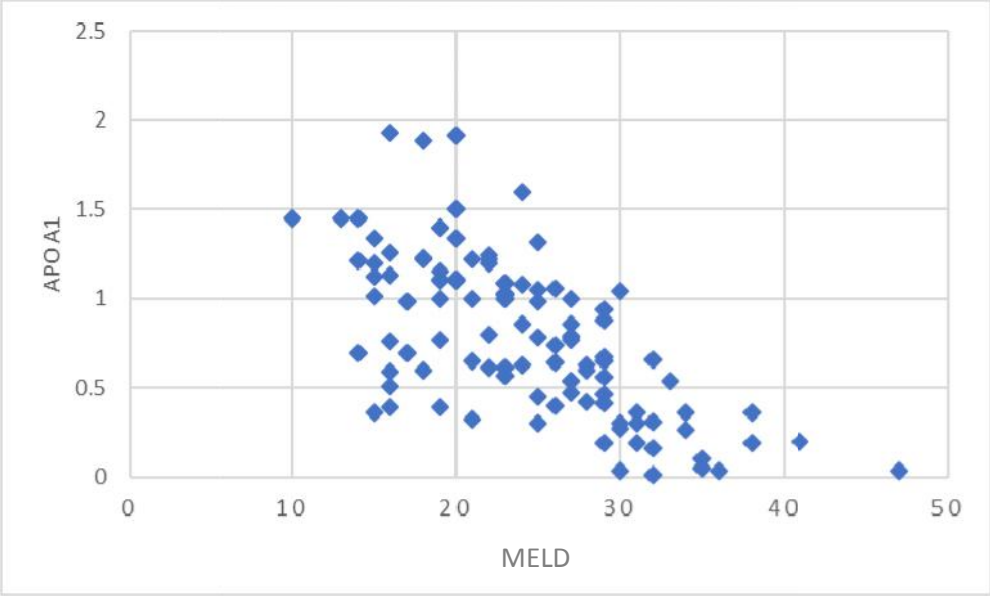


According to the above table, majority of the patients belonged to Child Pugh class C, that is 59 out of 106 (55.66 %) and only 8 patients belonged to class A of Child Pugh Score .

TABLE 5.17 - CORELATION OF MELD SCORE WITH VARIOUS COMPONENTS OF LIPID PROFILE

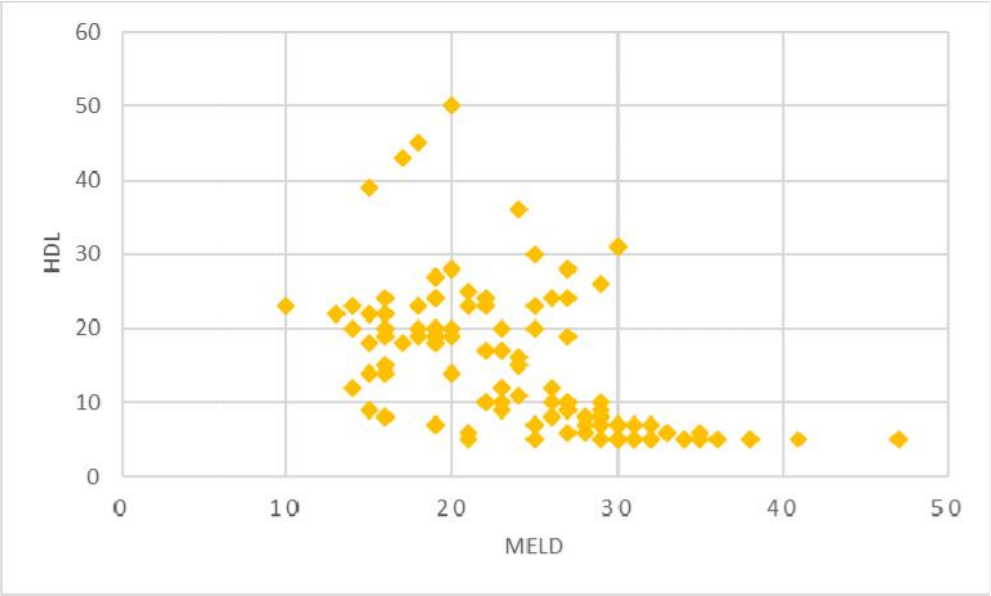
	r	p VALUE
APO A1	-0.6604	<0.0001
TOTAL CHOLESTEROL	-0.0611	0.5340
LDL	-0.0611	0.5340
HDL	-0.5450	<0.0001
TG	-0.0086	0.9304
VLDL	0.0312	0.7507

a) GRAPH 5.17-CORRELATION OF APO A1 WITH MELD SCORE



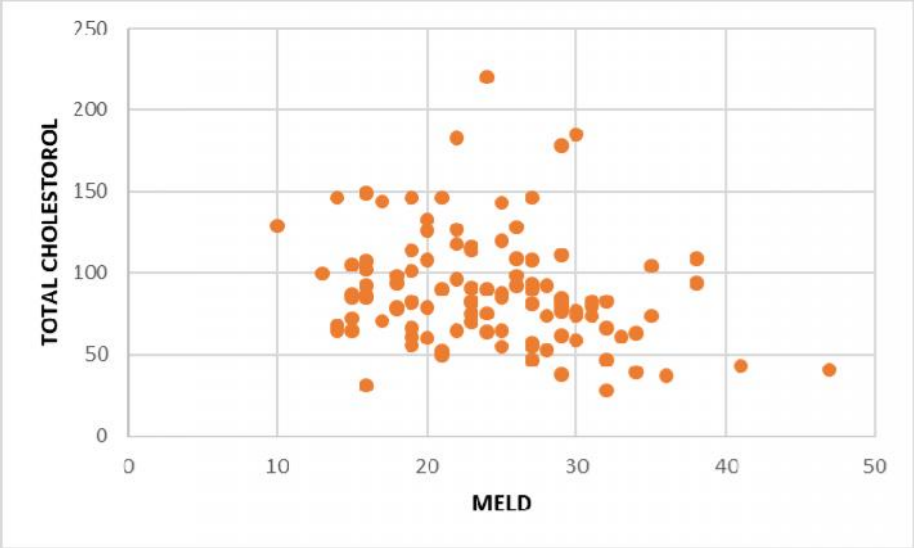
The study of correlation between level of Apo A1 with MELD score revealed that there was a negative correlation(r = -0.6604) between the two. Hence, it can be inferred that, as the MELD score increases, the level of Apo A1 decreases. This correlation is statistically significant (p<0.0001). Therefore with worsening of the cirrhosis, the level of Apo A1 decreases.

b) GRAPH 5.18-CORRELATION OF HDL CHOLESTEROL WITH MELD SCORE



The above graph depicts that there is a negative correlation between value of HDL cholesterol with MELD score ($r = -0.5450$) and this correlation was statistically significant ($p < 0.0001$). This implies that with worsening of cirrhosis, the value of HDL cholesterol decreases.

c) GRAPH 5.19 – CORRELATION OF TOTAL CHOLESTEROL WITH MELD



d) GRAPH 5.20 – CORRELATION OF LDL CHOLESTEROL WITH MELD

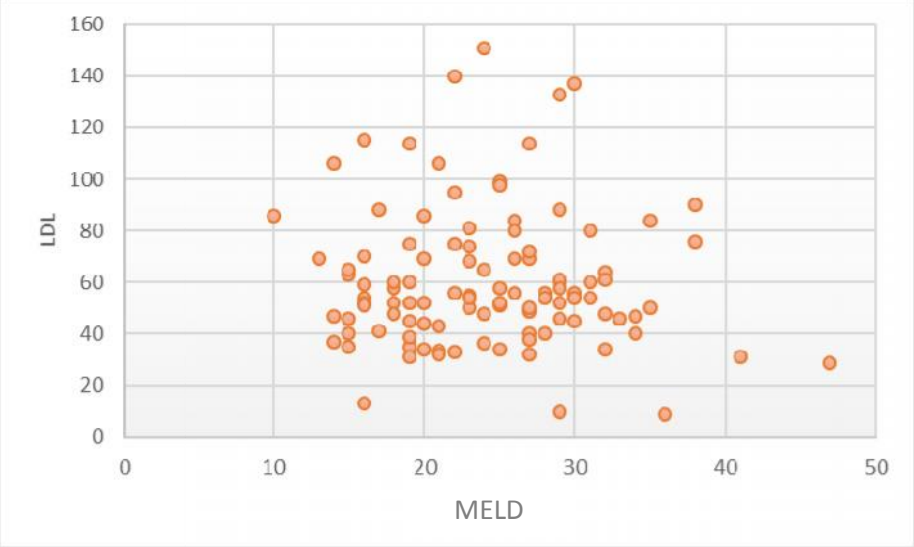


Table 5.17 shows that there is a negative correlation of MELD score with other components of lipid profile like total cholesterol (r=-0.0611), LDL (r=-0.0611) and triglycerides (r=-0.0086), however these correlations are not statistically significant. The graphs 5.19 and 5.20 depict negative correlation of total cholesterol and LDL with MELD score

ASSOCIATION OF APO A1 WITH CHILD PUGH SCORE

Table 5.18-ONE WAY ANALYSIS OF VARIANCE WITH RESPECT TO THE CLASSES OF CHILD PUGH SCORE

APO A1					
VARIATION	Sum of Squares	df	Mean Square	F	p VALUE
Between Groups	9.388	2	4.694	42.826	<0.0001
Within Groups	11.289	103	.110		
Total	20.677	105			

Using Scheffe'sPosthoc test

BETWEEN	**p VALUE**
A AND B	0.0107
A AND C	<0.0001
B AND C	<0.0001

One-way analysis of variance (ANOVA) of APO A1 levels with Child Pugh score class revealed that the variance of means of Apo A1 levels were different between all classes of Child Pugh score. Their differences were statistically significant between class A and class B ($p = 0.0107$), between Class A and Class C ($p<0.0001$) and between class B and C ($p < 0.0001$) . Hence it can be inferred that there is statistically significant difference between different Classes of Child Pugh score with respect to level of Apo A1.

ASSOCIATION OF TOTAL CHOLESTEROL WITH CHILD PUGH SCORE

Table 5.19- ONE WAY ANALYSIS OF VARIANCE WITH RESPECT TO THE CLASSES OF CHILD PUGH SCORE

TOTAL CHOLESTEROL					
VARIATION	Sum of Squares	df	Mean Square	F	p VALUE
Between Groups	9638.324	2	4819.162	4.306	0.0160
Within Groups	115272.582	103	1119.151		
Total	124910.906	105			

Using Scheffe'sPost-hoc test

BETWEEN	**p VALUE**
A AND B	0.9684
A AND C	0.2273
B AND C	0.0304

The above table shows that, the heterogeneity of levels of mean total cholesterol in different classes of Child Pugh Score was statistically significant (p = 0.0160). On using Scheffe's post-hoc test, our study found that the statistically significant difference in level of mean total cholesterol was mostly between class B and class C (p 0.0204).

ASSOCOATION OF HDL WITH CHILD PUGH CLASS

Table 5.20 - ONE WAY ANALYSIS OF VARIANCE WITH RESPECT TO THE CLASSES OF CHILD PUGH SCORE

HDL						
VARIATION	Sum of Squares	df	Mean Square	F	p VALUE	**INFERENCE**
Between Groups	4050.918	2	2025.459	36.177	<0.0001	HS
Within Groups	5766.742	103	55.988			
Total	9817.660	105				

Using Scheffe's Post-hoc test

BETWEEN	**p VALUE**
A AND B	0.1385
A AND C	<0.0001
B AND C	<0.0001

ANOVA of level of mean HDL cholesterol between classes of Child Pugh Score showed that there is statistically significant variance between the different groups ($p<0.0001$). This difference is mostly seen between class A and C ($p<0.0001$) and between class B and C ($p< 0.0001$).

ASSOCIATION OF OTHER COMPONENTS OF LIPID PROFILE WITH CHILD PUGH SCORE

ONE WAY ANALYSIS OF VARIANCE WITH RESPECT TO THE CLASSES OF CHILD PUGH SCORE

TABLE 5.21- CHILD PUGH SCORE WITH LDL

VARIATION	Sum of Squares	df	Mean Square	F	p VALUE
Between Groups	487.059	2	243.530	.338	0.7142
Within Groups	74291.641	103	721.278		
Total	74778.700	105			

TABLE 5.22- CHILD PUGH SCORE WITH TRIGLYCERIDES

VARIATION	Sum of Squares	df	Mean Square	F	p VALUE
Between Groups	470.848	2	235.424	.208	0.8128
Within Groups	116754.595	103	1133.540		
Total	117225.443	105			

TABLE 5.23- CHILD PUGH SCORE WITH VLDL

VARIATION	Sum of Squares	df	Mean Square	F	p VALUE
Between Groups	20.656	2	10.328	.225	0.7987
Within Groups	4722.106	103	45.846		
Total	4742.762	105			

ANOVA tests done for levels of LDL, VLDL and triglycerides showed there is no statistically significant difference between the 3 groups of Child Pugh Score , in other words , there is homogeneity in the means of LDL, VLDL and triglycerides among the 3 groups , this has been depicted in the above 3 tables .

DISCUSSION

A total of 106 patients with cirrhosis of the liver, irrespective of etiology admitted in the Dept. of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical research centre were studied during the period January 2017 to December 2017. The study was done to evaluate the lipid profile and levels of Apo A1 in patients with cirrhosis and also to determine its association with Child-Pugh and MELD scores.

AGE DISTRIBUTION

The mean age in our study population was 48.96 ± 13.29 years with majority of the patients (50.94%) in the age group off 41-60 years. This was in concordance with a study conducted by Jyoti Prakash Phukan et al., in a teaching hospital in North-east India where in the most common age group affected was 41 to 50 years (41%)[3]. Similarly, in another study done by Amanullah Abbasi et al., the mean age was found to be 40.32 ±13.594 years[100].

GENDER DISTRIBUTION

In the present study, 95.28% of the patients with cirrhosis were males which is similar to a study done by Lílian Bassani et al., in which 95 % of the subjects were males[13]. In a study done by Jyoti Prakash Phukan et al. all cases except one were males[3].

ETIOLOGY OF CIRRHOSIS

Alcohol was the most common etiology for cirrhosis in our study, i.e. 73.58 %. This is in concordance with the study done by Jyoti Prakash Phukan et al in a teaching hospital in North-east India ,in which majority of the cases (53%) consumed

a daily amount of 75- 100 g of alcohol , followed by 43% of cases consuming 50 – 75 g of alcohol[3].However in another study , Hepatitis C virus was the prevalent cause (53.3%), followed by alcohol (32%) and HCV and alcohol (14.6%)[101].

CLINICAL SIGNS

BILIRUBIN

In the present study, the value of total bilirubin ranged from 0.39mg/dl to 46mg/dl with a mean of 5.62±7.68mg/dl. Similarly, in a study published in BMJ, the mean bilirubin was 1.7 and the values of total bilirubin ranged from 0.3 to 12 among cirrhotic patients[102].

ALBUMIN

In our study the mean value of albumin among cirrhotic patients was found to be 2.56±0.53g/dl, and it ranged from 1.2g/dl to 4.4g/dl. However, in a similar study done in Europe showed a mean albumin level 3.5g/dl with a range of 2.4g/dl to 5g/dl[102].

INR

In the same study done in Europe, the mean INR value was 1.6 with a range of 1.0 to 2.9[102]. Our findings are concordant with the study, with mean INR of 1.91±0.65, ranging between 0.99 and 5.36.

CREATININE AND SODIUM

The present study showed a mean creatinine value of 1.41±0.92mg/dl among the patients with cirrhosis of liver and a serum sodium value ranging from 116 mEq/L

to 150 mEq /L. The study published in BMJ showed mean creatinine value of 0.9mg/dl (range 0.6 to 1.3)[102]. Angeli P et al. conducted a multicentre study with 997 patients with liver cirrhosis and in their study found that serum sodium concentration of <135 mEq/l was found in 49.4% of the patients[103]. Similarly, in our study, a large number of patients were found to have hyponatremia, 70.7 % of our patients had serum sodium concentration of <135 mEq/L

CHILD PUGH AND MELD SCORE

In our study, 55.66 % belonged to class C and 36.79 % belonged to class C, and only 7.55 % belonged to class A as per Child Pugh Score. However, a study done by Amanullah Abbas showed that 34 patients (29.8%) presented with Child-Pugh class A, 34 patients (29.8%) in class B and 46 patients (40.4%) were in class C[100].

APO A1

In our study, the mean apolipoprotein A1 level was 0.79 ±0.44 (79 ±44 mg/dl) among cirrhotic patients. In a study titled, Apolipoprotein A1 and Alcoholic Liver Disease, the results showed that apolipoprotein A1 concentration is highly related to the degree of liver injury[104].

LIPID PROFILE

In our study, low total cholesterol (<100 mg/dl) was found in 69.81% of patients with cirrhosis, low LDL level (<70 mg/dl) was found in 73.58 % of the patients, low triglycerides (<70 mg/dl) in 54.71 % and low HDL (<40 mg/dl) was found in 97.16 % of the patients. However, a study done by Bassini et al.[13] revealed that low total cholesterol (<100 mg/dl) was found in 15% of patients with cirrhosis,

low LDL level (<70 mg/dl) was found in 43 % of the patients, low triglycerides (<70 mg/dl) in 39.2 % and low HDL (<40 mg/dl) was found in 30.7 % of the patients.

MELD SCORE AND LIPID PROFILE

Our study found that there was a negative correlation between MELD SCORE and HDL (r =-0.5450) and Apo A1 levels (r=-0.6604). This negative correlation between MELD score and Apo A1 and between MELD score and HDL cholesterol was statistically significant (p<0.0001).In other words , higher the MELD score , lower was the level of HDL and Apo A1 .Though there was a negative correlation between MELD score and other components of lipid profile like total cholesterol, LDL, VLDL and triglycerides , these differences were not statistically significant .In a study done by Bassini et al.[13],it was found that the increase in MELD score inversely correlated with levels of TC (P<0.001), HDL (P<0.001), LDL (P<0.001), VLDL (P=0.030) and TG (P=0.003)[13].

CHILD PUGH SCORE AND LIPID PROFILE

In our study, ANOVA test done for comparing means of Apo A1 levels between different classes of Child Pugh Score was found to be statistically significant. The mean value of Apo A1 was lower in class C(0.54g/L) and class B(1.04 g/L) as compared to class A(1.43 g/L) of Child Pugh Score. Similarly, the comparison of means of total cholesterol and HDL cholesterol between different classes of Child Pugh Score was also found to be statistically significant, which means the mean value of HDL was lower in Child Pugh Class C(9.69 mg/dl) and B(20.79 mg/dl) as compared to Child Pugh class A(26.62 mg/dl) and mean of total cholesterol in Child Pugh class C (80.89 mg/dl) and class B (99.46 mg/dl) was lower than class A(102.27

mg/dl).In other words the mean value of Apo A1 reduced significantly with disease progression as defined by the Child-Pugh score.

Patients with Child-Pugh B and C scores had lower serum levels of LDL, VLDL and triglycerides as compared to Child Pugh class A. However, these differences in the means of LDL, VLDL and triglycerides between different classes of Child Pugh classes was not statistically significant. Similarly, a study done in Karachi showed that Serum cholesterol (total) and triglycerides have significant correlation with Child-Pugh class ($p = 0.001$ and $p = 0.004$ respectively) but in their study LDL and HDL had no statistically significant relation with Child-Pugh class[100]. Bassini et al[13] concluded that the total cholesterol levels decreased significantly with disease progression as defined by the Child-Pugh score and statistically significant inverse correlations were observed between the Child-Pugh and all lipid fractions analyzed ($P<0.001$).

CONCLUSION

The study population consisted of 106 patients diagnosed to have cirrhosis of liver. The mean age of the study population was 48.96±13.29 years and 95.28% of them were males. Among the 106 patients 78 of them (73.58%) had alcohol as the etiology of cirrhosis.

The patients admitted to the hospital came with varied presentations like jaundice, ascites, pedal edema and hepatic encephalopathy. Clinical jaundice was present in 68.87% of the patients, 66.04% had mild to moderate ascites, 79.25% had pedal edema and 44.34 % had grade 1 to grade 2 encephalopathy.

Laboratory evaluation showed hyperbilirubinemia, with 65% of the patients having a serum total bilirubin of >2 mg/dl. Hypoalbuminemia (serum albumin < 3.5 g/dl) was found in 96% of the patients with cirrhosis. Deranged clotting parameters, with INR of >1.5 was found in 72.63% of the patients. Deranged renal function with a serum creatinine of > 1.2 mg/dl was found in 45.28 % of the patients. Hyponatremia (serum sodium < 135 mEq/L) was seen in 70.7 % of the study subjects.

On further evaluation, all components of the lipid profile were found to be low in patients diagnosed with cirrhosis. Low Apolipoprotein A1 levels (< 1.2 g/L) was seen in 71.64% of the patients. Low total cholesterol (<100 mg/dl) was found in 69.81% of patients with cirrhosis, low LDL level (<70 mg/dl) was found in 73.58 % of the patients, low triglycerides (<70 mg/dl) in 54.71 % and low HDL (<40 mg/dl) was found in 97.16 % of the patients.

Prognostic indices like MELD score and Child Pugh score were applied to the patients. Around 50.94% of the patients belonged to MELD score range of 20-29 , 17.92% in a MELD score range of 30-39 and 1.89% of the patients had a MELD score of ≥40. Majority of the patients belonged to Child Pugh class B (36.79%) and C(55.66%).

Correlation of MELD score with different components of the lipid profile was studied using the Pearson's correlation co-efficient. This revealed that there is negative correlation of MELD score with all components of the lipid profile (total cholesterol, LDL, HDL, VLDL, triglycerides) and Apo A1, which implies that as the liver disease progressively worsens, the value of lipid profile and Apo A1 reduces. However, statistically significant negative correlation of MELD score was seen only with Apo A1 levels ($p< 0.0001$) and HDL levels ($p< 0.0001$).

ANOVA test was applied to study variation of means of different components of lipid profile in the different classes of Child Pugh classification. It was found that there was statistically significant variance in the means of Apo A1, total cholesterol and HDL levels between the 3 classes of Child Pugh scoring classification. This implies that with worsening of liver disease (Child Pugh class B to Child Pugh class C) there is statistically significant reduction the mean values of Apo A1, total cholesterol and HDL levels. Thus, it can be inferred that worsening of liver function in cirrhosis (as per MELD and Child Pugh classification) leads to significantly lower levels of lipid profile and Apo A1.

SUMMARY

The study of lipid profile in cirrhotic patients of various etiologies helps to identify the severity of liver damage.

As per our study, a reduction in the lipid profile including Apo A1 in patients with cirrhosis was significantly associated with worsening liver function as determined by higher Child-Pugh and MELD prognostic scores.

These results suggest that the lipid profile, in particular HDL, Total cholesterol and Apo A1 may be used as a tool to assist in evaluating liver functions in cirrhosis. Studies on a larger scale with follow-up are required to include lipid profile with Apo A1 levels into prognostic scoring systems of liver disease.

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ANNEXURE I –

INFORMED CONSENT FORM

APO A1 AND LIPID PROFILE IN CIRRHOTIC PATIENTS AND ITS CORRELATION WITH PROGNOSTIC SCORES: A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR.PRABHAKAR KORE HOSPITAL AND MRC,BELAGAVI

Objective and purpose of the study:

This research is intended to study the Apo A1 and lipid profile levels in cirrhotic patients and also to correlate these with prognostic indices like Child-Pugh Score and MELD score.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history in relation to liver cirrhosis and will be subjected for clinical examination and certain investigations like ultrasonography of abdomen and blood investigations.

Risk and Benefits:

There is no risk associated with study.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part and later change your mind, you may withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor may stop your participation in this study

any time. If you choose not to take part in the study, you will receive the standard treatment for your condition.

Privacy and Confidentiality:

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

Institution / Sponsor's policy:

Does not apply to this research

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

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

Financial incentives for participation

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

Authorization to publish the results

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

QUESTIONS:

In case of queries regarding your right as a participant you may contact:

DR. GANGA PILLI,

Chairman,

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

Professor, Department of Pathology, JNMC Belgaum

Phone number: 0831-2471350.

Extn: 1527

CONSENT FORM

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

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

Participant's Name/ : …….

Signature/ Left Thumb

Impression of the participant's : …….

Witness's Name : …….

Signature/ Left Thumb

Impression. :…….

Investigators name and Signature : …….

Date and Place : ……

ANNEXURE-II

PROFORMA FOR STUDY OF APO A1 AND LIPID PROFILE IN CIRRHOTIC PATIENTS

1. SL.NO

2 NAME:

3. AGE:

4. SEX

5. OCCUPATION:

6. RELIGION:

7. I.P. NO./O.P. NO.:

8. ADDRESS:

9. DATE OF ADMISSION: 10.DATE OF DISCHARGE:

11. OUTCOME :

HISTORY:

COMPLAINTS

Abodiminal distension

Pedal edema

Jaundice

Fever

Drowsiness/ altered sensorium

Malena

Hemetemesis

PAST HISTORY:

Similar complains

Jaundice

Blood transfusions

Co-morbidities

SIGNIFICANT PERSONAL HISTORY:

Alcohol consumption

High-risk behavior

SIGNIFICANT FAMILY HISTORY

Similar complaints

TREATMENT HISTORY:

Received any treatment for similar complaints in the past

GENERAL PHYSICAL EXAMINATION

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITAL SIGNS :

Pulse

Blood Pressure

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N.S.:

LIVER FUNCTION TESTS

TOTAL BILIRUBIN

DIRECT BILIRUBIN

TOTAL PROTEINS

ALBUMIN

SGOT

SGPT

ALP

PT

INR

RENAL FUNCTION TESTS-

UREA

SERUM CREATININE

SODIUM

POTASSIUM-

RBS

USG ABDOMEN

LIPID PROFILE-

TOTAL CHOESTEROL

LDL

HDL

TRIGLYCERIDES

APO A1 LEVELS:

Table 1: Modified "Child-Pugh" classification

Parameters	Value	Point
Encephalopathy	none Grade I-II Grade III-IV	1 2 3
Ascites	none mild uncontrolled	1 2 3
Bilirubin (mg/dL)	< 2 2-3 >3	1 2 3
Albumin(g/dL)	> 3.5 2.8-3.5 < 2.8	1 2 3
Prothrombin time (INR)	< 1.7 1.7-2.3 >2.3	1 2 3

Group A= 5–6 points; Group B= 7–9 points; Group C=10–15 points

MELD SCORE –

MELD = 3.78×**ln**[serum bilirubin (mg/dL)] + 11.2×**ln**[INR] + 9.57×**ln**[serum creatinine (mg/dL)] + 6.43

MELD-Na = MELD + 1.32 * (137-Na) - [0.033*MELD* (137-Na)]

ANNEXURES III - MASTER CHART

Sl.No	age	gender	icterus	ascitis	edema	encephalopathy	BILIRUBIN	ALBUMIN	INR	CREATININE	Na	TOTAL CHOLESTEROL	LDL	HDL	TG	VLDL	MELD	CLASS MELD	CHILD PUGH	ETIOLOGY	APO A1
1	56	M	1	2	1	1	7.46	2.9	1.82	0.94	130	143	99	30	90	14	25	2	B	1	0.98
2	42	M	1	1	1	1	3.52	2.7	1.62	1.47	138	133	44	50	110	22	20	2	B	1	1.92
3	43	M	0	1	0	1	1.97	3.2	1.1	1.48	135	85	54	15	80	16	16	1	B	1	0.51
4	54	M	1	2	1	2	2.62	2.5	1.89	0.64	134	56	35	7	67	13.4	19	1	C	1	0.39
5	32	M	1	2	1	1	26.90	2.4	2.04	0.56	129	59	45	5	125	25	30	3	C	1	0.03
6	36	M	1	3	1	1	30.00	1.9	1.49	1.3	130	185	137	31	85	17	30	3	C	1	1.04
7	55	M	0	2	1	1	0.70	2.7	1.17	1.6	130	101	60	27	68	13.6	19	1	B	1	0.77
8	53	M	1	2	1	2	5.07	3.6	1.37	0.63	138	149	115	14	97	19	16	1	C	1	0.59
9	58	F	0	1	0	1	2.27	3.7	2.75	0.61	140	52	33.6	5	67	13.4	21	2	B	5	0.65
10	38	M	0	2	1	1	0.93	2.6	1.45	1.68	138	92	52	19	105	21	16	1	B	1	0.76
11	45	M	1	1	1	2	2.40	2.9	1.23	2.22	130	64	36.6	16	57	11.4	24	2	B	1	0.63
12	35	M	1	2	1	2	2.86	2.3	1.14	0.5	123	81	49	24	39	7.8	27	2	C	1	0.77
13	36	M	1	2	1	1	5.90	2.6	1.89	2.1	133	178	133	26	92	14	29	2	C	1	0.94
14	47	M	1	2	1	1	6.06	2.4	1.77	0.41	129	120	97.6	5	87	17.4	25	2	C	1	0.30
15	42	M	1	2	1	2	7.99	2.9	1.46	1.4	116	80	60	5	139	27.8	29	2	C	1	0.19
16	58	M	1	2	0	2	2.44	2.0	1.42	0.7	129	50	32	6	58	11.6	21	2	C	1	0.32
17	59	F	0	2	0	1	1.09	2.2	2.37	0.69	141	31	13	8	49	9.8	16	1	C	6	0.39
18	62	M	0	1	0	2	1.31	4.4	1.38	0.8	131	144	88	43	66	13.2	17	1	A	2	0.98
19	70	M	1	1	0	2	2.44	3.0	1.56	1.36	121	146	114	19	65	13	27	2	B	2	0.54
20	56	M	1	2	1	2	2.86	2.3	2.18	0.5	123	108	69	28	53	10.6	27	2	C	1	0.79
21	66	M	0	2	1	2	0.40	2.5	1.39	0.54	133	146	106	23	85	17	14	1	B	1	0.69
22	90	M	0	2	1	1	1.22	3.1	1.36	0.87	132	85	35	39	53	10.6	15	1	B	3	1.01
23	68	M	1	2	1	2	2.91	2.2	2.44	2.43	136	38	10	7	104	20.8	29	2	B	1	0.41
24	42	M	1	2	1	1	2.80	2.5	1.51	1	138	87	63	9	76	15.2	15	1	B	6	0.36
25	47	M	1	2	1	2	10.00	1.8	2.9	0.82	126	28	64	5	45	9	32	3	C	2	0.16
26	59	M	0	2	1	1	1.87	2.1	1.64	0.74	134	71	41	18	61	12.2	17	1	B	1	0.69
27	65	F	1	2	1	2	5.41	2.3	1.97	4.06	134	39	40	5	80	16	34	3	C	5	0.26
28	33	M	0	2	1	1	1.30	1.8	2.35	3.55	131	83	80	5	82	16	31	3	C	1	0.19
29	65	M	0	2	1	2	1.27	2.6	1.86	0.67	133	94	58	23	64	12	18	1	B	2	0.60
30	73	M	0	2	0	1	1.53	2.6	1.68	1.75	133	96	56	17	114	22.8	22	2	B	1	0.61
31	53	M	0	2	1	1	0.86	2.8	1.32	3.13	131	220	151	36	167	33.4	24	2	B	1	1.08
32	36	M	0	2	1	3	0.71	2.6	2.06	0.56	128	116	74	12	151	30.2	23	2	C	1	0.57
33	35	M	1	2	1	2	16.99	2.0	2.38	2.8	122	94	76	5	64	12.8	38	3	C	1	0.19
34	82	M	0	2	1	2	1.42	2.7	1.94	2.17	130	93	72	9	62	12.4	27	2	C	6	0.47
35	52	M	0	3	1	3	0.80	2.1	1.18	2.29	128	114	81	10	113	22.6	23	2	C	2	0.61

36	45	M	1	1	0	1	4.60	2.2	1.89	1.02	134	183	140	24	95	19	22	2	B	6	1.24
37	43	M	1	2	1	2	2.40	2.7	3.77	0.97	124	74	54	7	67	13.4	31	3	C	2	0.30
38	33	M	1	2	1	2	2.70	2.5	1.65	1.79	129	109	84	10	76	15.2	26	2	C	1	0.74
39	64	M	1	3	1	2	3.08	1.9	1.74	2.85	124	83	61	5	80	16	32	3	C	1	0.31
40	23	M	1	2	1	2	2.43	2.3	1.81	1.88	127	92	56	8	141	28.2	28	2	C	1	0.42
41	70	M	1	3	1	1	5.26	1.7	1.03	0.69	132	118	95	10	69	13.8	22	2	C	2	0.80
42	39	M	1	2	1	2	22.10	2.2	2.82	1.4	121	37	9	5	114	22.8	36	3	C	1	0.03
43	48	M	0	3	1	2	0.70	1.5	1.94	4.1	133	83	52	9	108	21.6	29	2	C	1	0.46
44	58	M	0	1	0	1	0.83	3.2	1.38	0.71	140	129	86	23	100	20	10	1	A	3	1.45
45	52	M	1	2	1	1	5.44	2.3	1.43	1.5	128	98	69	12	86	17.2	26	2	C	1	0.64
46	38	M	1	2	1	2	46.00	1.9	2.59	0.7	132	66	48	5	66	13.2	32	3	C	1	0.01
47	46	M	1	2	1	2	24.47	2.5	2.09	1.65	123	74	50	6	88	17.6	35	3	C	2	0.05
48	50	M	1	1	1	1	5.29	2.5	2.3	0.76	131	128	80	24	120	24	26	2	B	1	1.06
49	65	M	1	2	1	2	4.94	2.1	1.79	1.59	120	77	56	5	78	15.6	30	3	C	2	0.27
50	65	M	1	2	1	1	4.80	2.2	1.36	1.33	128	55	34	7	72	14.4	25	2	C	1	0.45
51	45	M	1	2	1	2	3.80	1.7	2.2	1.7	122	80	60	5	139	27.8	31	3	C	1	0.36
52	45	M	1	2	0	1	4.84	2.2	2.08	1.81	130	111	88	10	66	13.2	29	2	C	1	0.88
53	36	M	1	1	1	1	2.90	2.7	1.54	0.56	133	146	114	19	65	13	19	1	B	1	1.40
54	30	M	1	1	0	1	2.90	2.8	1.89	0.97	134	108	69	28	53	10.6	20	2	B	1	1.11
55	45	M	1	1	1	1	0.70	2.3	1.81	0.6	128	146	106	23	85	17	21	2	B	1	1.00
56	56	M	1	2	1	2	2.80	2.3	2.08	1.4	129	90	50	6	169	33.8	27	2	C	1	0.54
57	47	M	1	2	1	2	8.40	3.1	2.83	1.4	134	74	54	7	67	13.4	30	3	C	1	0.30
58	32	M	1	2	1	1	5.51	1.6	1.73	3.95	120	104	84	5	76	15.2	35	3	C	1	0.10
59	53	M	1	2	1	1	6.00	1.6	1.8	1.97	132	85	61	8	80	16	29	2	C	1	0.67
60	33	M	0	3	1	2	0.43	2.4	2.4	1.05	124	92	56	8	141	28.2	26	2	C	1	0.40
61	58	M	1	2	1	2	10.44	2.4	2.8	0.8	135	74	54	7	67	13.4	28	2	C	1	0.63
62	62	M	1	1	0	1	1.74	3.0	1.8	0.88	147	72	46	14	60	12	15	1	A	1	1.20
63	40	M	1	2	1	1	1.80	2.6	1.52	1.4	133	126	86	20	100	20	20	2	B	1	1.50
64	69	M	1	1	0	1	1.30	2.6	1.37	1.1	128	60	34	19	35	7	20	2	B	2	1.10
65	65	M	1	2	1	3	2.60	2.8	1.8	1.7	128	47	32	9	30	6	27	2	C	3	0.78
66	50	M	0	2	1	2	1.50	2.5	2	3.38	140	57	40	10	35	7	27	2	C	1	0.86
67	33	M	1	2	1	1	3.37	3.3	1.99	1.12	138	79	52	14	65	13	20	2	B	1	1.34
68	30	M	1	2	1	2	10.80	1.6	1.99	1.62	133	62	46	7	45	9	29	2	C	1	0.56
69	34	M	1	2	1	1	29.80	2.6	3.04	1.3	146	63	47	5	55	11	34	3	C	1	0.36
70	40	M	0	1	0	1	0.60	2.8	1.24	0.7	132	65	37	20	40	8	14	1	A	2	1.45
71	40	M	1	3	1	2	22.90	1.6	2.24	2.9	132	109	90	5	68	13.6	38	3	C	1	0.36
72	39	M	1	2	1	1	7.23	3.2	2.08	0.58	137	127	75	10	211	42	22	2	B	1	1.22
73	56	M	1	1	0	2	8.90	2.7	2.22	0.86	147	90	65	11	58	11.6	24	2	C	1	0.86
74	55	M	1	1	0	1	1.14	3.0	1.51	0.4	130	98	60	45	66	13.2	18	1	A	1	1.89
75	42	**M**	1	1	0	1	0.96	3.3	1.18	0.63	131	105	65	22	98	18.4	15	1	A	2	1.34

76	32	M	1	1	0	1	2.23	3.6	2.4	1.06	135	90	43	25	110	22	21	2	B	1	1.22
77	59	M	1	3	1	2	3.93	1.2	3.86	0.84	131	77	58	8	55	11	29	2	C	1	0.65
78	40	M	1	2	1	1	3.86	1.8	2.71	0.84	137	83	55	20	40	8	23	2	C	1	1.02
79	33	M	1	1	0	1	5.09	3.0	2.47	1.03	133	85	51	23	55	11	25	2	B	1	1.32
80	39	M	1	2	1	2	3.56	2.8	1.65	1.13	128	88	58	20	50	10	25	2	C	1	1.05
81	60	M	1	2	1	1	8.25	2.4	2.19	0.99	143	91	68	12	88	11	23	2	C	2	1.03
82	41	M	0	2	1	1	1.67	2.9	1.59	0.88	131	114	75	20	98	19.6	19	1	B	1	1.15
83	42	M	0	1	1	1	0.96	3.3	1.31	0.63	131	107	70	22	79	6	16	1	A	1	1.26
84	75	F	0	1	1	2	0.39	3.4	1.02	1.4	132	65	40	18	35	7	15	1	B	5	1.12
85	58	M	1	2	1	1	2.50	2.3	1.68	1.87	141	65	33	23	45	9	22	2	B	1	1.20
86	33	M	1	2	1	2	5.09	3.0	2.47	0.81	138	70	54	9	35	7	23	2	C	1	1.09
87	51	M	1	2	1	2	4.02	3.2	1.77	1.01	127	65	52	7	30	6	25	2	C	1	0.78
88	55	M	0	2	1	2	1.64	3.0	1.43	1.59	136	78	52	19	35	7	18	1	B	1	1.23
89	60	M	1	2	1	2	26.50	2.6	1.25	0.86	126	53	40	6	35	7	28	2	C	2	0.60
90	47	M	0	2	0	1	1.61	3.1	1.12	0.73	134	100	69	22	78	9	13	1	B	1	1.45
91	45	M	0	2	1	1	1.49	2.4	1.89	1.24	134	61	31	19	58	11.6	19	1	B	1	1.10
92	59	M	0	2	1	1	1.26	2.0	1.86	0.85	150	68	47	12	49	9.8	14	1	B	1	1.21
93	76	M	0	2	1	2	1.71	2.5	1.54	2.96	130	55	38	10	39	7.8	27	2	C	3	1.00
94	50	M	1	2	1	1	4.49	2.9	2.88	1.69	123	61	46	6	48	13.8	33	3	C	2	0.54
95	38	M	1	2	1	2	3.21	3.0	1.35	0.79	127	82	50	17	79	15.8	23	2	C	1	1.00
96	44	M	1	1	0	1	9.28	3.1	1.31	0.94	138	75	54	17	22	4.4	23	2	B	1	1.09
97	32	M	1	1	1	1	3.30	2.6	1.89	0.86	137	79	48	20	58	11.6	18	1	B	1	1.22
98	37	M	0	2	1	2	1.41	2.3	2.59	4.03	140	47	34	7	32	6.4	32	3	C	1	0.66
99	33	M	0	1	0	2	0.81	3.1	1.96	0.66	135	86	51	20	75	15	16	1	B	1	1.13
100	44	M	1	1	1	1	3.23	2.5	1.98	0.88	136	82	45	24	65	13	19	1	B	1	1.40
101	21	M	0	1	1	1	1.19	3.0	1.87	2.16	140	102	59	24	98	19.6	16	1	A	7	1.93
102	66	F	1	2	1	2	22.60	2.1	5.365	3.2	132	41	29	5	38	7.6	47	4	C	6	0.03
103	45	M	1	2	1	1	3.91	2.7	1.66	0.94	135	83	52	20	58	11.6	19	1	C	1	1.11
104	58	M	1	2	1	1	8.92	3.0	2.17	0.93	136	75	48	15	63	12.6	24	2	B	1	1.60
105	56	M	0	3	1	2	1.02	2.4	0.99	0.69	126	66	39	18	45	9	19	1	C	1	1.00
106	44	M	1	2	1	1	11.88	2.5	2.95	4.04	134	43	31	5	36	7.2	41	4	C	1	0.20

ANNEXURE-IV

KEY TO MASTER CHART

A - SL.NO – SERAL NUMBER

B - AGE (in years)

C - GENDER –M-MALE, F-FEMALE

D - ICTERUS - 0-NO, 1- YES

E - ASCITES- 0-NO, 1- mild to moderate, 2- severe

F - EDEMA- 0-NO, 1- YES

G - ENCEPHALOPATHY- 0-No, 1- grade 1-2, 2 – grade 3-4

H - BILIRUBIN- total bilirubin (in mg/dl)

I - ALBUMIN – serum albumin (in g/dL)

J - INR – International Normalised Ratio

K - CREATININE- serum creatinine (in mg/dl)

L - Na-SODIUM- serum sodium (in mEq/L)

M - TOTAL CHOLESTEROL- (in mg/dl)

N - LDL- low density lipoprotein (in mg/dl)

O - HDL – high density lipoprotein (in mg/dl)

P - TG – triglycerides (in mg/dl)

Q - VLDL- Very Low-DensityLipoprotein (in mg/dl)

R - MELD score

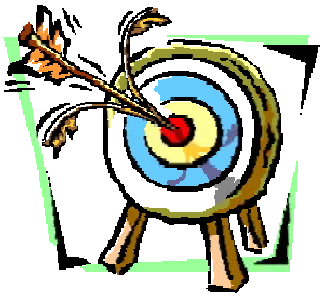
S - CLASS MELD –1=10-19, 2=0-29,3=30-39,4= ≥40

T - CHILD PUGH SCORE classification

U - ETIOLOGY 1-alcohol, 2- hepatitis B, 3- Hepatitis C, 4- NAFLD, 5-cryptogenic ,6- others

V - APO A1- Apolipoprotein A1 (in g/L)

Introduction



Objectives

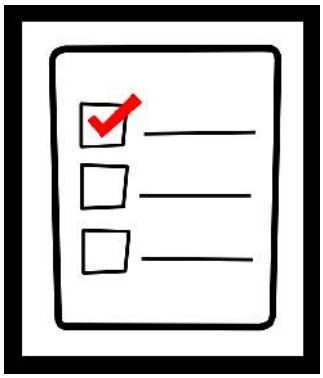
Review of Literature

Methodology

Results

Discussion

Conclusion

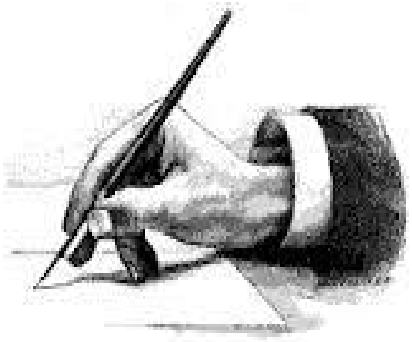


Limitations

Recommendations

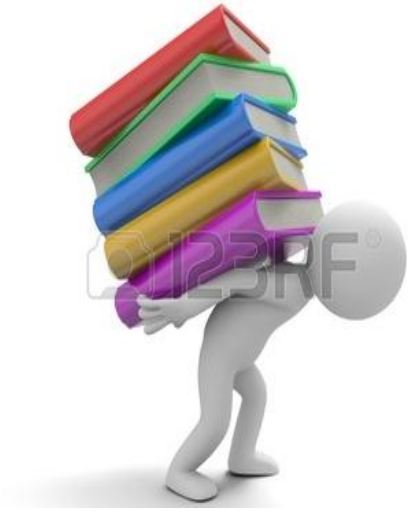
Summary

Bibliography



Annexure-I

Annexure-II



Annexure-III

Annexure-IV

Annexure-V