“CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN PATIENTS OF CIRRHOSIS OF LIVER IN A TERTIARY CARE HOSPITAL - A CROSS SECTIONAL STUDY”

BY

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ABSTRACT

TITLE: "CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN PATIENTS OF CIRRHOSIS OF LIVER IN A TERTIARY CARE HOSPITAL-A CROSS SECTIONAL STUDY"

BACKGROUND: Liver cirrhosis accounts for 4% of deaths worldwide. India contributes one-fifth of the overall deaths due to cirrhosis of liver globally. The child Pugh scoring system provides long-term severity of the liver disease and helps in predicting mortality among patients with cirrhosis of liver. With rising incidence of cirrhosis of liver, particularly in Asian countries, there is a need for incorporating additional markers that help in assessment of severity of liver disease in addition to the Child Pugh scoring system.

Our study involves in assessment of one such marker, Serum Prolactin by correlating its levels to Child Pugh scoring system, which can provide further insights into the disease severity and potential complications.

AIM: The study is designed to evaluate the prognostic corelation of Serum Prolactin level to Child Pugh scores in patients with cirrhosis of Liver in a Tertiary Care Hospital.

METHODS: Individuals with diagnosis of liver cirrhosis admitted to the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi Between 1st January 2023 to 31st December 2023 over a period of one year were included in the study. The study design was a hospital based cross sectional study. All patients of liver cirrhosis underwent clinical examinations, biochemical tests, ultrasound abdomen, including Serum Prolactin levels. Patients were classified as per Child Pugh scoring system and Serum prolactin levels were correlated.

RESULTS: The mean age of study participants was 52.95 ± 12.91 years. Majority of the study participants were male (n=62, 86.1%) (Female: n=10, 13.9%). Comparison of prolactin levels with severity of ascites was statistically significant (p=0.027). Median value of prolactin among mild, moderate, severe and no ascites groups were 27.1 (14.91), 32.07 (35), 31 (41.04) and 11.2 (5.32) respectively. Correlation of Prolactin with grades of hepatic encephalopathy was statistically significant (0.001). Median Prolactin levels of Grade 1, Grade 2, Grade 3, Grade 4 and no hepatic encephalopathy groups were 29 (9.57), 42.5 (44.96), 66.7 (7.91), 28 (0), and 21 (18.03) respectively. The median (IQR) of serum prolactin levels of Class A was 12 (11.93, 15.72). The median (IQR) of serum prolactin levels of Class B was 28.6 (17, 32.6). The median (IQR) of serum prolactin levels of Class C was 35 (24, 64). The Child Pugh class and serum prolactin levels were not statistically significant (p=0.733).

However, when the patients were grouped into two classes i.e, Child Pugh class c (severe) vs Child pugh Class A&B (Mild and Moderate), serum Prolactin level came to be statistically significant with Child Pugh Score with Chi-square value of 8.496 and p value of 0.003.

CONCLUSION: Prolactin has a strong correlation with the severity of liver disease, as well as complications of cirrhosis of liver. As a result, Prolactin can be used as an alternate prognostic marker and can help predict the likelihood of cirrhosis related complications.

LIST OF ABBREVIATIONS

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HSC	Hepatic Stellate cells
WHC	West Haven Criteria
AST	Aspartate Aminotransferase
ALT	Alanine aminotransferase
CT	Computer Tomography
PH	Portal hypertension
HE	Hepatic Encephalopathy
HVPG	Hepatic venous pressure gradient
HPS	Hepatopulmonary syndrome
HRS	Hepatorenal syndrome
TIPS	Transjugular intrahepatic portosystemic shunt
GFR	Glomerular Filtration Rate
NO	Nitric oxide
CVS	Cardiovascular system
CKD	Chronic Kidney disease
AKI	Acute Kidney Injury
LT	Liver transplant
V/Q ratio	Ventilation (V)/ perfusion (Q) ratio

NOS	Nitric Oxide Synthase
PaO2	Partial pressure of oxygen
AVS	Arteriovenous shunt
MELD score	Model for End-stage liver disease
INR	International Normalized Ratio
USG	Ultrasonography
IQR	Inter quartile range
CBC	Complete blood count
LFT	Liver function test
RFT	Renal function Test
APTT	Activated Partial thromboplastin Time
PT INR	Prothrombin Time

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INTRODUCTION

Cirrhosis of liver is a condition when the liver is scarred and had a permanent damage to it. The healthy tissues in the liver is replaced by scar tissues and it hinders the function of liver (Figure 1) (1).

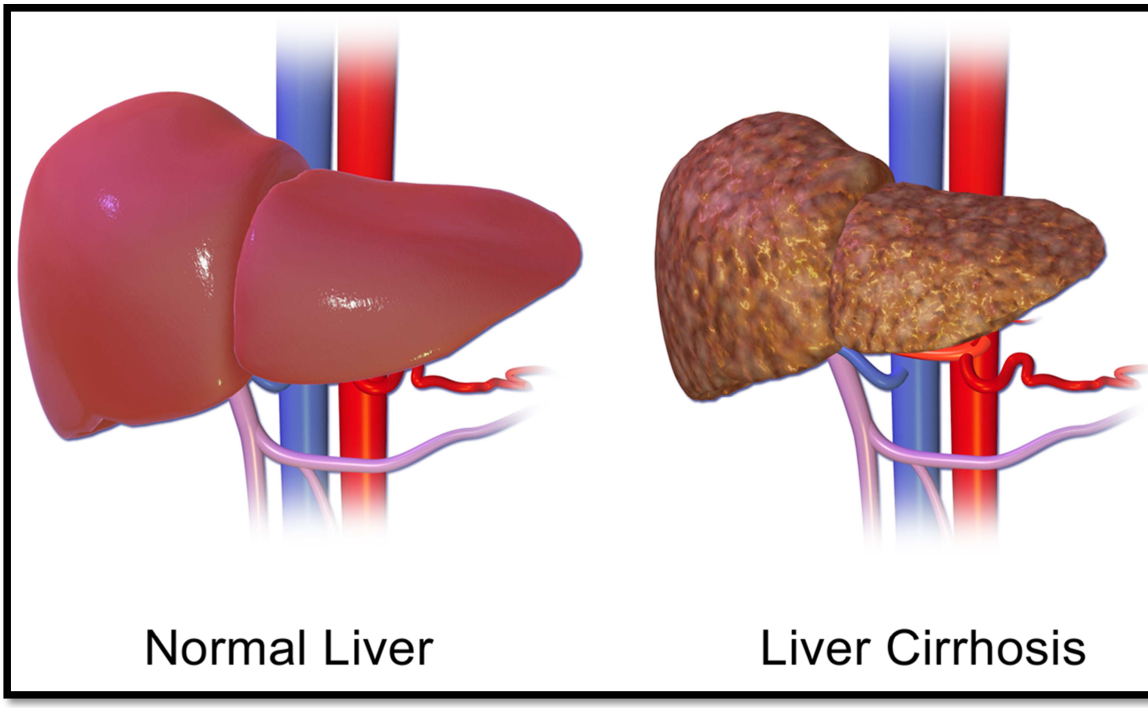

Figure 1: Healthy liver and Cirrhosis of liver

Liver diseases accounts for 4% of death worldwide. Around two-thirds of death of all liver- related deaths occur in men. Around 2 million deaths happen due to liver disease every year (2). In 2017 in India, 2.95% happen due to liver diseases. India contributes one-fifth of overall deaths due to liver diseases globally(3).

Prolactin is a polypeptide hormone. It helps in the regulation of homeostatis, breast development and lactation. It is composed of 199 amino acids. Prolactin primarily produced by anterior pituitary. But it can also be produced by central nervous system, immune system, uterus and mammary glands. Low levels of prolactin is present in males, non-lactating and non-pregnant women (4).

Prolactin levels in the body exhibit a circadian rhythm characterized by nocturnal rise. Prolactin levels rise immediately after sleep onset and its fall is seen after waking up. In patients with liver cirrhosis, there is a loss of the circadian rhythm of serum prolactin secretion which leads to a 24-hour elevation of serum prolactin level in the body. Increase in prolactin is associated with increased grade of the disease and increased development of complications of the disease.

Many theories can attribute to hyperprolactinemia in liver cirrhosis. One, because of increased levels of oestrogen in the blood, that occurs secondary to reduced excretion of estrogen by the liver, which causes anterior pituitary to directly affect the hypothalamus and interfere with dopamine secretion, so stimulating the release of prolactin. Second, abundant production of pseudo neuro transmitters like octopamine, phenyl ethanolamine etc., These in turn reduce dopamine secretion which eventually leads to a hyperprolactinemia. The child Pugh scoring system provides long-term assessment of the degree of liver disease and helps in anticipating the mortality among patients with cirrhosis of liver (5).

Study Rationale

With the rising incidence of liver cirrhosis, particularly in Asian countries, there is a need for incorporating additional markers that help in assessment of severity of liver disease in addition to traditional prognostic criteria such as the Child-Pugh scoring system. Consequently, incorporating biomarkers like prolactin, which provide insights into the disease severity and potential complications, becomes crucial. Utilizing prolactin levels as a biomarker aid in early intervention, enabling more effective management of liver cirrhosis. By establishing a correlation between serum prolactin levels and Child Pugh score, this study could pave the way for enhanced prognostic tools in management of liver cirrhosis. This increases the patient outcomes and helps in providing targeted interventions.

AIM OF THE STUDY

To correlate the level of serum prolactin to Child Pugh scoring system in patients with Cirrhosis of Liver and to know its utility as an alternative prognostic marker.

REVIEW OF LITERATURE

Cirrhosis of liver is a condition when the liver is scarred and had a permanent damage to it. The healthy tissues in the liver is replaced by scar tissues and it hinders the function of liver.

Cause of Cirrhosis of Liver

Some common causes of cirrhosis of liver are as follows (2):

- Viral hepatitis (Hepatitis C or B)
- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Storage disease
    - Hemochromatosis
    - Wilson disease
    - Alpha1 antitrypsin deficiency
- Immune-mediated
    - Autoimmune hepatitis (1, 2, 3)
    - Primary biliary cholangitis
    - Primary sclerosing cholangitis
    - Immunoglobin G4 cholangiopathy
- Cardiovascular disease
    - Veno-occusive disease
    - Congestive heart failure
- Chronic biliary disease
    - Recurrent bacterial cholangitis
    - Bile duct stenosis

- Other causes
    - Medications like methotrexate, and amiodarone
    - Erythropoietic protoporphria
    - Sarcoidosis
    - Schistosomiasis

Pathophysiology of Cirrhosis

Hepatic fibrosis and inflammation are brought on by chronic liver damage. Whatever the reason, this may result in the hepatic parenchyma and vascular architecture being distorted, liver structures collapsing, and fibrous septae and nodules forming. Reduced metabolic and synthetic hepatic function, which raises bilirubin and decreases thrombopoietin and clotting factor production, leads to progressive fibrosis and cirrhosis. It also causes splenic platelet sequestration, elevated portal pressure, ascites, and esophageal varices. Any source of prolonged liver injury can lead to cirrhosis (2) (Figure 2).

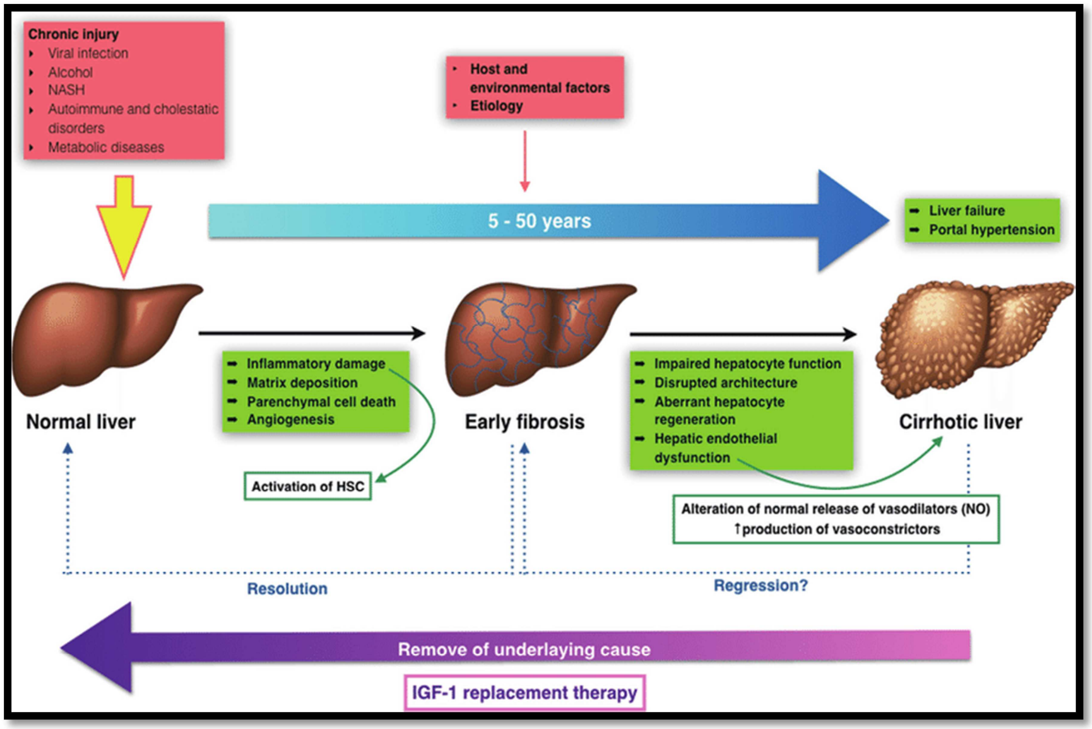

Figure 2: Development of Liver Cirrhosis

Age, medical comorbidities (especially in individuals co-infected by human immuno deficiency virus and Hepatitis C virus), and gender, especially men (except from alcoholic liver disease, when women advance quickly) are risk factors linked to an increased chance of progression to cirrhosis (6). More recent studies have shown that even early cirrhosis is reversible and that liver fibrosis is a dynamic process. Research has shown patients with HBV and HCV who receive antiviral therapy have 88% positive response from treatment in fibrosis confirmed via a biopsy. While patients with non-alcoholic steatohepatitis who have bariatric surgery had rates as high as 85% (7).

Inflammation and the stimulation of hepatic stellate cells (HSCs) cause fibrogenesis, angiogenesis, and parenchymal lesions, which are partially brought on by vascular obstruction, during the shift from chronic liver disease to cirrhosis.

Hepatic microvascular rearrangement results from these modifications, which include hepatic endothelial dysfunction, intrahepatic shunt development, and sinusoidal remodelling. Via endothelial dysfunction, vasodilators—most notably nitric oxide—are not released normally. Vasoconstrictors are also being produced at a higher rate. When structural abnormalities and all of these modifications come together, the result is an increased hepatic resistance to portal blood flow, which raises portal pressure and has clinical ramifications (Figure 3, 4, 5 and 6) (8).

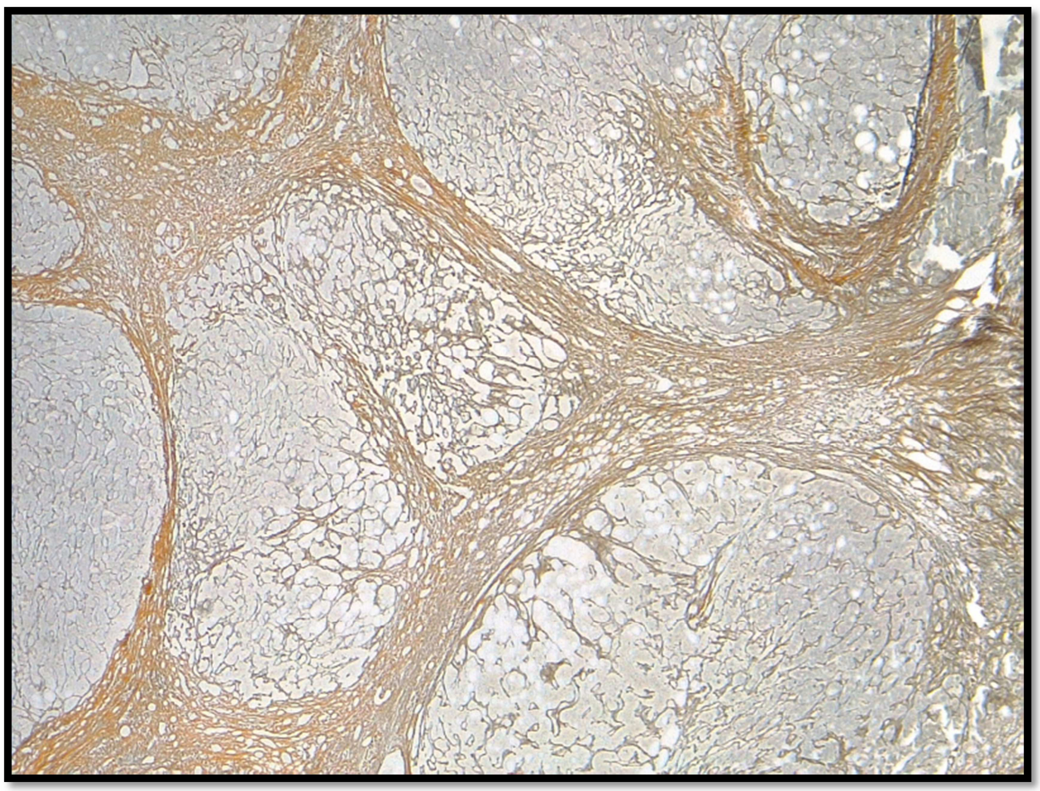

Figure 3: Cirrhosis of Liver (Reticulin stain)

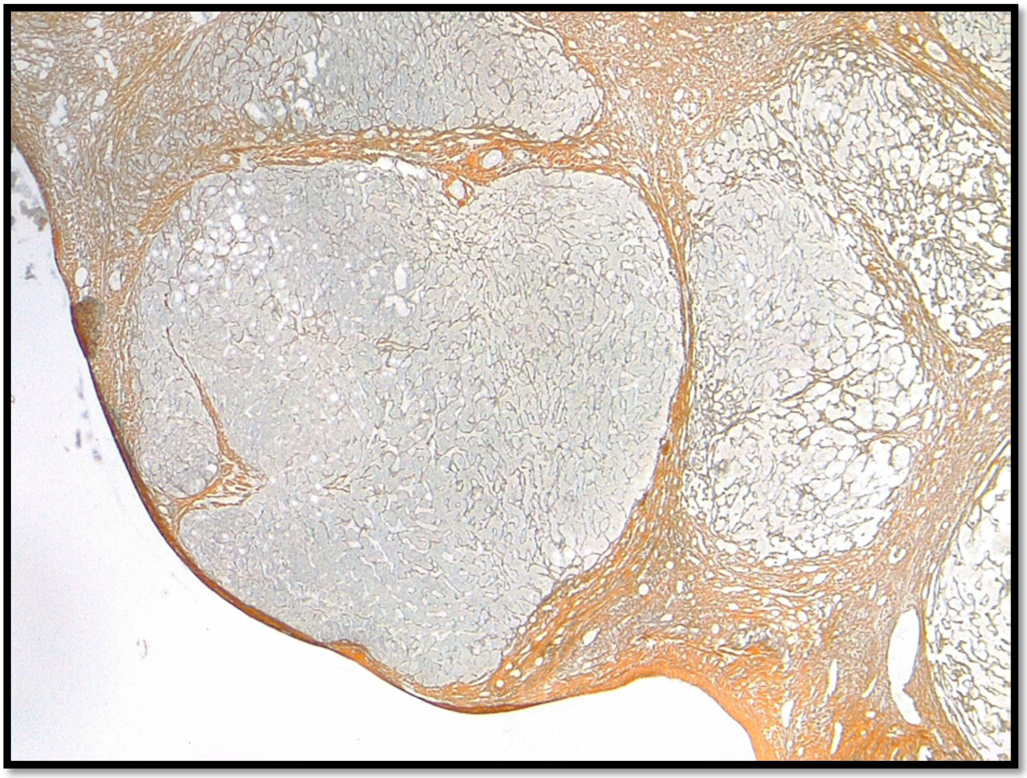

Figure 4: Liver cirrhosis (Reticulin stain)

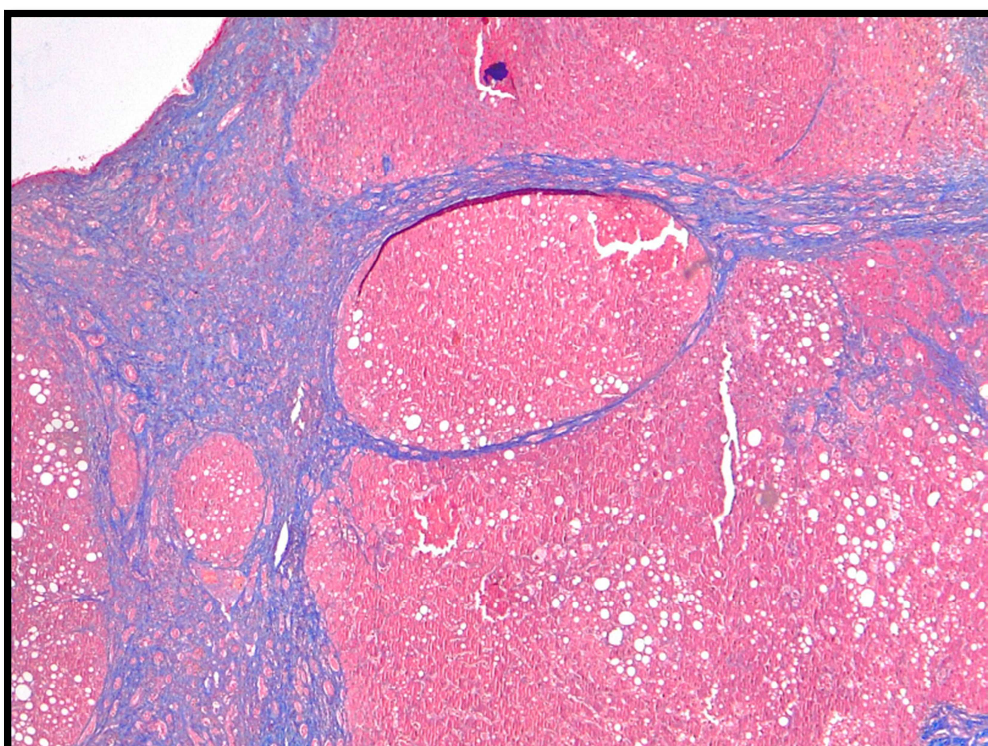

Figure 5: Liver cirrhosis (Tricromic stain)

Figure 6: Cirrhosis (Portal space in fibrous septa)

Symptoms of cirrhosis of liver

Early symptoms of liver cirrhosis include (9):

- Tiredness or weakness
- Itching of skin
- Poor appetite
- Weight loss
- Nausea and vomiting
- Mild pain or discomfort in the upper right side of abdomen
- Muscle loose and muscle weakness
- Muscle cramps

Some severe symptoms of liver cirrhosis include (6):

- Brusing and bleeding
- Confusion, difficulty thinking, memory loss, personality changes or sleep disorders
- Internal bleeding example varices
- Edema in lower leg, ankles or feet
- Darkening of skin
- Jaundice

Types of Cirrhosis of Liver

Two classifications of liver cirrhosis: Morphological and aetiology.

Morphological types	Aetiology
a. Micronodular cirrhosis: The uniform nodules less than 3 mm in diameter. Cirrhosis of liver happens due to alcohol, hemochromatosis, hepatic venous overflow obstruction, chronic biliary obstruction, jejunoileal bypass and Childhood cirrhosis. b. Macronodular cirrhosis. Irregular Nodule more than 3 mm in diameter. Cirrhosis happens due to hepatitis B, hepatitis C, alpha 1-antitrypsin deficiency and primary bilial cholangitis. c. Mixed Cirrhosis: Features of both Micronodular and macronodular cirrhosis are present.	a. Viral (due to Hepatitis B, C and D) b. Toxins (Due to alcohol and drugs) c. Autoimmune hepatitis d. Cholestatic (Primary biliary cholangitis, primary sclerosing cholangitis) e. Vascular (Cardiac cirrhosis, sinusoidal obstruction syndrome) f. Metabolic (hemochromatosis, non-alcoholic steatohepatitis, Wilson disease, alpha 1-antitrypsin deficiency and cryptogenic cirrhosis)

Figure 7: Classification of Cirrhosis of liver

Three types of cirrhosis based on morphological types includes micronodular cirrhosis, macronodular cirrhosis and mixed cirrhosis. In aetiology, six types were present including metabolic, vascular, presence of toxins, microbials, autoimmune and cholestatic aetiology (Figure 7) (10).

Diagnosis of Cirrhosis of Liver

Laboratory findings

Mild to moderate raise in the Aminotransferases level with AST is more than ALT. These can be within the normal range for few individuals with cirrhosis. Usually, the ratio of AST/ALT is less than one is most of the chronic hepatitis other than alcoholic hepatitis. When the chronic hepatitis further develops to cirrhosis of liver, the AST/ALT ratio is reversed. Changes in values of prothrombin time, serum albumin and immunoglobulins were recorded. Normocytic anemia can be recorded. Macrocytic anemia is recorded in alcoholic cirrhosis of liver.

For diagnosis of viral hepatitis, serology and polymerase chain reaction tests can be conducted. For diagnosis of autoimmune hepatitis, Serum IgG and autoimmune antibodies can be tested. For biliary cholangitis, anti-microbial antibody can be checked (10) (Figure 8).

Imaging

Fibro scan (Transient elastography), ultrasound, computerized tomography and magnetic resonant imaging can be used. Ultrasound is economical, easily assessable, non-invasive test for diagnosis. This detects nodularity and level of echogenicity in liver. Main disadvantage of this tool is, these findings are also present in fatty liver. So further investigation required to diagnose the individual have fatty liver or cirrhosis of liver. Computer tomography and magnetic resonance imaging will diagnose hepatocellular cancer and vascular lesions. Magnetic resonance imaging report is more reliable than CT in this diagnosis. Stiffness in the liver which can provide the level of fibrosis can be detected using Fibro scan (10).

TABLE 3

Clinical, Laboratory, and Imaging Findings to Identify Etiology of Chronic Liver Disease

Etiology	Characteristics and risk factors	Laboratory and imaging findings
Alcoholic liver disease	Positive screening tests for alcohol use disorder History of excessive alcohol intake	Aspartate transaminase ≥ 2 times alanine transaminase level in 70% of patients, especially if 3 times Elevated gamma-glutamyl transferase and/or mean corpuscular volume Ultrasonography may show fatty change
$Alpha_1$-antitrypsin deficiency	Autosomal recessive trait European ancestry All other evaluations unrevealing	$Alpha_1$-antitrypsin phenotype
Autoimmune hepatitis	Young and middle-aged women (in type 1, the most common)	Antinuclear antibody and/or antismooth muscle antibody positive in titers ≥ 1:80 Total serum immunoglobulin G (polyclonal hypergammaglobulinemia > 1.5 times the upper limit of normal supports diagnosis)
Hemochromatosis	Autosomal recessive trait Northern European ancestry	Ferritin ≥ 250 to 300 ng per mL in men, ≥ 200 ng per mL in women Transferrin saturation (serum iron × 100/total iron-binding capacity) ≥ 45% If ferritin or transferrin saturation is abnormal, order human hemochromatosis protein gene mutation analysis
Nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis	Obesity, diabetes mellitus Improvement with weight loss	Lipids, A1C (not needed for diagnosis) Ultrasonography may show fatty change May need biopsy to diagnose nonalcoholic steatohepatitis
Primary biliary cholangitis (primary biliary cirrhosis)	Associated with other autoimmune disorders (80% with Sjögren syndrome; 5% to 10% with autoimmune hepatitis) Middle-aged women	Cholestasis (elevated alkaline phosphatase and glucose tolerance test) Antimitochondrial antibody positive
Primary sclerosing cholangitis	Middle-aged men Associated with inflammatory bowel disease (70%)	Cholestasis (elevated alkaline phosphatase and glucose tolerance test) Perinuclear antineutrophil cytoplasmic antibodies positive in 70% of patients Frequently positive antinuclear antibodies, antismooth muscle antibodies, other antibodies Magnetic resonance cholangiography
Viral hepatitis B (chronic)	Born in endemic country	Hepatitis B surface antigen Hepatitis B core antibody If either is positive, order hepatitis B virus DNA
Viral hepatitis C (chronic)	Born 1945 to 1965 Specific risk factors for hepatitis C virus*	Anti–hepatitis C virus antibody If positive, order hepatitis C virus RNA
Wilson disease	Autosomal recessive trait Age younger than 40 years with chronic liver disease or fatty liver and negative workup for the above Kayser-Fleischer rings	Low serum ceruloplasmin If abnormal, serum copper, urinary copper excretion, liver biopsy, hepatic tissue copper measurement, and genetic marker testing can be considered

*—Specific risk factors for hepatitis C virus include history of injection drug use (even once); men who have sex with men (especially if HIV infected); history of a blood transfusion before 1992; long-term hemodialysis; being born to a hepatitis C virus–infected mother; incarceration; intranasal drug use; having an unregulated tattoo (not performed in a regulated tattoo parlor); and other percutaneous exposures (see U.S. Preventive Services Task Force guidelines: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening).

Information from references 19, 21, and 22.

Figure 8: Chronic liver disease and imaging/ laboratory tests

Biopsy

Biopsy is the gold standard for diagnosis of liver cirrhosis. It detects the grade and stage of fibrosis. Direct and indirect serum markers which are non-invasive methods, were used to diagnose the individuals with fibrosis or liver cirrhosis (10).

Management of Liver Cirrhosis

The liver damage is permanent. While starting the treatment, first work is to prevent further damage to the liver. Avoiding alcohol, Hepatitis B and C virus vaccination, a balanced diet, and reduction of weight are few general managements of chronic liver disease. Routine monitoring of volume status, renal function, development of varices and progression to hepatocellular cancer should be done (10).

Individual therapy depends upon the etiology of the disease. For viral hepatitis, anti-viral medications and steroids, for autoimmune hepatitis use of immunosuppressants, and for primary biliary cholangitis use of ursodeoxycholic acid and obeticholic acid (10).

Complications of Liver Cirrhosis

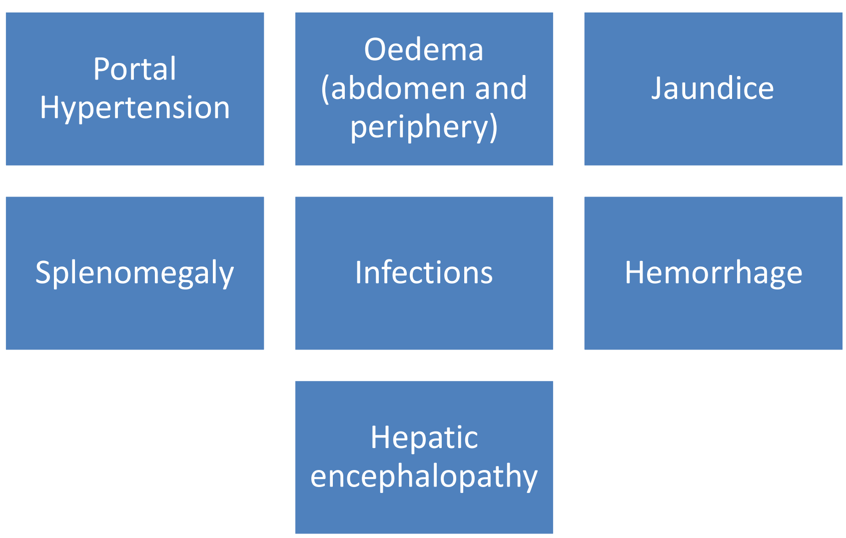

Figure 9: Complications of cirrhosis of liver

If untreated properly, liver cirrhosis can lead to (10) multiple complications listed in Figure 9.

Portal Hypertension

The majority of the clinical problems of cirrhosis are caused by portal hypertension (PH), which leads to an increase in portal (and hepatic artery) blood flow in conjunction with increasing intrahepatic resistance. Increased intrahepatic resistance results from endothelial dysfunction causing vasoconstriction, leading to development of vascular intrahepatic shunts, and architectural distortion (fibrous tissue, regenerating nodules). These portal-central anastomoses, further causes stellate cell and myofibroblast activation leading to fibrosis (11).

The most accurate indicator of the onset of PH in clinical praxis is the gradient of hepatic venous pressure (HVPG), which indirectly measures portal pressure. 3–5 mm Hg is the typical HVPG. individuals in stages 3 or 4 of fibrosis nearly always have an gradient of approximately 6 mm Hg, while individuals beyond 10 mm Hg are considered to be at increased risk of esophageal varices and other clinical complications. Therefore, the presence of "clinically significant portal hypertension" is defined as HVPG > 10 mm Hg. Interestingly, when the gradient is less than 12 mm Hg (i.e., clinically severe PH), ascites and variceal haemorrhage do not occur; so, this threshold is intimately associated with the occurrence of decompensating events (11).

Oesophageal Varices

Among the individuals diagnosed with cirrhosis of liver, around 5 to 15% develop varices each year. Majority of the individuals with cirrhosis of liver develop gastroesophageal varices at some point of their life time. The development of this condition shows the progression of the disease. Majority of the varices were found in later stages of the disease. Portal venous system and systemic veins had collaterals between. Generally, the resistance in the portal vessel is lower than the resistance in the collateral circulation. Hence, the blood moves from systemic to portal bed.

In portal hypertension, the pressure in the portal venous system is higher than the pressure in the systemic veins. Hence, the blood flow is reversed. Angiogenesis is formed and new blood vessels develops to reduce the pressure in the portal circulation. However, these may not be sufficient leading to bleeding. These varices were formed mainly in gastroesophageal region. When hepatic venous pressure gradient increases above 10 mmHg, oesophageal varices were developed. Varices in the submucosal lining of the oesophageal area has a superficial area which is lower than 2 cm to 3 cm. The wall is thinner. The varices are not linked with the periesophageal veins. Hence, it could not be decompressed. Hence, the bleeding occurs (12).

Hepatic Encephalopathy

Advanced liver malfunction can cause hepatic encephalopathy, a potentially reversible but dangerous illness. The accumulation of hazardous chemicals in the bloodstream causes a variety of neuropsychiatric and neuromuscular disorders that ultimately affect brain function. Although it is frequently linked to underlying liver diseases like cirrhosis, acute liver failure can also occur in people who have never had hepatic problems before. Hepatic encephalopathy owing to acute liver failure can result in brain oedema and be difficult to treat, even though it may be reversible in chronic liver failure such as cirrhosis. This syndrome can also occur in patients with portosystemic shunts. The symptoms of hepatic encephalopathy may be caused by either portosystemic shunting, which is the redirection of blood flow away from the liver, or liver insufficiency. Hepatic encephalopathy manifests as diminished consciousness, disorientation, altered personality, and bewilderment. Patients frequently experience a disturbed sleep-wake cycle in the early phases, with a propensity to sleep during the day and remain up at night. Patients often experience increasing degrees of disorientation, lethargy, and personality changes as the illness moves through its intermediate stages. Hepatic encephalopathy in its severe stages might finally result in coma, often referred to as coma hepaticum or hepatic coma, which can be fatal. Within the first year, the mortality rate surpasses 50% in cases of severe encephalopathy among patients with acute liver failure or known cirrhosis (13).

The most popular system for rating HE is the West Haven criteria (WHC). This grading scheme distinguishes between four clinically apparent HE ratings. Patients in grade I exhibit inattention and mild personality changes that are primarily apparent to their family members. The most interesting result in grade II is disorientation for time when combined, for instance, with inappropriate behaviour and sluggishness. Patients in grade III are comatose but react to stimuli. They may also behave strangely and are confused about where they are and what to do. Patients in grade IV are unconscious (14) (Figure 10).

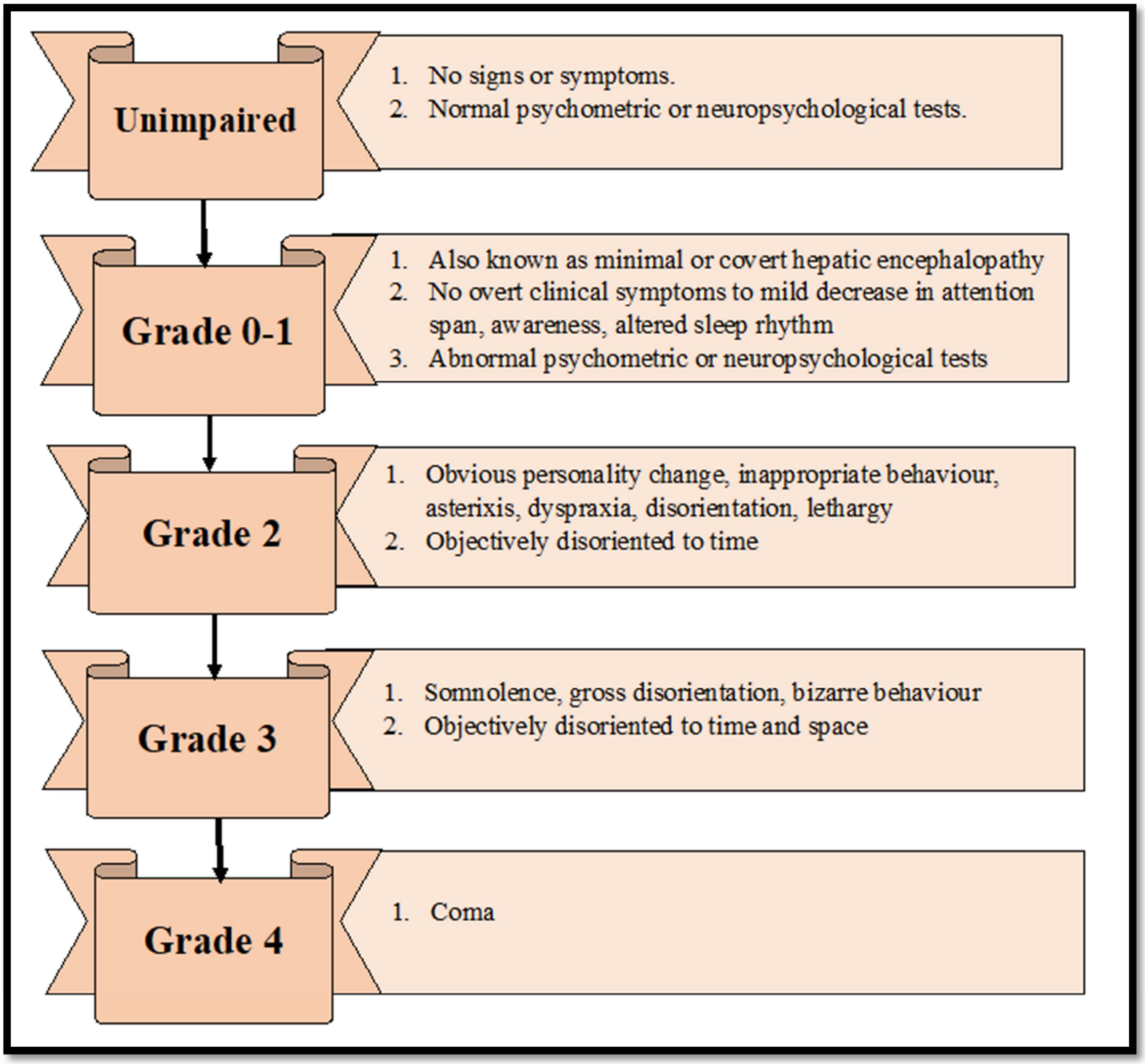

Figure 10: Grades of Hepatic Encephalopathy

Ascites

The pathologic build-up of fluid in the peritoneal cavity is known as ascites. About 50% of patients with decompensated cirrhosis experience this most frequent consequence within ten years. When ascites appears, compensated cirrhosis changes to decompensated cirrhosis. Complications including hepatorenal syndrome and spontaneous bacterial peritonitis enhance mortality. The annual mortality rate might range from 15% to 44% in five years. In addition to highlighting the importance of team-based, interprofessional care for afflicted people, this activity discusses the assessment, diagnosis, and management of ascites. When cirrhosis occurs, portal hypertension is the first anomaly to appear. Vasodilatation results from an increase in circulation nitric oxide levels and portal pressure above a crucial threshold. Hepatic decompensation occurs when renal function deteriorates, ascitic fluid accumulates, and plasma levels of vasoconstrictor sodium-retentive hormones rise as the state of vasodilatation worsens. Ascites can also be brought on by peritoneal carcinomatosis, as tumour cells lining the peritoneum produce a proteinous fluid. Effective arterial blood volume is lowered in high-output or low-output heart failure or nephrotic syndrome, and the sympathetic nervous system, vasopressin, and renin-aldosterone are activated, resulting in renal vasoconstriction and sodium and water retention (15).

Grades of ascites

Based on the volume of fluid in the abdominal cavity, ascites is categorised into three grades: grade 1, or mild ascites, which can be identified by an ultrasound examination; grade 2, or moderate ascites, which is marked by a mild symmetrical abdominal distension; and grade 3, or large ascites, which can be identified by a significant abdominal distension (according to International Ascites Club) (16) (Figure 11).

Grade of ascites	Definition
Grade 1 ascites	Mild ascites only detectable by ultrasound
Grade 2 ascites	Moderate ascites evident by moderate symmetrical distension of abdomen
Grade 3 ascites	Large or gross ascites with marked abdominal distension

Figure 11: Grades of Ascites

Hepatorenal and Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) and hepatorenal syndrome (HRS) are two significant complications of liver disease that harm the kidneys, lungs, heart, and liver in addition to the liver itself. In clinical practice, patients with HRS and HPS have poor prognoses and high death rates that impact their respiratory and circulatory systems. Other than liver transplantation, there is no other viable treatment available. Transjugular intrahepatic portosystemic shunt (TIPS) primarily helps in buying some time for patients of portal hypertension and ascites as it efficiently lowers portal pressure. TIPS has been shown to be an effective technique in extending the life expectancy of individuals with end-stage liver diseases.

Hepatorenal syndrome (HRS) mostly seen in cirrhosis patients, frequently during the decompensated stage of the disease, when circulatory malfunction results in renal failure. HRS affects not just the liver but also the heart and blood vessels, resulting in alterations to the body's renin-angiotensin system, a reduction in glomerular filtration rate (GFR), and other related issues. Furthermore, cirrhosis patients' abdominal lymph nodes harbour pathogenic microorganisms that enhance circulating inflammatory chemicals such tumour necrosis factor and nitric oxide (NO), which in turn promote renal vasoconstriction and visceral vasodilation. The notion that inflammation helps in the evolution of HRS in becoming more widely accepted as a result of these findings.

HRS was divided into two types by the International Club of Ascites: type 1 and type 2. Renal vasoconstriction and vasodilation in the CVS generated by sudden events are thought to be the primary causes of type 1 HRS. On the other hand, type 2 HRS advances more slowly than type 1. It is primarily distinguished by presence of refractory ascites. HRS is classified into three categories: chronic kidney disease

(CKD), acute kidney injury (AKI), and non-AKI. The most frequent and dangerous side effect of decompensated cirrhosis is known as HRS-AKI, and its most frequent cause is thought to be spontaneous bacterial infection (Figure 12) (12).

New classification	New criteria
HRS-AKI	1) Absolute increase in SCr ≥0.3 mg/dL within 48 h
	Or
	2) Percent increase in SCr ≥50% using the last available value of outpatient SCr within 3 months as the baseline value
	and/or
	3) Urinary output ≤0.5 mL/kgBW. ≥6 h
HRS-AKD	1) eGFR <60 mL/min per 1.73 m^2 for <3 months in the absence of other (structural) causes
	2) Percent increase in SCr <50% using from the last available value of outpatient SCr within 3 months as the baseline value
HRS-CKD	1) eGFR <60 mL/min per 1.73 m^2 for ≥3 months in the absence of other (structural) causes

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Figure 12: Classification of HRS-AKI

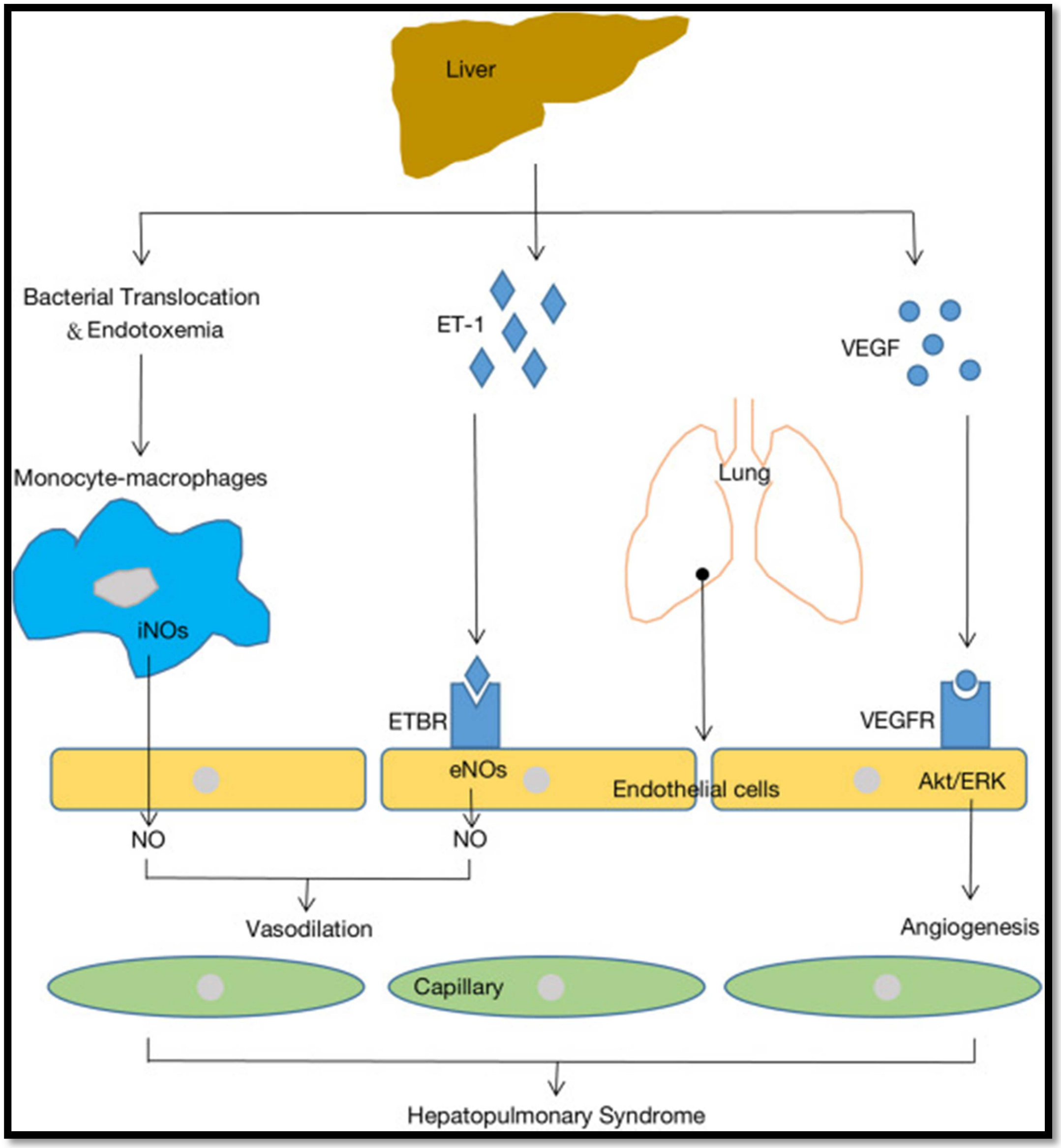

Figure 13: Mechanism of Hepatopulmonary Syndrome

Patients with cirrhosis commonly experience respiratory system complications in addition to kidney damage, and anomalies in the pulmonary vasculature are thought to be a sign that liver transplantation (LT) is necessary. Hepatopulmonary syndrome (HPS), one of the most prevalent anomalies, is characterised by hypoxia along with intrapulmonary vasodilation, with a prevalence ranging from 5% to 32%. The traditional definition of HPS is hypoxemia resulting from vasodilatation of the pulmonary vasculature in individuals with an increase in alveolar–arterial oxygen gradient of greater than 15 mmHg (greater than 20 mmHg in elder patients). Patients with advanced cirrhosis are more likely to get HPS; pulmonary vasodilation, namely the vasodilating impact of nitric oxide, is thought to be primarily caused by overproduction of vasodilators. Nitric oxide synthase in the endothelium is activated by endothelin B receptors in individuals with cirrhosis who also have high plasma levels of endothelin-1. Endotoxemia and bacterial translocation in the lung cause an increase of monocytes and macrophages in the lung, which in turn triggers inducible NOS.

Increased NO production is facilitated by the two forms of NOS secreting. Furthermore, lung endothelial cells that express vascular endothelial growth factor A stimulate angiogenesis through the extracellular-regulated kinase/protein kinase B signalling pathway. Patients have hypoxemia due to an irregular V/Q ratio and a ventilation (V)–perfusion (Q) mismatch between alveoli and arteries caused by aberrant changes in the pulmonary vasculature (Figure13).

There are two types of HPS: type 1 is linked to arteriolar dilatation, while type 2 is linked to arteriovenous shunts. To repair hypoxia, 100% oxygen should be given to the patient when their V/Q ratio falls. Type 1 refers to a patient whose partial pressure of oxygen (PaO2), following pure oxygen intake, is less than 600 mmHg; hypoxia due to AVS is identified if PaO2 does not increase to 150–200 mmHg or above. Additionally, HPS is classified into four categories to better measure the risk: mild, moderate, severe and extremely severe (Figure 14) (12).

Classification	Pathogenesis	Criteria
HPS-1	Precapillary dilatations	$PO_2 \geq 600$ mmHg after 100% oxygen treatment
HPS-2	Arteriovenous shunts (AVS)	$PO_2 < 150–200$ mmHg after 100% oxygen treatment

Figure 14: Classification of Hepatopulmonary syndrome

Child Pugh Scoring System

The Child-Pugh scoring system was created to forecast death among individuals diagnosed with liver cirrhosis. It was first developed in 1964 by Child and Turcotte to help in the process of choosing patients who would benefit from elective portal decompression surgery. Patients were classified into three groups according to this system: A stood for good hepatic function, B for moderately impaired hepatic function, and C for advanced hepatic dysfunction. Serum bilirubin, albumin, grade of ascites, neurological disease and nutritional status were used to classify (17). Pugh and colleagues subsequently adjusted the grading method by replacing clinical nutrition status with prothrombin time. They also added changeable points based on increasing severity for each criterion (Figure 15) (18).

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

Figure 15: Child Pugh Scoring System

The Child-Pugh score is a reliable indicator of the risk of death following portocaval shunt surgery and has also been shown to predict mortality following other major surgeries. Following abdominal surgery, the mortality rate for child class A patients is lower with ten percent, for child class B patients a moderate level with thirty percent, and for child class C severe with more than seventy or eighty percentage. Patients in child class A are typically regarded as safe candidates for elective surgery. Surgery for child class B patients is still more risky even after medical optimisation. Elective surgery is not recommended for patients in Child class C. The Child-Pugh score can also be used to predict the risk of developing other liver dysfunction-related problems, such as variceal haemorrhage, as well as the risk of dying from all causes (17).

MELD Sodium Score

Model for End-stage liver disease called as MELD score is a model which identifies the short-term mortality among patients with cirrhosis of liver. Serum bilirubin, creatinine, and international normalized ratio (INR) were used to derive the MELD score. This score predicts mortality within next three months. MELD Na score is a recently developed score that also benefits in enlisting of patients for liver transplantion based on priority. (10).

Prolactin

Prolactin is a polypeptide hormone. It has a significant role in physiology of development of breast, lactation in females. Changes in the prolactin levels significantly disrupts the milk production and menstrual cycle. Increase or decrease in prolactin levels causes pathophysiological changes. Low levels of prolactin lead to reduced milk supply, whereas higher levels lead to amenorrhoea, infertility and galactorrhoea in non-lactating women and men. In men, higher levels of prolactin cause headache, reduced libido and disruption of hypothalamus-pituitary reproductive axis. Deficiency of prolactin occurs when the destruction of anterior pituitary occurs. Increased secretion of prolactin can be caused due to prolactin-secreting tumours.

Normal range of serum prolactin in males and females ranges from 2 to 18 ng/ml and 2 to 30 ng/ml respectively. If the value of serum prolactin increases more than 200 ng/ ml, the condition is called prolactinomas (2).

Hyperprolactinemia in cirrhosis of liver occurs due to two reasons. Due to increased levels of oestrogen in the blood, that occurs secondary to reduced excretion of oestrogen by the liver, which causes anterior pituitary to directly affect the hypothalamus and interfere with dopamine secretion, so stimulating the release of prolactin. Next, due to the abundant production of pseudo neuro transmitters like octopamine, phenyl ethanolamine etc., These in turn reduce dopamine secretion which eventually leads to a hyperprolactinemia (5).

A study done to measure prolactin among patients of cirrhosis of liver and also aimed to establish the relationship between the disease severity and prolactin levels. In the study, 114 study participants were included. The mean age of the study participants was 57. Prevalence of alcohol-induced cirrhosis, cryptogenic cirrhosis, and viral cirrhosis were 77.2%, 14% and 7.8% respectively. The mean child Pugh score among the study participants was 8. Mean prolactin levels was 14.79 µg/l. Prolactin levels were significantly corelated with the grades of hepatic encephalopathy and ascites. Prolactin was significantly related with child Pugh Score (p=0.016). The study concluded increase in serum prolactin levels increases the grades and severity of ascites as well as hepatic encephalopathy. High prolactin levels was considered to have a negative corelation with prognosis of liver cirrhosis (19).

A common endocrine condition known for its detrimental impact on bone metabolism and the reproductive system is hyperprolactinemia. In addition to prolactinomas, hyperprolactinemia has been linked to a number of medications and conditions, including hypothyroidism and renal failure. Although the exact mechanisms are still unknown, it has also been proposed that liver cirrhosis causes hyperprolactinemia based on earlier research. A study was conducted to estimate the prevalence and predictors of hyperprolactinemia. This study included 178 individuals with cirrhosis of liver with different aetiology. According to the findings, hyperprolactinemia was primarily linked to drug consumption or the presence of comorbidities that are known to potentially induce hyperprolactinemia rather than being a prevalent finding in individuals with liver cirrhosis. Therefore, the study postulates that, contrary to earlier research, liver cirrhosis is not a common cause of hyperprolactinemia and that, in the absence of co-morbidities or medications known to potentially raise prolactin levels, patients with liver cirrhosis who exhibit marked hyperprolactinemia should have their condition further investigated (20).

A prospective cohort study conducted in Uttar Pradesh among patients with viral hepatitis or liver cirrhosis. They were compared with healthy individuals. A total of 70 patients with subgroups of 10 healthy individuals, 25 patients of acute viral hepatitis and 35 patients of liver cirrhosis were included in the study. Median age of the study participants was 56 (34-68) years. Male to female ratio was 2:1 in this study. Among the patients of cirrhosis of liver, status of encephalopathy was statistically significant ($p<0.05$). Amongst patients of viral hepatitis, there was a difference noted in the status of hepatic encephalopathy. However, they were not statistically significant. Serum prolactin levels were significantly associated with serum bilirubin and AST (aspartate aminotransferase) ($p=0.04$ and $p=0.72$ respectively). The cut-off value for prediction of mortality by serum prolactin was 50 ng/ml. The study concluded that serum prolactin has a significant corelation with the severity of liver disease and could be used to predict mortality (21).

A cross-sectional study among 60 individuals in Madhya Pradesh was done to predict the relation of serum prolactin with child Pugh score among liver cirrhosis patients and also to find the prognostic significance in liver cirrhosis. The mean age of participants was 44 ± 12.8 years. Prevalence of alcohol-related cirrhosis and Hepatitis B related cirrhosis were 55% and 18.3% respectively. Mean prolactin levels among the study participants was 18.1 ± 11.3 µg/l. Serum prolactin was found to be significantly associated with serum bilirubin ($p=0.003$) and prothrombin time ($p=0.003$). Serum prolactin was also significantly associated with Child Pugh Scoring system (p=0.003). The study concluded that child Pugh score can be used as an indicator for prediction of development of high-risk and mortality due to cirrhosis of liver (3).

Another study in Karnataka aimed to compare prolactin level to child Pugh system in cirrhosis of liver and to establish serum prolactin as a marker for development of cirrhosis related complications. This study included 60 patients above age of 18 years. Alcohol was the cause of development of cirrhosis of liver among 73% of the individuals. Portal hypertension, oesophageal varices, oesophageal varices with upper gastrointestinal bleeding, and hepatic encephalopathy were present in 83.3%, 65%, 36.7% and 25% of the study participants. Elevated serum prolactin was found in 73% of study participants. The study concluded that individuals with higher levels of serum prolactin had greater incidence of complications of liver cirrhosis. Thus it can be used as a marker to estimate the severity and complications of liver cirrhosis as prolactin is considered as affordable and a non-invasive blood marker (22).

A cross-sectional study conducted in Karnataka, India among individuals with cirrhosis of liver and above the age of 18 years. In this study, the Child Pugh score was compared with the serum prolactin levels. A total of 69 study participants were included in this study. The mean age of the study participants was 50.93 years. Majority of the study participants were male (85.51%). Serum prolactin levels and Child Pugh class were statistically significant. The study concluded that prolactin might be considered as a cost-effective biomarker for liver cirrhosis. (23).

A study was conducted to examine the clinical characteristics and measure the serum prolactin level in liver cirrhosis, paying particular attention to the Child Pugh Score. a cross-sectional observational study conducted on seventy patients admitted to the JMCH Department of Medicine between July 2020 and June 2021. Every patient undergoes a routine work-up for chronic liver disease, which includes a measurement of serum prolactin. 70 patients in all were examined in this study. 47 years old is found to be the mean age. Out of the 70 patients, 59 (84.3%) had prolactin levels that were higher than 19 ng/ml and had different clinical characteristics. The study revealed a range of clinical manifestations, including portal hypertension in 63 patients (90%), ascites in 69 patients (98.5%), oesophageal varices in 44 patients (62.85%), upper gastrointestinal bleeding in 31 patients (44.3%), and hepatic encephalopathy in 50 patients (71.42%). Of the 70 patients, 55 patients (78.5%) had child Pugh score C, and their mean prolactin value was 43.638 ng/ml. In contrast, all patients of Class A Child Pugh had normal blood prolactin levels, with a p value of less than 0.001. The child Pugh score and blood prolactin level had a significant positive association (stronger than 0.830), as indicated by the Spearmen coefficient value. When predicting the severity of the disease, the serum prolactin level and the Child Pugh score linked. Individuals with elevated serum prolactin levels are more likely to experience portal hypertension, hepatic encephalopathy, and esophageal varices, among other cirrhosis consequences (24).

A similar study was conducted to corelate severity of liver cirrhosis with serum prolactin levels in Mysore tertiary care institution during an 18-month period. Purposive sampling was used to enroll 75 participants with Cirrhosis of liver in the trial. The Child Pugh score was determined using the complete hemogram, renal function test, liver function test, and USG performed upon admission as part of the standard work-up of cases. Using the chemiluminescence method, serum prolactin was estimated and corelated with the Child Pugh class. Patients in class C had higher serum prolactin levels (mean prolactin 22.9 ng/ml). Patients of class C ($p<0.001$) and those with elevated MELD scores ($p<0.0001$) had significantly higher levels of prolactin. A noteworthy positive connection was seen between elevated prolactin levels and grades of hepatic encephalopathy ($P < 0.001$). A higher mortality rate was linked to higher admission prolactin levels ($P < 0.0001$). Increased prolactin was found to be positively correlated with the severity of liver disease in this study. Among the study subjects, elevated prolactin levels were also substantially linked to consequences such hepatic encephalopathy and mortality (25).

METHODOLOGY

Source of Data

Patients with cirrhosis of liver admitted to the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi Between 1st January 2023 to 31st December 2023 over a period of one year.

Study Design

A hospital-based cross-sectional study.

Study Period

January 2023 to December 2023 (One Year)

Sample Size

In a study published by Sarin et al. on "Liver cirrhosis" in World Gastroenterology Organization: Global Guardian of Digestive Health. Serving the world, had reported that the global prevalence of cirrhosis from autopsy studies ranges from 4.5% to 9.5% of the general population.

So, considering an incidence rate of 4.5% (prevalence of cirrhosis), and population size of 20000 (equal to general population), we used the following incidence formula for calculating the sample size.

The sample size n and margin of error E are given by:

x = Z(c/100)2r(100-r)

n = N x/((N-1) E2 + x)

E = Sqrt [(N - n) x/n(N-1)]

Where N is the population size (N=20000), r is the fraction of responses that you are interested in (r=4.5%), and Z(c/100) is the critical value for the confidence level c (Z=1.96).

Putting the above values in the above formula, the sample size obtained was 66 patients of cirrhosis of liver, at a confidence interval of 95% and 80% power of the study. Considering an attrition rate of 10%, we intend to include 72 patients with cirrhosis of liver in our study.

Sampling technique

Convenient Sampling Technique

Inclusion Criteria and Exclusion criteria

Inclusion and exclusion criteria were elaborated in Figure 16.

Inclusion criteria	Exclusion criteria
All patients with Cirrhosis of Liver who give consent were enrolled in the study.	History of chest wall trauma Cranial surgery/ irradiation Pituitary or hypothalamic disease Chronic renal failure Herpes zoster Seizure disorder Patient on medications known to alter prolactin level.

Figure 16: Inclusion and exclusion criteria of the study

Study protocol

A one-year Hospital based cross sectional study from January 2023 to December 2023 at a Tertiary care hospital in Karnataka.

Data collection procedure

An informed consent was obtained from all patients enrolled for the study. In all the patients, relevant information was collected in a predesigned proforma. All patients underwent clinical examinations, biochemical tests like CBC, LFT, RFT, serum electrolytes, APTT, PT INR, Serum Prolactin levels and ultrasound abdomen. Patients were classified as per Child Pugh scoring system and prolactin levels were correlated with the child Pugh score in assessing the severity of liver disease (Refer Figure 15).

Data processing and analysis

The data was initially captured into the customized proforma which was developed as the specific requirement of the study. Then this data was transferred to Microsoft Excel for analysis. Statistical Software IBM SPSS Version 20.0. was used for calculating the P value. Descriptive statistics was presented in the form of numbers and percentages. Proportional comparisons were done using Z test for two sample proportions, association between two non-parametric variables was tested using Pearson Chi-square test and comparison of means of more than two groups were done using One-Way ANOVA test. A p value of less than 0.05 was taken as statistically significant.

RESULTS AND OBSERVATIONS

Age

A total of 72 study participants were included in the study based on the inclusion and exclusion criteria. The mean age of study participants was 52.95 ± 12.91 years. Minimum and maximum age of the study participants were 30 and 80 years respectively (Table 1). Majority of the study participants were distributed among the age group of 46 to 60 years (n=33, 45.8%), followed by 30 to 45 years age group (n=21, 29.2%) and above 60 years group (n=18, 25%) (Table 2 and Figure 17).

Table 1: Mean age of study participants

Age (In years)	Number
N	72
Mean	52.95
SD	12.91
Min	30
Max	80

Table 2: Distribution of Age among the study participants

Age (In years)	Number (%)
30-45	21 (29.2%)
46-60	33 (45.8%)
Above 60	18 (25%)

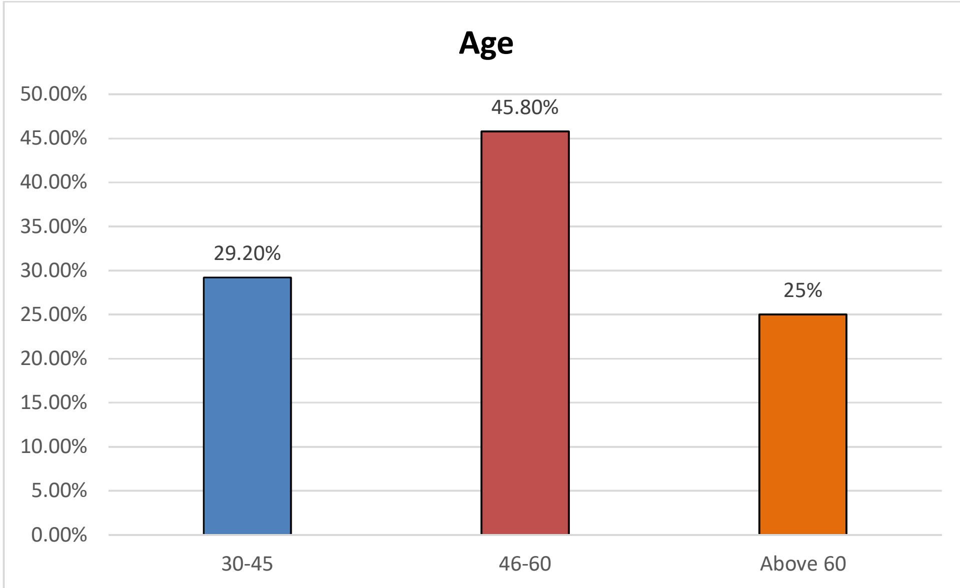

Figure 17: Age distribution among study participants

Gender

Majority of the study participants were male (n=62, 86.1%) (Female: n=10, 13.9%) (Table 3 and Figure 18).

Table 3: Gender of the study participants

Gender	Number	Percentage
Male	62	86.1%
Female	10	13.9%

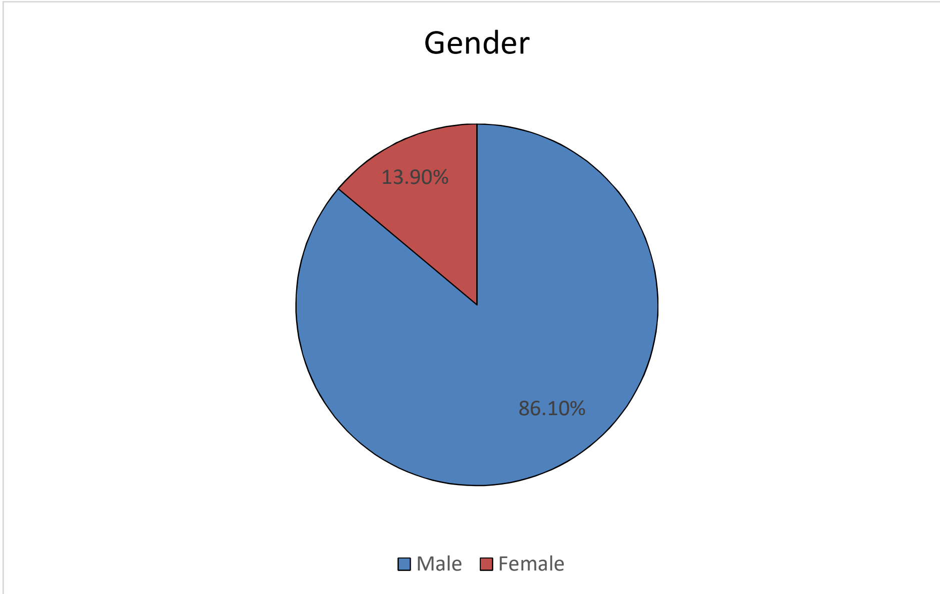

Figure 18: Gender distribution among study participants

Alcohol dependance

Alcohol dependance was present in 42 study participants (58.3%) (Table 4 and Figure 19).

Table 4: Alcohol dependance among study participants

Alcohol Dependance	Number	Percentage
Yes	42	58.3%
No	30	41.7%

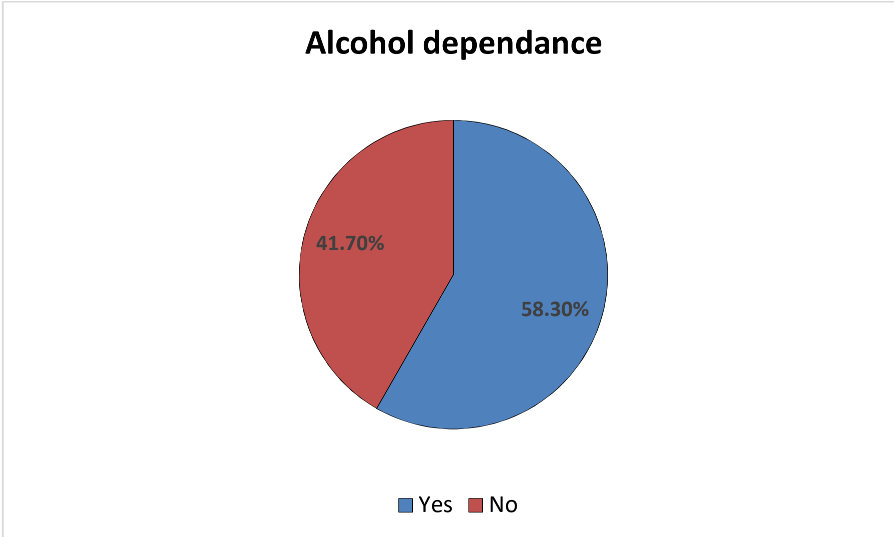

Figure 19: Alcohol dependance of the study participants

Serum Prolactin levels

Mean serum prolactin among the study participants was 38.65 with a standard deviation of 30.05. The minimum and maximum serum prolactin were 5.41 and 148 respectively (Table 5).

Table 5: Mean value of serum prolactin

Serum Prolactin	Number
N	72
Mean	38.65
SD	30.05
Min	5.41
Max	148

Severity of Ascites

Severity of ascites were recorded as mild, moderate, severe. Majority of the study participants who had ascites were in moderate ascites group (n=26, 36.1%), followed by mild (n=20, 27.8%) and severe group (n= 20, 27.8%). Among the study participants, 8.3% (n=6) did not have ascites (Table 6 and Figure 20).

Table 6: Severity of Ascites

Severity	Number (%)
Mild	20 (27.8%)
Moderate	26 (36.1%)
Severe	20 (27.8%)
None	6 (8.3%)

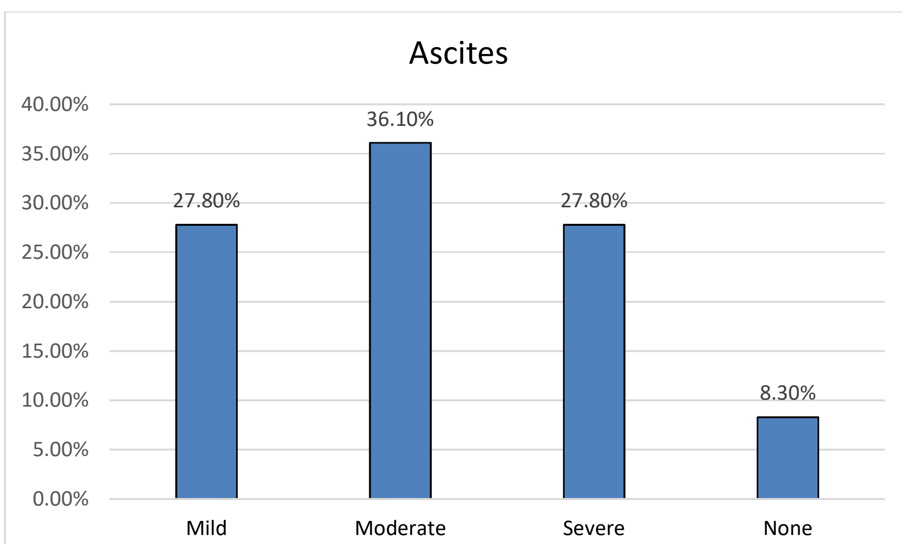

Figure 20: Severity of ascites in study population

Hepatic Encephalopathy

Hepatic encephalopathy was graded as Grade 1 to 4. Majority of the study participants had hepatic encephalopathy of Grade 2 (n=16, 22.2%), followed by Grade 1 (n=13, 18.1%), Grade 3 (n=7, 9.7%) and Grade 4 (n=1, 1.4%). Among the study participants, 48.6% (n=35) didn't have hepatic encephalopathy (Table 6 and Figure 21).

Table 6: Hepatic Encephalopathy grading among study population

Grade	Number (%)	Percentage
Grade 1	13	18.1%
Grade 2	16	22.2%
Grade 3	7	9.7%
Grade 4	1	1.4%
None	35	48.6%

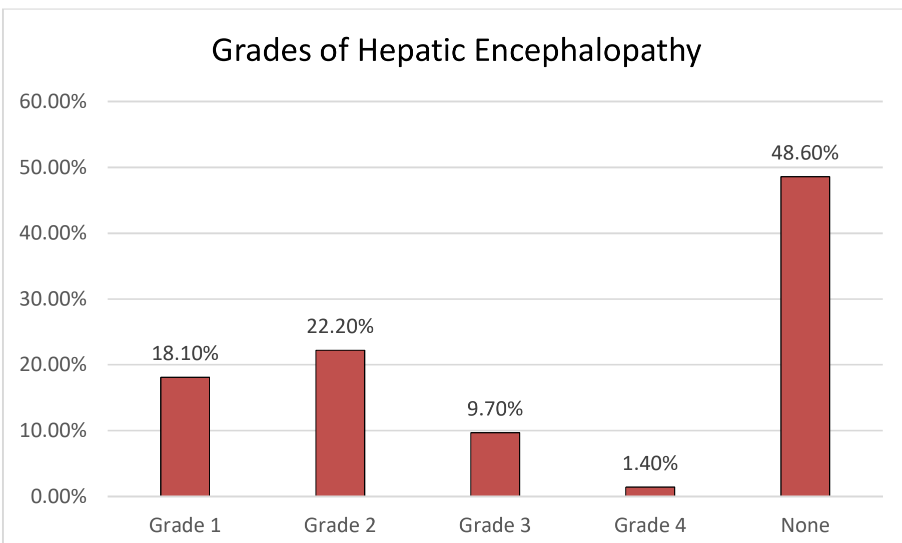

Figure 21: Hepatic Encephalopathy grading among study population

Prolactin Vs Ascites

Comparison of prolactin levels and severity of ascites was statistically significant (p=0.027). Median value of prolactin among mild, moderate, severe and no ascites groups were 27.1 (14.91), 32.07 (35), 31 (41.04) and 11.2 (5.32) respectively (Table 7 and Figure 22).

Table 7: Comparison of prolactin with ascites in the study population

Parameter	ASCITES				Kruskal Wallis Test (P-value)
	Mild (n=20)	Moderate (n=26)	Severe (n=20)	Absent (n=6)	
Prolactin	27.1 (14.91)	32.07 (35)	31 (41.04)	11.2 (5.32)	0.027

(Median and IQR)

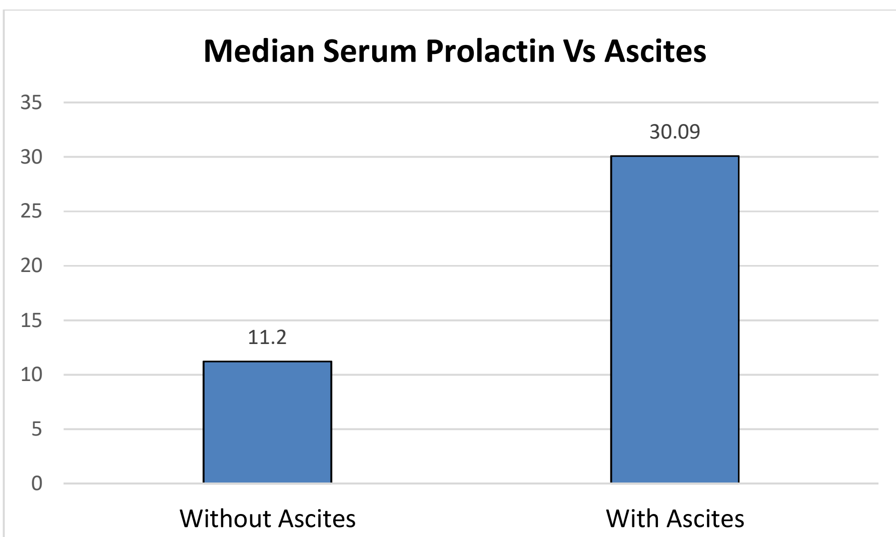

Figure 22: Median serum prolactin levels among study participants with and without ascites

Prolactin Vs Hepatic Encephalopathy

Prolactin values corelated with the grades of hepatic encephalopathy were statistically significant (0.001). Median Prolactin levels of Grade 1, Grade 2, Grade 3, Grade 4 and no hepatic encephalopathy groups were 29 (9.57), 42.5 (44.96), 66.7 (7.91), 28 (0), and 21 (18.03) respectively (Table 8 and Figure 23).

Table 8: Comparison of prolactin with hepatic encephalopathy in the study population

Parameter	**HEPATIC ENCEPHALOPATHY**					**Kruskal Wallis Test (P-value)**
	Grade 1 (n=13)	Grade 2 (n=16)	Grade 3 (n=7)	Grade 4 (n=1)	None (n=35)	
Prolactin	29 (9.57)	42.5 (44.96)	66.7 (7.91)	28 (0)	21 (18.03)	0.001

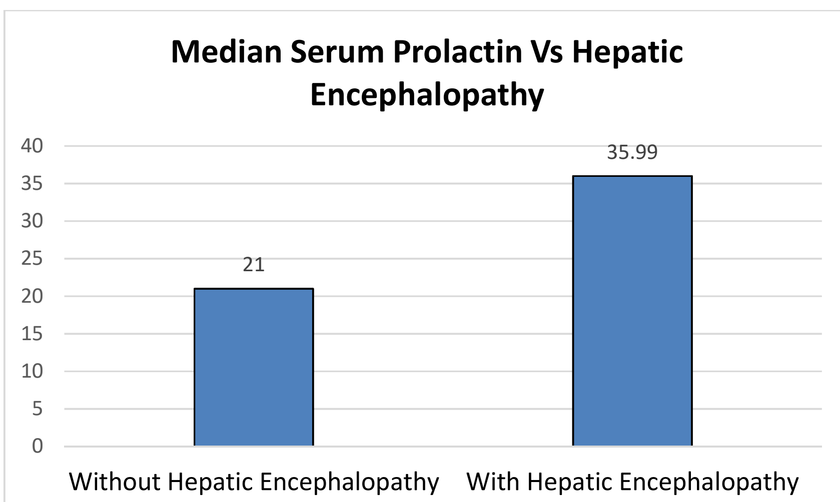

Figure 23: Median serum prolactin levels among study participants with and without hepatic encephalopathy

Serum prolactin and Child Pugh class

Child Pugh Class was classified as three classes: A, B and C. There were 5, 30 and 37 study participants in Class A, Class B and Class C respectively. The median (IQR) of serum prolactin levels of Class A was 12 (11.93, 15.72). The median (IQR) of serum prolactin levels of Class B was 28.6 (17, 32.6). The median (IQR) of serum prolactin levels of Class C was 35 (24, 64). Prolactin values were found to be higher in Child Pugh Class C followed by Class B and Class A, But the Child Pugh class and serum prolactin levels were not statistically significant (p=0.733) (Table 10).

Table 10: Comparison of serum prolactin with Child Pugh Class in the study population

	Child Pugh Class		
	A (n=5)	**B (n=30)**	**C (n=37)**
Prolactin	12 (11.93, 15.72)	28.6 (17, 32.6)	35 (24,64)
P value	0.733		

However, Prolactin levels were found to be statistically significant after classifying the participants into two groups - Class C (Severe) and Class A and B (Mild and Moderate) with Chi-square value of 8.496 and p value of 0.003. In severe Child Pugh class (Class C) group, 17 participants (45.9%) had serum prolactin values>39.5 and 20 study participants (54.1%) had serum prolactin levels<39.5. In mild and moderate Child Pugh class (Class A&B) group, 14.3% (n=5) had serum prolactin levels>39.5 and remaining 85.7% (n=30) had serum prolactin levels <39.5 (Table 9).

Table 9: Comparison of serum prolactin with child Pugh score in the study population

Serum Prolactin	Child Pugh Score		Chi-square	P-value
	Class C Severe (n=37)	Class A&B Mild to Moderate (n=35)		
>39.5	17 (45.9%)	5 (14.3%)	8.496	0.003
≤39.5	20 (54.1%)	30 (85.7%)		

The serum prolactin had a sensitivity of 45.95% in predicting the Child Pugh score (Figure 24 and Table 11). The specificity, positive predictive and negative predictive values were 85.71%, 77.27%, and 60% respectively. The total diagnostic accuracy of the tool was 65.28%. The area under the curve was 0.658.

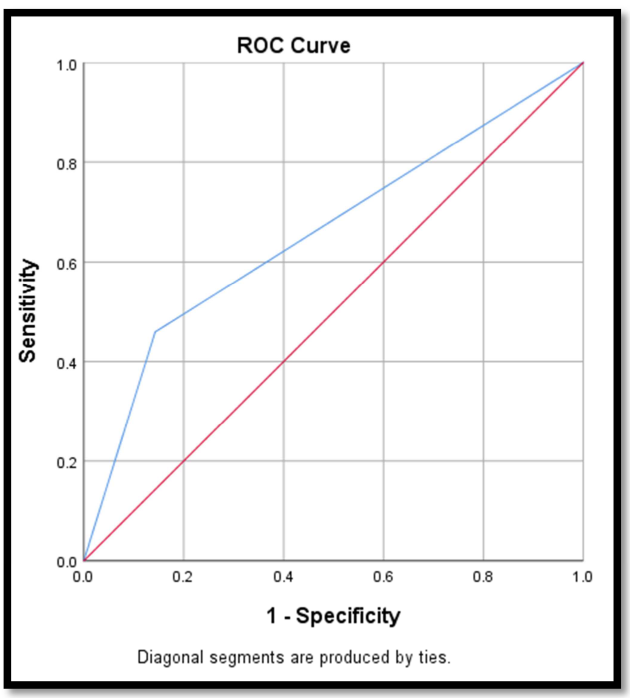

Figure 24: Receiver Operating Curve for Serum Prolactin in predicting Severity

Table 11: Sensitivity, Specificity, Positive and Negative predictive values of Serum prolactin levels in predicting severity

Sensitivity	45.95%
Specificity	85.71%
Positive predictive value	77.27%
Negative predictive value	60%
Accuracy	65.28%

DISCUSSION

There are various theories that explain the rise of prolactin in patients of liver cirrhosis. One such theory is that liver cirrhosis leads to dysfunction of the HPG axis (hypothalamo-pituitary gonadal axis). Among neurotransmitters altered, dopamine was the first to be reported. Literature demonstrated prolactin's role as a prognostic marker, likely due to dopamine's negative regulation of prolactin (26 and 27).

The decrease in dopamine levels is the primary cause for the elevation of prolactin levels. Few researchers have examined the hormonal disturbance associated with cirrhosis; their findings include elevated prolactin levels in the serum and decreased levels of cortisol and T3 in the serum. It has been discovered that liver dysfunction causes a rise in the levels of aromatic amino acid in the CNS that inturn leads to increased levels of erroneous neurotransmitters such as phenylethanolamine and octopamine (28). These neurotransmitters have an inhibitory effect on dopamine causing rise in Prolactin levels in the body.

Liver dysfunction also causes increased estrogen. This is because of increased aromatization of testosterone through androstenedione in the peripheries and a smaller contribution is due to decreased elimination by the liver. These estrogens stimulate release of prolactin by disrupting dopamine release from hypothalamus and impacting anterior pituitary directly (22).

Human prolactin release is linked to a pulsatile pattern; nevertheless, individuals with cirrhosis of liver have been observed to exhibit a continuous 24-hour rise in prolactin secretion. There have also been cases of hypogonadism documented in cirrhosis patients with hyperprolactinemia (29 and 30).

In our study, with 72 study participants, majority of them belonged to the age group of 46 to 60 years. The mean age of study participants was 52.95 ± 12.91 years. Majority of the participants were male (86.1%). The mean age of study participants in Payer J et al was 57 years (19). The median age of the participants in Jha S et al was 56 (34-68) years (21). The mean age of the study participants was 47 ± 13 years in Animesh D et al (24).

The mean serum prolactin in our study was 38.65 ± 30.05. Mean prolactin levels among the study participants was 14.79 µg/l in Payer J et al (19). The median serum prolactin levels among healthy individuals, participants with viral hepatitis and study participants with cirrhosis were 11.2 (6.2, 18.6), 71.2 (30.6, 119.7) and 73.6 (37.6, 210.7) respectively in a study done by Jha S et al (21). Mean prolactin levels among males and females were 36.9 ± 15.3 and 42.8 ± 14.2 ng/ dl respectively in a study conducted by Animesh D et al (24).

In our study, Median Prolactin levels of Grade 1, Grade 2, Grade 3, Grade 4 and no hepatic encephalopathy groups were 29 (9.57), 42.5 (44.96), 66.7 (7.91), 28 (0), and 21 (18.03) respectively. Prolactin values corelated with the grades of hepatic encephalopathy were statistically significant (0.001). Median serum prolactin levels among study participants with and without hepatic encephalopathy were 35.99ng/ml and 21ng/ml respectively. Our results were comparable to the study done by Mukherjee et al (31) where the mean prolactin values in patients with and without encephalopathy were 56ng/ml and 8ng/ml. In Payer J et al, mean serum prolactin levels of study participants with and without hepatic encephalopathy were 19.41 and 13.93 with p value of 0.017 (19). Jha S et al study also showed a statistical significance between serum prolactin levels when compared with patients with and without hepatic encephalopathy with a p value of less than 0.05 (21).

In our study, median value of prolactin among mild, moderate, severe and no ascites groups were 27.1 (14.91), 32.07 (35), 31 (41.04) and 11.2 (5.32) respectively. Correlation of serum Prolactin levels with severity of ascites was statistically significant (p=0.027). Median serum prolactin levels among study participants with and without ascites were 30.09 and 11.2. Mean serum prolactin levels of study participants with and without ascites were 19.99 and 11.97 in Payer J et al (19). Comparison of prolactin levels with ascites severity was statistically significant (p=0.027). In Balakrishnan CH et al, 88.3% of the study participants had ascites and 54.7% among them had an elevated serum prolactin level (22). Vemanamanda et al reported 26.09% of mild ascites, 18.84% of moderate ascites and 10.14% of severe ascites. Median prolactin levels in mild, moderate, severe ascites and with no ascites were 43.50 (40 to 48.75), 52 (40 to 58), 58 (44 to 68.5) and 27 (25 to 30) respectively (23).

In our study, Prolactin value significantly correlated with the Child Pugh Class, though it included a small number of patients in each category. The median prolactin value in Child Pugh Class A, B, and C was determined to be 12 (11.93, 15.72); 28.6 (17, 32.6); and 35 (24, 64) ng/ml, respectively in the current study. When the patients were grouped into two classes i.e, Child Pugh class c (severe) vs Child pugh Class A&B (Mild and Moderate), serum Prolactin was found to be statistically significant with Chi-square value of 8.496 and p value of 0.003. Prolactin levels were associated with the progression of liver disease that was detected by child Pugh class (Class A, Class B and Class C) with a p value of less than 0.01 in Ress C et al (20). Serum prolactin and child pugh scores were significant in Payer J et al with a p value of 0.016 (19). Child Pugh score had a positive correlation with serum prolactin levels in Animesh et al study (24). Similar results were also recorded in Rao BMA et al (25).

In our study. Serum prolactin had a sensitivity of 45.95% in predicting the Child Pugh score. The specificity, positive predictive and negative predictive values were 85.71%, 77.27%, and 60% respectively.

Therefore, prolactin level aids in determining the disease's severity and its complications.

LIMITATIONS

There are few limitations in this study.

- Small sample size
- Data collection method used (convenient sampling).
- Study design (Cross sectional study). To get better outcomes, a prospective follow-up multi-centre study could be done which will produce results that can be generalized.

CONCLUSION

Serum Prolactin has a strong positive correlation with the severity of liver disease. It also shows a positive correlation with severity of complications of cirrhosis like ascites and hepatic encephalopathy. Hence it can be used as an alternate prognostic marker and can help determine the severity of cirrhosis related complications.

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ANNEXURE I- CONSENT FORM

"CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN PATIENTS OF CIRRHOSIS OF LIVER IN A TERTIARY CARE HOSPITAL- A CROSS SECTIONAL STUDY"

Objective: To compare the level of serum prolactin to that of child pugh scoring system in patients of Chronic liver disease and thus assess its utility as an alternate prognostic marker.

Introduction: The Child Pugh Scoring system is a reliable predictor of survival and used to assess the prognosis in cirrhosis of liver. Comparing the serum prolactin level to the child pugh scoring system in patients of Cirrhosis of liver will help us assess its utility as an alternate prognostic marker and thus help in predicting the risk of complications.

Explanation of procedure: If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood samples for the necessary investigations.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. Withdrawal from the study will not change the standard of care you receive. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not have any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study except for a little discomfort while collection of blood samples.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: **REG NO. BG0121019** If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study **"CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORING SYSTEM IN PATIENTS OF CIRRHOSIS OF LIVER IN A TERTIARY CARE HOSPITAL- A CROSS SECTIONAL STUDY"**

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II- PROFORMA

CASE NO	
NAME	
IP NO	
AGE	**YEARS**
SEX	**MALE** **FEMALE**
ADDRESS	
OCCUPATION	

Complaints at presentation	
Past history	
Family history	
Personal history	

Vitals :

Temperature	
Pulse	
Respiratory rate	
Blood pressure	

PHYSICAL EXAMINATION:

	Yes	No
Pallor		
Icterus		
Lymphadenopathy		
Cyanosis		
Clubbing		
Edema		

SYSTEMIC EXAMINATION:

C.V.S	
R.S.	
C.N.S	
PER ABDOMEN	

INVESTIGATIONS:

a) Complete blood count

b) Renal function test

c) Liver function test

d) Serum electrolyte

e) Prothrombin time, aPTT and INR

f) Serum prolactin

g) Ultrasound abdomen

Child pugh criteria	***Values***
Total Bilirubin	
Serum Albumin	
PT-INR	
Ascitis	
Hepatic Encephalopathy	

Serum Prolactin	***Values***

ANNEXURE III- MASTERCHART

		Child-Pugh Score							
Sl	**Patients**	**Total Bilirubin**	**Serum Albumin**	**PT INR**	**Ascites**	**Hepatic Encephalopathy**	**Points Scored (Total)**	**Class**	**Serum Prolactin Levels**
1	Laxman Shambhaji Halgekar	3	2.8	1.73	Moderate	Grade 2	10	C	55.14
2	Gajanan Appaji Pradnan	0.71	3.8	1.36	Severe	Grade 2	8	B	20.07
3	Paramanand Mauappa Khundekar	12.87	2.9	0.94	None	Grade 0	8	B	9.76
4	Sanjay Shivappa Hunashikatti	1.98	2.1	1.77	Severe	Grade 0	9	B	111.3
5	Ramesh Irappa Hosamani	3.92	3	0.99	Severe	Grade 0	10	C	22.18
6	Jagadish Malikarjun Pujar	2	2.2	1.22	None	Grade 2	8	B	7.52
7	Kempanna Balappa Jinagi	15.72	2.4	1.91	Moderate	Grade 1	11	C	87.16
8	Suresh Nalsidappa Kaaragi	6.68	2.6	1.52	Severe	Grade 0	10	C	92.46
9	Abhijeet Laxmanrao Mitagar	3.75	3	1.64	None	Grade 3	10	C	43.19
10	Kasturi Sintre Suresh	2.16	2.7	1.61	Moderate	Grade 0	8	B	35.87

11	Narayan Maruti Badiger	2.74	3.9	0.92	Mild	Grade 0	7	B	31.48
12	Manjunath Gangappa Ulavi	7.37	2.3	2.22	Mild	Grade 0	10	C	20
13	Iswarappa Rudrappa Pattar	1.89	2.3	1.44	Moderate	Grade 0	7	B	116.6
14	Tukaram Hanmant Patil	8.55	1.9	3.56	Severe	Grade 0	12	C	15.27
15	Basappa Singappa Yauappanavar	5.62	1.51	2.22	Moderate	Grade 0	10	C	10.94
16	Gajanan Irappa Jadhav	0.72	3.1	1.08	Severe	Grade 1	9	B	13.64
17	Gaurabai	7.91	1.9	1.28	Severe	Grade 0	10	C	20
18	Suresh Jaya Moolya	1.75	4.2	0.92	Moderate	Grade 0	6	A	15.72
19	Prakash Gokuldas Kama	4.93	2.3	2.21	Severe	Grade 3	13	C	64
20	Parvtevva Rudrappa Kumbar	2.54	3.7	1.55	Severe	Grade 1	9	B	28.02
21	Shobha Ramesh Pawar	2.42	2.9	1.8	Mild	Grade 0	9	B	16
22	Samyagoud Paruthgouda Patil	7.18	2.6	1.96	Moderate	Grade 0	10	C	21
23	Auabax Mehboobsab Nadaf	8.08	2.1	2.24	Moderate	Grade 2	11	C	29.1
24	Sanjay Dattaray Patil	4.37	3.2	1.11	Mild	Grade 0	9	B	5.41

25	Anant Fakira Kamble	18.42	2.6	1.96	Moderate	Grade 3	12	C	59.59
26	Kauappa Baluti	17.28	1.6	2.32	Moderate	Grade 2	12	C	30
27	Suresh Halsidappa Karagi	4.82	2.5	1.65	None	Grade 0	8	B	15.72
28	Parvtevva Rudrappa Kumar	6.72	3.7	2.31	Moderate	Grade 4	12	C	28
29	Chandu	10.5	2.8	2.34	Severe	Grade 2	13	C	35
30	Asangappa Bailappa	3.02	1.5	3.12	Moderate	Grade 1	12	C	49.47
31	Raghavendra Kulkarni	8.9	1.5	2.38	Mild	Grade 0	11	C	30.18
32	Ramachandra Vasanth Rajput	4.64	2.8	2.75	Severe	Grade 3	14	C	66.7
33	Ashok	1.06	3	1.28	None	Grade 0	6	A	12
34	Rajabee Vajeersab Talaklal	2.16	3.8	1.38	Mild	Grade 1	8	B	29.59
35	Govind Dattu Subedar	3.72	2.4	1.38	Mild	Grade 0	9	B	32.7
36	Sulochana	1.68	2.6	1.9	Severe	Grade 2	10	C	27
37	Iranna Shivanappa Kuttur	1.42	2.7	0.99	Moderate	Grade 1	8	B	29
38	Rajabee	2.99	2.8	1.82	Mild	Grade 0	9	B	12

39	Irappa Appayya Kalluhol	1.53	2.7	1.78	Severe	Grade 3	11	C	67
40	Shivanandayya Virayya Ganachari	2.01	2.2	1.8	Mild	Grade 2	10	C	148
41	Parashuram	14.7	3.4	2.16	Severe	Grade 2	12	C	46.2
42	Revanappa Basappa Tobakar	2.32	2.7	1.33	Mild	Grade 0	8	B	12
43	Maruti Fakkirappa Satyanayak	8.42	2.2	1.53	Moderate	Grade 0	9	B	22
44	Amargunda Uppanna	1.63	2.9	1.69	Moderate Grade 1	Grade 1	8	B	20
45	Rameshappa Chandrappa	0.97	2.3	1.9	Mild	Grade 2	9	B	111
46	Anand Basavanappa Doddabasannavar	1.89	4.9	1.32	Moderate	Grade 0	6	A	11.93
47	Jagannath Jyotiba Patil	0.69	3.9	1.07	Mild	Grade 0	6	A	19.18
48	Hanamnth Chanamallappa Kurbet	8.25	3.1	1.8	Moderate	Grade 3	12	C	84
49	Kallappa Jayapal Doddatamma	8.8	2.8	1.46	Mild	Grade 0	9	B	34.8
50	Krishna	2.18	2.8	2.21	Severe	Grade 1	11	C	35.99

51	Sidalingappa Guruwanavar	0.47	3.1	0.9	None	Grade 0	6	A	10.4
52	Basavaraj Godi	0.79	3.2	1.14	Moderate	Grade 0	7	B	31.9
53	Amargunda Maligoudar	15.2	3	2.04	Mild	Grade 0	10	C	24
54	Bhimappa Kankanwadi	1.47	2.6	1.34	Severe	Grade 1	9	B	29.5
55	Arun Sawant	4.88	2.2	1.97	Moderate	Grade 0	10	C	8.04
56	Parappa Ganiger	1.91	2.3	1.79	Moderate	Grade 2	9	B	41
57	Chandravva Limbi	0.89	4.3	1.29	Mild	Grade 1	7	B	26
58	Vinayak	1.23	2.6	1.96	Moderate	Grade 2	9	B	31.22
59	Mohan Lankkenavar	3	2.6	3.46	Moderate	Grade 1	11	C	32.24
60	Seema	3.01	2.3	1.79	Severe	Grade 0	11	C	26.43
61	Laxman Salari	4.33	2.8	2.02	Moderate	Grade 2	11	C	60.53
62	Ramchandra Rajput	4.82	3.1	3.2	Severe	Grade 3	14	C	74.45
63	Govind Vishwakarma	3.05	1.8	2.9	Severe	Grade 0	12	C	32.5
64	Vishwanath Chougule	4.53	4	1.5	Mild	Grade 0	8	B	32.3

65	Amol Shinde	21.9	2.4	2.06	Moderate	Grade 2	11	C	97.2
66	Appanna Ashok Kalal	3.85	3	1.32	Mild	Grade 2	10	C	88.5
67	Ballappa	8.02	3.6	3.03	Moderate	Grade 2	11	C	44
68	Mahalingappa	1.17	2.4	1.8	Severe	Grade 1	10	C	12.4
69	Basavaraj Mallappa Baragali	0.31	0.8	1.33	Mild	Grade 1	8	B	20.9
70	Anand	2.44	2.8	1.56	Moderate	Grade 0	8	B	57
71	Ajay Virabhadrappa Shirol	36.37	3.4	2.03	Mild	Grade 0	10	C	13.8
72	Pramod Babu Hannamant	18.5	3.3	1.62	Mild	Grade 0	9	B	28.2