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IN

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"COMPARISON OF ZINC LEVELS IN LIVER CIRRHOSIS AND EVALUATING THE SEVERITY USING CHILD PUGH SCORE"

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Dr. VIDYADHARI KAKUMANU

ABBREVIATIONS

ALD	:	Alcoholic Liver Disease
ALT	:	Alanine Aminotransferase
AST	:	Aspartate Aminotransferase
BLDE	:	Bijapur Liberal District Education
BMI	:	Body Mass Index
CBC	:	Complete Blood Count
CP	:	Child-Pugh
CPS	:	Child-Pugh Score
CTP	:	Child-Turcotte-Pugh
DNA	:	Deoxyribonucleic Acid
ELISA	:	Enzyme-Linked Immunosorbent Assay
GABA	:	Gamma-Aminobutyric Acid
HBV	:	Hepatitis B Virus
HCC	:	Hepatocellular Carcinoma
HCV	:	Hepatitis C Virus
HE	:	Hepatic Encephalopathy
HVPG	:	Hepatic Venous Pressure Gradient
IL	:	Interleukin
INR	:	International Normalized Ratio
IPD	:	In-Patient Department
MELD	:	Model for End-Stage Liver Disease
MT	:	Metallothionein
NASH	:	Non-Alcoholic Steatohepatitis
OPD	:	Out-Patient Department

PT	:	Prothrombin Time
ROS	:	Reactive Oxygen Species
SBP	:	Spontaneous Bacterial Peritonitis
SD	:	Standard Deviation
SOD	:	Superoxide Dismutase
TIBC	:	Total Iron Binding Capacity
TNF	:	Tumor Necrosis Factor
Zn	:	Zinc

ABSTRACT

COMPARISON OF ZINC LEVELS IN LIVER CIRRHOSIS AND EVALUATING THE SEVERITY USING CHILD PUGH SCORE

Background and Objectives:

“Liver cirrhosis represents the final common pathway for chronic liver diseases, characterized by extensive fibrosis and hepatocyte dysfunction. Zinc, an essential micronutrient with critical roles in protein synthesis, enzymatic reactions, and antioxidant defense, has been implicated in liver pathophysiology. However, the relationship between zinc deficiency and cirrhosis severity remains incompletely characterized in the Indian population. This study aimed to evaluate serum zinc levels in patients with liver cirrhosis and correlate them with disease severity as measured by the Child-Pugh classification.”

Methods:

“This hospital-based cross-sectional study was conducted among 85 patients with cirrhosis of liver attending the outpatient and inpatient departments of BLDE University's Shri BM Patil Medical College Hospital. Detailed clinical evaluation, biochemical investigations including serum zinc levels, and Child-Pugh scoring were performed. Zinc deficiency was defined as serum levels below 51 µg/dL. Statistical analysis included descriptive statistics, chi-square tests, and ANOVA to assess relationships between variables.”

Results:

The study cohort comprised predominantly middle-aged males (95.3%), with alcoholic etiology (89.4%) being the leading cause of cirrhosis. Advanced disease was common, with 67.1% of patients categorized as Child-Pugh Class C. Zinc deficiency was observed in 97.6% of patients, with mean zinc levels showing a

significant progressive decrease from Child-Pugh Class A (50.4±4.31 µg/dL) to Class B (42.32±4.86 µg/dL) to Class C (37.02±3.68 µg/dL) ($p<0.001$). There was a perfect parallelism between zinc and albumin deficiency (both 97.6%). The mortality rate during the study period was 15.3%.

Conclusion:

This study demonstrates an extraordinarily high prevalence of zinc deficiency in liver cirrhosis with a significant inverse correlation with disease severity. The progressive decline in zinc levels with worsening Child-Pugh scores suggests that zinc deficiency may be both a marker of advanced disease and potentially a contributor to disease progression. These findings support the incorporation of zinc assessment into the routine evaluation of cirrhotic patients and suggest that zinc supplementation could be considered as an adjunctive therapy, particularly in advanced disease.

Keywords:

Zinc deficiency, Liver cirrhosis, Child-Pugh score, Albumin, Alcoholic liver disease, Micronutrients, Disease severity, Nutritional status

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INTRODUCTION

"Liver cirrhosis represents a critical endpoint in chronic liver disease, characterized by the progressive replacement of normal hepatic architecture with fibrotic tissue and regenerative nodules." This irreversible condition poses a significant global health burden, with mortality rates steadily increasing over the past decades.[1] While various factors contribute to the pathogenesis and progression of cirrhosis, growing evidence suggests that micronutrient homeostasis, particularly zinc metabolism, is essential for both liver function and disease progression.[2]

Zinc is an essential trace element, serves as a vital component in over 300 enzymatic systems and plays fundamental roles in protein synthesis, immune function, wound healing, and antioxidant defense mechanisms. "The liver plays a central role in zinc homeostasis, and conversely, zinc status significantly influences hepatic function."[3] In patients with liver cirrhosis, zinc deficiency is remarkably prevalent, with studies reporting deficiency rates ranging from 52% to 88% depending on the severity of disease.[4]

The relationship between zinc deficiency and liver cirrhosis presents a complex interplay of pathophysiological mechanisms. Cirrhotic patients often experience decreased zinc absorption, altered distribution, and increased urinary zinc excretion. These alterations can be attributed to various factors, including portal hypertension, increased inflammatory cytokines, and compromised protein synthesis capacity.[5] The resulting zinc deficiency may further exacerbate liver injury through increased oxidative stress, impaired immune response, and compromised hepatic regeneration capacity.

The assessment of disease severity in liver cirrhosis remains crucial for proper patient management and prognostication. The Child-Pugh score, first introduced in

1964 and modified in 1973, continues to serve as one of the most widely used tools for evaluating the severity of liver dysfunction.[6] "This scoring system includes five clinical parameters: serum albumin, bilirubin, prothrombin time, ascites, and hepatic encephalopathy." Patients are classified into three classes (A, B, and C) with increasing severity, which helps guide clinical decision-making and predict survival outcomes.

"Recent research has suggested a potential correlation between serum zinc levels and the severity of liver cirrhosis as assessed based on the Child-Pugh score." Several studies have demonstrated that zinc deficiency becomes more pronounced as liver disease progresses, with the lowest zinc levels observed in Child-Pugh class C patients.[7] This relationship raises important questions about the potential role of zinc status as both a prognostic indicator and a therapeutic target in cirrhotic patients.

The clinical implications of zinc deficiency in cirrhosis extend beyond direct hepatic effects. Low zinc levels have been associated with various complications commonly observed in cirrhotic patients, including hepatic encephalopathy, immune dysfunction, and impaired wound healing.[8] Moreover, some studies suggest that zinc supplementation may improve clinical outcomes in selected patients, although the evidence remains heterogeneous and sometimes contradictory.[9]

Despite the growing recognition of zinc's importance in liver cirrhosis, several knowledge gaps persist. The exact mechanisms linking zinc deficiency to disease progression remain incompletely understood. Furthermore, the optimal methods for assessing zinc status in cirrhotic patients and the potential role of zinc parameters in disease monitoring require further investigation. Questions also remain regarding the most effective strategies for zinc supplementation, including optimal dosing, timing, and patient selection criteria.[10]

This research aims to contribute to the current understanding by conducting a comprehensive analysis of zinc levels across different stages of liver cirrhosis, as classified by the Child-Pugh scoring system. By examining the relationship between zinc status and disease severity, this study seeks to elucidate potential patterns that could inform both prognostic assessment and therapeutic strategies. Additionally, this investigation may help identify specific patient subgroups who might benefit most from zinc monitoring and supplementation.

Understanding the intricate relationship between zinc homeostasis and liver cirrhosis severity could have significant implications for clinical practice. If strong correlations are established, zinc status assessment could potentially serve as an additional tool in the evaluation of cirrhotic patients. Moreover, this knowledge could guide more targeted approaches to zinc supplementation, potentially improving outcomes in selected patient populations.

AIM & OBJECTIVES

Objectives:

1. To compare zinc levels in liver cirrhosis.
2. To evaluate the severity of cirrhosis using Child Pugh score.

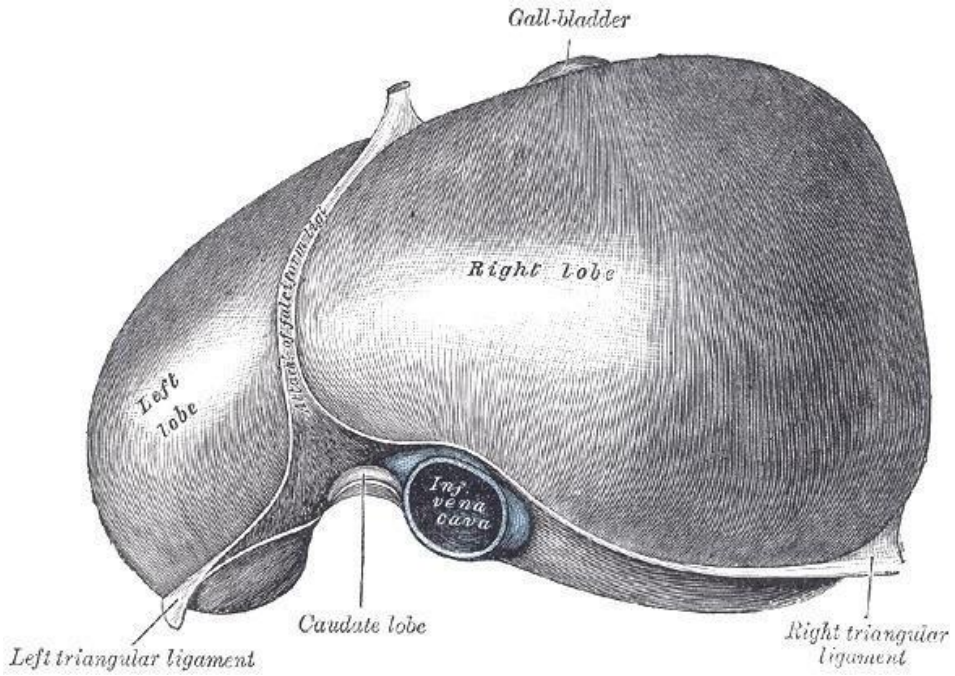
REVIEW OF LITERATURE

STRUCTURE AND FUNCTION OF LIVER

The liver is the largest organ, accounting for two to three percent of the average body weight. The quadrate, caudate, left, and right are the four anatomical lobes that make up the liver. The right lobe's inferior surface is home to the quadrate lobe . The caudate lobe is situated superiorly and anteriorly between the left and right lobes.

"The largest gland in the body, the liver, is in a prime position to absorb and cleanse drugs and other harmful compounds. The liver protects the body from toxic compounds that are consumed from the gastrointestinal (GI) tract by digesting and metabolising them at the lobule level. Phase-II activities, which conjugate molecules with substrates such as sulphate, glutathione, and glucuronide, are catabolised by the cytochrome P-450 enzyme system."

Figure 1: The superior surface of the Liver



"It carries out both exocrine and endocrine actions. The liver's exocrine system is primarily responsible for the conjugation of bilirubin and its excretion into the gut, as well as the synthesis and excretion of bile salts into the common hepatic duct. Insulin and glucagon are two of the liver's endocrine activities that control blood sugar levels. The liver converts other proteins into peptide hormones and enzymes and synthesises important proteins such as fibrinogen, albumin, prothrombin, and other amino acids. The liver participates in the metabolism of fatty acids and also creates lipoproteins, cholesterol, and phospholipids. As carbs are metabolised, it also contributes to gluconeogenesis and glycogen storage. It also assists in the metabolism of lactic acid and converts ammonia to urea. The liver stores vitamins and minerals like iron. To sum up, the liver serves as a vital channel between the blood and the gut and is necessary for the metabolism of exocrine and endocrine substances, hormones, blood plasma components, and macronutrients."[11]

LIVER CIRRHOSIS

DEFINITION

"The histological formation of regenerating nodules encircled by fibrous bands in response to chronic liver injury is defined as cirrhosis, and it causes portal hypertension and end-stage liver disease."[12]

BURDEN OF THE DISEASE

Cirrhosis is one of the most prevalent liver disease-related causes of death worldwide. The prevalence of cirrhosis worldwide is unclear.[13] "Nearly two million people die each year from liver diseases, one million from complications related to cirrhosis, and another million from viral hepatitis and hepatocellular carcinoma. Cirrhosis is currently the tenth leading cause of death globally." Cirrhosis-related mortality and morbidity increases dramatically after decompensation; the one-year

case-fatality rate might reach 80%, depending on the cause of decompensation. Last but not least, patients have just two options: they can either die or get a liver transplant, which puts a severe financial burden upon the individuals, healthcare systems, and the administration and financing of medical care. [14]

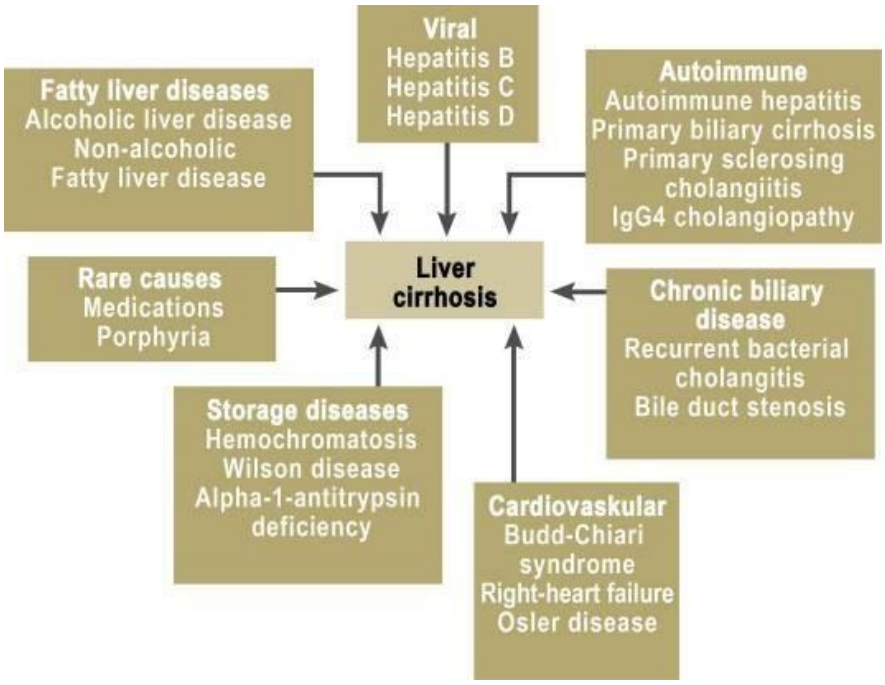
"Hepatitis B virus (HBV) (29%), hepatitis C virus (HCV) (9%), non-alcoholic fatty liver disease (NAFLD) (60%) and alcoholic liver disease (ALD) (2%) were the leading causes of chronic liver disease (CLD), which affected 1.6 billion people globally in 2017. Additionally, cirrhosis contributed to approximately 132 million deaths (95% UI: 127–145) worldwide in 2017, with 883,000 deaths (838,000–967,000, 66.7%) among men and 440,000 deaths (416,000–518,000, 33%) among women. In 1990, 899,000 deaths in both sexes were attributed to CLD (829,000-948,000)." This is a noteworthy rise. Between 1990 and 2017, these deaths accounted for 2.4% (2.3-2.6) of all deaths worldwide, up from 1.9% (1.8-2.0) in 1990. "The estimated incidence of cirrhosis is 16.5 cases per 100,000 in East Asia and 23.6 cases per 100,000 in Southeast Asia. There were 20.7 cases of cirrhosis per 100,000 people in 2015, up 13% from 2000, according to data from the Global Burden of Disease survey. Over the past 20 years, cirrhosis has become 1.5–2 times more common."[15]

AETIOLOGY

The aetiology of cirrhosis can usually be ascertained by a serologic and histologic study in addition to the patient's medical history. Hepatitis B is more widespread throughout most of Asia and sub-Saharan Africa, while hepatitis C and alcoholic disease of liver are the most common causes in the West. "The diagnosis of cirrhosis without obvious aetiology, or cryptogenic cirrhosis, has decreased since the identification of the hepatitis C virus in 1989 and the identification of non-alcoholic steato-hepatitis (NASH) in obese and diabetic individuals. Knowing the origin of

cirrhosis is important since it can affect treatment decisions and predict issues. Furthermore, it enables the evaluation of (genetic) tests and preventive advice for family members of patients with hereditary disorders such as hemochromatosis or Wilson's disease, as well as the discussion of preventive measures with family members of patients with alcoholic liver cirrhosis or chronic viral hepatitis. Multiple etiological factors frequently contribute to the development of cirrhosis, as demonstrated by epidemiological studies that identified regular (moderate) alcohol consumption, age over 50, and male gender as risk factors in chronic hepatitis C,[16,17] or older age obesity, insulin resistance/type 2 diabetes, hypertension, and hyperlipidaemia (all features of the metabolic syndrome) in NASH."[18, 19]

Figure 2: Aetiology of Liver Cirrhosis

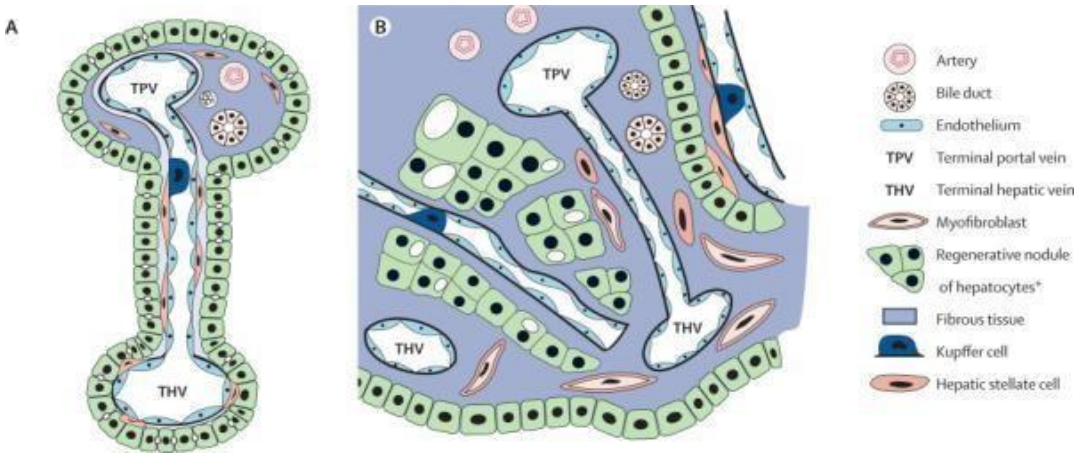


PATHOGENESIS AND PATHOPHYSIOLOGY OF CIRRHOSIS

"Fibrosis is the term used to describe the encapsulation or replacement of injured tissue by a collagenous scar. When the normal wound healing response continues, fibrogenesis— the development and deposition of connective tissue— occurs inappropriately, leading to liver fibrosis." Fibrosis progresses at varying rates

depending on the host, environment, and the underlying cause of the liver disease.[20,21] "Cirrhosis, a more severe form of liver fibrosis, coexists with hepatic vascular distortion. It disrupts the information flow between the hepatic sinusoids and the hepatocytes that reside adjacent to the liver parenchyma by directing the portal and arterial blood supplies directly into the hepatic outflow (central veins)." The gap of Disse, a layer of permeable connective tissue that encircles the hepatic sinusoids, contains hepatic stellate cells (HSC) and a small number of mononuclear cells. There is fenestration of the endothelia. Most known liver functions are performed by hepatocytes, which line the other side of the Disse gap. When endothelial fenestrations are lost and the Disse space fills with scar tissue in cirrhosis, a process known as sinusoidal capillarization takes place. [22] Vascularised fibrotic septa that link portal tracts to central veins and to each other are histopathologically indicative of cirrhosis. This results in islands of hepatocytes without a central vein and encircled by fibrotic septa (Figure 1). Increased intrahepatic resistance (portal hypertension), hepatocellular carcinoma (HCC), and compromised hepatocyte (liver) function are the main clinical outcomes of cirrhosis. "Hepatic vascular changes and the consequent portal hypertension are intimately related to the general circulatory abnormalities in cirrhosis, including splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, and increased cardiac output." Despite the belief that cirrhosis and the vascular distortion it causes are irreversible, recent studies suggest that the condition may be able to regress or even reverse.[23, 24]

Figure 3: Vascular and Architectural Changes in Cirrhosis



Based on its morphology or aetiology, cirrhosis is categorised.

Morphology Classification[6]

"There are three morphological types of cirrhosis: (1) micronodular, (2) macronodular, or (3) mixed. This categorisation is not as clinically relevant as the etiologic classification."

- Indian childhood cirrhosis, alcoholism, chronic biliary blockage, hepatic venous outflow obstruction, hemochromatosis, and micronodular cirrhosis (uniform nodules with a diameter of less than 3 mm).
- Alpha-1 antitrypsin deficiency, hepatitis B and C, and primary biliary cholangitis can all cause macronodular cirrhosis. irregular nodules that vary in diameter by more than 3 mm.
- When traits of macro- and micronodular cirrhosis coexist, it's known as mixed cirrhosis: Micronodular cirrhosis usually develops into macronodular cirrhosis eventually.

Etiology Classification

"Based on the cause of cirrhosis which is sub-classified as follows":

- Toxins: alcohol, narcotics;
- Autoimmune: autoimmune hepatitis;
- Viral: hepatitis B, C, and D
- Cardiovascular: Budd-Chiari syndrome, sinusoidal obstruction syndrome, cardiac cirrhosis;
- "Cholestatic: primary biliary cholangitis, primary sclerosing cholangitis;
- Metabolic: hemochromatosis, NASH, Wilson disease, alpha-1 antitrypsin deficiency, and cryptogenic cirrhosis."

DIAGNOSIS OF LIVER CIRRHOSIS

History and physical examination

Although compensated cirrhosis is typically asymptomatic, lab testing, imaging, and physical examinations may inadvertently show the illness. An enlarged liver or spleen may be seen during the examination, and gamma-glutamyl transpeptidase or aminotransferases are frequently reported to be mildly to moderately increased. Conversely, individuals with decompensated cirrhosis frequently exhibit a variety of symptoms that are brought on by the co-occurrence of liver disease and portal hypertension. "The transition from a compensated to a decompensated phase of cirrhosis is indicated in patients with ascites, jaundice, hepatic encephalopathy, variceal haemorrhage, or hepatocellular carcinoma." Additional cirrhosis problems that plague people with ascites include spontaneous bacterial peritonitis and hepatorenal syndrome.

Multiple Organs Affected Gastrointestinal

"Portal hypertension can cause ascites and prominence of the periumbilical abdominal veins in addition to hepatosplenomegaly and caput medusa." With a minimum 20% fatality rate six weeks after a bleeding episode, esophageal varices are another cirrhosis-related consequence that arises from increased blood flow in the collateral circulation. 25 Gallstones are more likely to form in people with chronic liver disease, while small intestine bacterial overgrowth and chronic pancreatitis are more common in people with alcoholic cirrhosis.[26, 27]

Hematologic

Hypersplenism, folate insufficiency, and haemolytic anaemia (spur cell anaemia in severe alcoholic liver disease) can all result in anaemia. Haemostasis, disseminated intravascular coagulation, pancytopenia from hypersplenism in portal hypertension, and other disorders can occur in patients with cirrhosis.

Renal

Underfilling is more common in cirrhosis patients due to renal vasoconstriction and systemic hypotension, which might result in hepatorenal syndrome. Reduced effective blood flow to the kidneys due to splanchnic vasodilation in cirrhosis sets off the RAAS system, resulting in salt and water retention and renal artery constriction.[28] "However, this effect is insufficient to reverse the systemic vasodilation brought on by cirrhosis, which worsens renal vasoconstriction and causes renal hypoperfusion, finally resulting in renal failure."[29]

Pulmonary

"Signs and symptoms of liver disease include hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax."

Skin

Spider nevi are large arterioles surrounded by many smaller arteries that resemble spiders, hence the name, and can form in patients with cirrhosis who have hyperestrogenemia as a secondary cause. Spider nevi develops as a result of an imbalance in sex hormones caused by liver disease, which also raises the ratio of oestrogen to free testosterone [30] Palmar erythema is another cirrhosis-related cutaneous disease linked to hyperestrogenemia. Decompensated cirrhosis with blood bilirubin levels greater than 3 mg/dL can cause jaundice, a yellowish discolouration of the skin and mucous membranes.

Endocrine

Gynaecomastia and hypogonadism are possible symptoms of alcoholic liver cirrhosis. A significant contributing aspect to the complex pathophysiology of cirrhosis is the hypersensitivity of these patients to androgen and oestrogen receptors. "Hypothalamic- pituitary dysfunction has also been connected to the development of these illnesses."[31] In addition to feminisation and the loss of secondary sexual characteristics, male hypogonadism can cause impotence and decreased desire. Women may experience amenorrhoea, irregular menstrual flow, and infertility.

Nail changes

"Clubbing, hypertrophic osteoarthropathy, and dupuytren contracture are seen."

Others

"Foetal hepaticus, a sweet, musty breath odour brought on by high blood levels of dimethyl sulphide and ketones, or asterixis, a fluttering tremor when the arms are extended and the hands are dorsiflexed, are two possible symptoms of hepatic encephalopathy in cirrhosis."[32] Cirrhosis can cause muscle cramping, an

umbilical hernia, hyperdynamic circulation, and a loss of lean muscle mass.

EVALUATION

Lab Findings

"Although they are usually mildly to moderately elevated, normal levels of aminotransferases do not rule out cirrhosis; aspartate aminotransferase (AST) is greater than alanine aminotransferase (ALT)."[33] With the exception of alcoholic hepatitis, most forms of chronic hepatitis have an AST/ALT ratio below one. As chronic hepatitis progresses to cirrhosis, this AST/ALT ratio reverses. Higher levels of 5'-nucleotidase, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) are linked to cholestatic disorders. "Albumin is low because the liver produces it and its functional capacity declines due to increasing prothrombin time (PT) caused by bilirubin and coagulation factor shortages. Serum albumin and PT are therefore trustworthy indicators of synthetic liver function." Although normochromic anaemia is linked to alcoholic liver cirrhosis, macrocytic anaemia is another possible presentation. Leukopenia and thrombocytopenia are sometimes seen as secondary outcomes of alcohol-induced bone marrow suppression and sequestration by the enlarged spleen. [34] Increased immunoglobulins, especially the gamma fraction, are often the consequence of impaired liver clearance.[35]

Specific Labs to Investigate Newly Diagnosed Cirrhosis

"In addition to serology and PCR techniques for autoimmune hepatitis, an order may be placed for serum IgG immunoglobulins, anti-smooth muscle antibodies (ASMA), anti-nuclear antibodies [ANA], anti-liver-kidney microsomal antibodies type 1 (ALKM-1), and anti-mt mitochondrial antibodies for primary biliary cholangitis. Ceruloplasmin and urine copper for Wilson disease, serum alpha-fetoprotein for hepatocellular carcinoma (HCC), alpha 1-antitrypsin level and

protease inhibitor phenotype for alpha 1-antitrypsin deficiency, and ferritin and transferrin saturation for hemochromatosis are other helpful tests."

Imaging

To help diagnose cirrhosis, a number of imaging modalities are used in addition to laboratory testing. These also have CT, MRI, ultrasound, and transient elastography (fibroscan).

Ultrasonography which is a widely accessible, reasonably priced, and noninvasive technique for assessing cirrhosis. It is nonspecific since fatty liver cases might also have high hepatic echogenicity and nodules, which are signs of cirrhosis.[36] "Additionally, it can measure the caudate width to right side lobe ratio, which usually increases in cirrhosis.[37] It is also a useful method for patients with cirrhosis to check for HCC. Duplex Doppler ultrasonography can be used to evaluate the patency of the hepatic, portal, and mesenteric veins."

Although MRI is a superior imaging modality, HCC and vascular lesions can be detected with CT or MRI with contrast.[38] Magnetic resonance cholangiography, or MRC, can also be used to detect biliary obstruction, iron levels, and liver fat accumulation for steatosis and hemochromatosis. [39, 40] However, MRI is expensive and not easily available.

"Transient elastography (fibroscan), a promising non-invasive method that assesses liver stiffness, which is associated with fibrosis, uses high-velocity ultrasonic pulses. A colloid liver spleen scan using technetium-99m sulphur colloid may show increased uptake in cirrhosis when comparing the uptake of colloid in the liver and spleen to that in the bone marrow. During an esophagogastroduodenoscopy (EGD), variations in the stomach or oesophagus could be a sign of portal hypertension."[2, 41]

Biopsy of the liver

"A liver biopsy is the gold standard for determining the level in fibrosis (stage) and inflammation (grade) of cirrhosis." However, it may sometimes fail to detect the diagnosis due to sample errors. The biopsy-based diagnosis of cirrhosis requires both fibrosis and nodules. Nodular patterns come in three varieties: mixed, macronodular, and micronodular. A distinct risk factor for increased disease severity and an enhanced hepatic venous pressure gradient (HVPG) is represented by each type of nodular pattern. [42]

In noninvasive testing, patients with significant fibrosis/cirrhosis are separated from those with moderate or mild fibrosis using direct and indirect serum markers.[43] "Recently a number of laboratory and ultrasonography-based approaches have been developed for the noninvasive diagnostic approach of cirrhosis. These noninvasive methods often avoid the need for a liver biopsy when the only thing to be ascertained for the stage of fibrosis, however, the information they provide must always be interpreted in light of the associated clinical symptoms." [44]

"The degree of hepatic fibrosis can be assessed using two different laboratory-based methods: those that utilise normal liver function tests[45] and those that use particular laboratory values associated with fibrosis, such as the amount of hyaluronic acid.[46] The AST-to-platelet ratio index (APRI), which is a screening tool for advanced fibrosis and cirrhosis, is simply calculated as the quotient of the platelet count and the AST (GOT)."[47]

NATURAL HISTORY AND PROGNOSIS OF CIRRHOSIS OF LIVER

A phase of cirrhosis known as "compensated cirrhosis," which is asymptomatic, is followed by a period known as "decompensated cirrhosis," which is progressing and marked by the onset of issues associated to portal hypertension

and/or liver dysfunction.

"Decompensation is indicated by the advent of ascites, portal hypertension GI haemorrhage, encephalopathy, or jaundice."[48] Cirrhosis occurs in two stages: compensated and decompensated. These phases differ in their traits, results, and indicators of mortality.[49]

Figure 4: Natural History of Liver Cirrhosis

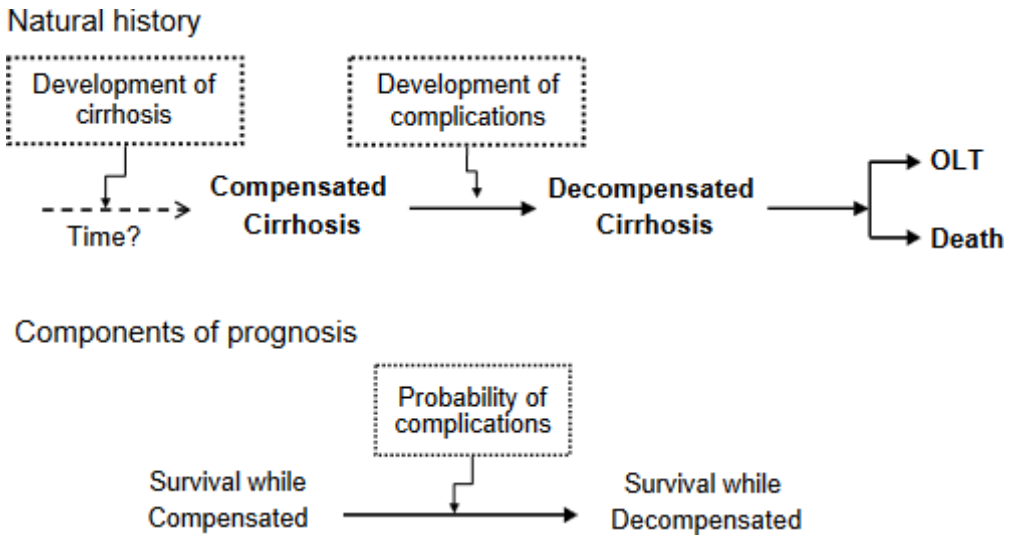
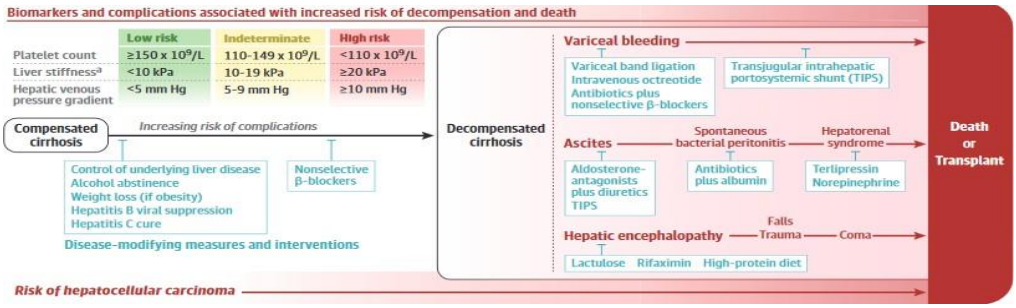


Figure 5: Natural History of Cirrhosis, its Complications and Modifiable factors



The term "acute-on-chronic liver failure" (ACLF) is being used more and more to describe the abrupt decline in liver function that cirrhosis patients encounter. One or more organs fail in this syndrome, which is typically brought on by a triggering event and has a high short- and medium-term mortality rate of 50–90%. Fifty Distinguishing between decompensated liver cirrhosis and ACLF may still be challenging. The potentially reversible nature of ACLF, as the precipitating factor

may be controlled, is arguably the most significant distinction between the two entities.[51]

"Predictive models anticipate a ten-year survival rate of 47% for those with compensated cirrhosis, but this drops to 16% if a decompensating event occurs. Several studies have attempted to develop a classification system based on laboratory and clinical data that may be used to determine the degree of liver impairment and predict the prognosis of people with cirrhosis."[6]

SCORING SYSTEMS TO PREDICT PROGNOSIS OF CIRRHOSIS OF LIVER

- "Child-Pugh scoring system
- Model For End-Stage Liver Disease(MELD) Score
- Model for End-stage Liver Disease-Na(MELDNa)
- MELD 3.0 Score
- ALBI SCORE"

CHILD-PUGH SCORING SYSTEM

"To predict death in patients with liver disease , the Child-Pugh scoring system also known as the Child-Pugh-Turcotte score was developed. Child and Turcotte initially created it in 1964 to aid in the selection of patients who would profit from elective portal decompression surgery. This approach was used to categorise patients into three groups: A represented good liver function, B moderately impaired liver function, and C advanced liver dysfunction. Their original score system included five clinical and laboratory criteria to categorise patients: ascites, neurological illness, serum bilirubin, serum albumin, and clinical nutrition status. [52] Pugh and associates later modified the grading scheme by substituting prothrombin time for clinical nutrition status. Additionally, they included modifiable points for each criterion depending on increasing severity."[8]

Figure 6: the Child-Pugh score

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)			

"*Frequently INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7 to 2.2 = 2 points, INR above 2.2 = 3 points The severity of cirrhosis"

Clinical significance

The Child-Pugh score has been demonstrated to predict mortality after various major procedures and is a valid measure of the risk of death after portocaval shunt surgery. "Children in class A have a 10% mortality rate after abdominal surgery, children in class B have a 30% mortality rate, and children in class C have a 70–80% mortality rate."[53] Generally speaking, children in class A are considered to be safe candidates for elective surgery. Even with medical optimisation, surgery is still riskier for children in class B. Patients in Child class C are not advised to have elective surgery. The chance of dying from all causes and the likelihood of acquiring further liver dysfunction-related issues, like variceal haemorrhage, can also be predicted using the Child-Pugh score. "At one year, the overall death rate for the patients in a specific study was 0% for Child class A, 20% for Child class B, and 55% for Child class C."[54] A popular method for selecting patients for hepatocellular carcinoma

resection and nonhepatic surgery is the Child-Pugh score. At the patient's bedside, it is easy to compute. [56]

Issues of concern

"The Child-Pugh classification was previously used to allocate liver transplants. Nevertheless, there were three primary limitations on its use":

1. Subjective grading of encephalopathy and ascites is required.
2. The categorisation scheme does not account for renal function.
3. Ascites and encephalopathy can only be scored with 10 possible points. Wait times significantly impacted prioritising because patients could not be adequately differentiated based on the severity of their conditions, which made this last constraint crucial. [57] Theoretically, a patient with a bilirubin of 14 and an INR of 6 would have the same Child- Pugh score as one with a 6.0 bilirubin and an INR of 2.3. "The MELD score, which offers a larger range of values for more continuous variables, was created to account for these variances. The initial MELD score was determined by considering the patient's bilirubin level, creatinine level, INR, and liver disease aetiology."[58] Since then, it has evolved to take into account the patient's serum sodium level and dialysis status in addition to ruling out other possible causes of sickness.

Role of Zinc in Liver Cirrhosis

Biological Functions of Zinc

With a wide range of biological uses, including cellular, metabolic, and immunological processes, zinc is a necessary trace element. Zinc has well-documented apoptotic, antioxidant, and anti-inflammatory properties. It mostly contributes to protein synthesis and cellular metabolism. Zinc is a modulator of cell proliferation, variety, and apoptotic activity in protein synthesis, exhibiting dynamic

expansion, revival, and cellular restoration. Zinc ions and zinc-binding protein activity are carried by the enzymatic catalytic domains of over 300 enzymes in the human proteome. [59] Additionally, it plays a major part in controlling immunological responses during various phases of the reaction. It also mediates its function in metabolism, gene expression, and cellular development and differentiation.

"The biological roles of zinc in human physiology are well documented, and about half of the world's population is at risk for deficiencies. According to a World Health Organisation (WHO) research, the fifth major risk factor for morbidity and mortality in developing or impoverished nations is zinc deficiency." A zinc shortage occurs when the normal threshold level in serum or plasma falls below the lower normal limit of 100 µg/dL. Immune system abnormalities, cognitive disorders, growth and oxidative depression, and other cellular and metabolic problems can result from zinc deficiency. Because of their important biological connection to protein activity, the enzymes have a role in collagen metabolism, which in turn affects the onset of fibrosis.[60]

Figure 7: Biological functions of Zinc in the human body

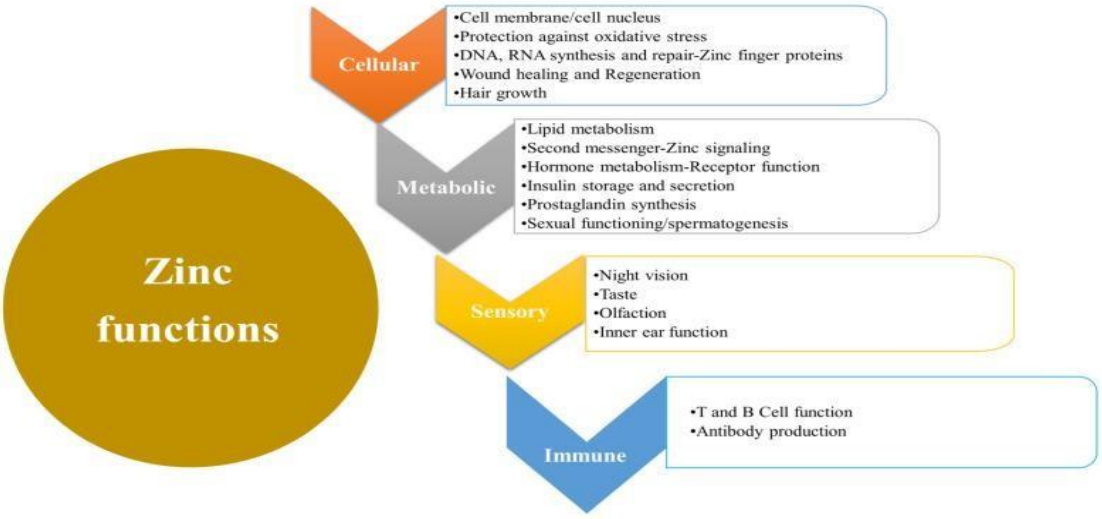


Figure 8: Role of zinc in human body

Physiological processes	Role/action
Immune system	Zinc is involved in the production and regulation of immune system cells, helps strengthen the body's defenses and accelerates healing.
Growth and Development	Zinc is required for proper growth and development in childhood, adolescence, and pregnancy. It is involved in protein synthesis and the process of cell division.
Cognitive Function	Zinc is involved in the transmission of nerve impulses in the brain, aiding memory, learning and cognitive function.
Reproductive Function	Zinc is essential for proper sperm production in men and is involved in the proper functioning of the female reproductive system.
Metabolism	Zinc is a structural constituent of many proteins and more than 300 enzymes, and 2000 transcriptional factors and it is involved in the metabolism of carbohydrates, lipids and proteins, aiding in digestion and nutrient absorption.
Skin Health	Zinc plays an important role in skin health. It can help reduce skin inflammation, heal wounds, and improve overall skin health.
Oxidative stress	Zinc does not undergo redox reactions and it protects the cell from oxidation damage by free radicals, that can lead to inflammation.

Clinical Implications of Zinc Deficiency

Zinc deficiency is complex and can result in a range of clinical manifestations. Malnutrition results from the precipitation of micronutrients and protein due to alterations in the metabolism of carbohydrates and fats in chronic liver disease. Clinical symptoms include testicular dysfunction, delayed wound healing, body hair loss, altered taste and smell, and decreased or absent hunger. Additionally, it lowers immunity and the body's ability to eliminate drugs.[61]

The primary mechanism of zinc's activity is its binding to acids and proteins (alpha 2- macroglobulin and albumin), which is directly correlated with the rate of zinc absorption. Reduced zinc absorption in hepatic cellular carcinoma may result from a decline in albumin levels in progressive liver disease. 61 Zinc insufficiency in liver cirrhosis is also caused by endotoxemia of the stomach and impaired zinc absorption brought on by cytokines (interleukin-6) that inflame the gut. This results in alterations to the GIT mucosa and reduces zinc absorption. Additionally, many medications, like as diuretics, increase the excretion of zinc and decrease its ability to bind to albumin, which causes a circulation-level zinc deficit. “Hepatic encephalopathy (HE), ascites, variceal haemorrhage, toxicity, infections, and hepatocellular carcinoma (HCC) are further complications of cirrhosis. It describes the range of chronic liver illnesses, regardless of their cause.”[62]

Mechanism of Zinc Activity and Effects of Deficiency

“Zinc is involved in a number of physiological processes involving enzymatic reactions, which catalyse the exchange of substrates and preserve the balance of enzyme assembly.” Additionally, it uses basic mechanisms to regulate transcription factors and hormones via influencing the hormone's receptors and the function/expression of particular

genes. Zn has a well-established involvement in development and metabolism. Additionally, it functions as a signalling ion, disrupts redox activity, and plays a crucial second messenger role. The primary cause of oxidative stress and cellular death is zinc deficiency. [62] However, Zn2+'s redox indolent gives it antioxidant properties. The most important antioxidant source of zinc is thought to be the protection of the sulfhydryl protein group from oxidative damage and the induction of strong redox conversion of metals like iron and copper. This component also plays a major role in the thyroid, insulin storage, development, metabolism, and reproduction of neurotransmitters. [63]

Since zinc ions are not bound by proteins, they are mostly needed in the intracellular components of different cells. It regulates intracellular control and serves as a messenger in intercellular communication. One of the most prevalent intracellular micronutrients in all bodily tissues is zinc. About 85% of zinc reserves are in the bones and muscles, with the remaining 11% being in the skin and liver. Two to three grammes of zinc are equal to 70 kg of weight in an adult. Meat is a major source of zinc, and in industrialised countries, the amount of zinc in the diet is typically enough to meet this need.

Zinc is a necessary co-factor for controlling the various caspases, a family of enzymes that include cysteine proteases and cause cellular death. Furthermore, its regulatory function has been demonstrated in intracellular signalling systems, growth factor, hormone, and cytokine activation, and molecular processes. Furthermore, in contrast to the calcium regulation mechanism, it is an effective intracellular secondary messenger. The development and course of many diseases are significantly impacted by the restriction of intracellular ionic Zn2+'s free movement. As a protein regulator for many metabolic processes, zinc's intracellular equilibrium is in jeopardy. These

kinds of switches highlight the significance of zinc. Zn carrier proteins called metallothioneins are essential components of this pathway's uptake and storage of zinc. Zinc enters and exits cells more quickly thanks to a group of distinct zinc transporters.

Human cells have zinc carriers (ZnT and SLC30 family) and zip transporters (Zip and SLC39 family). Through cellular efflux or into the cell's vesicles, ZnT condenses the intracellular accessibility of zinc. However, by stimulating its extracellular counterparts, the Zip transporters improve the intracellular trafficking of zinc. Additionally, it might trigger the release of zinc from the cytoplasmic vesicle. Equally, both types of transporters are precisely expressed in every tissue and play improbable roles in regulating the biological activities of cytokines and hormones as well as nutritional zinc deficiency or excess. Furthermore, many zinc transporters coordinate the transit of zinc ions within cells, subcellular spaces, and organelles.

“The proteins that target the regulatory Zn2+ ions, inhibit the activity of enzymes, sensor proteins, protein–protein interactions, and the transient zinc-binding sites on membrane receptors all contribute to the regulation of cell gene expression.” Certain proteins that allow metal ions to separate are necessary for the control of zinc through a number of mechanisms. These results validate the vital roles of zinc and its metalloproteins in cellular functioning.

Independent of dietary zinc, the expression of Zn carrier genes (Zip1, mRNA of ZnT) is well synchronised. ZnT mRNA expression is widely distributed among certain transporters. Zip1, ZnT1, and ZnT7 are the transporters that are highly expressed. Therefore, the intracellular zinc shortfall is represented by the increased expression of the recycled zinc transporter, which is comparable to ferritin consumption in iron deficiency. Aberrations in zinc metabolism also disrupt

mitochondrial functions, which can lead to congenital birth abnormalities, developmental problems, and DNA damage. “It has been shown that an oxidative environment increases the availability of zinc ions, while a reductive environment diminishes that availability.” It is hypothesised that Zn deficiency may increase our knowledge of the factors that damage DNA and decrease DNA repair processes by disrupting the antioxidant activity.[65]

Metabolism of Zinc in the Liver

The circulating zinc balance in the body is mostly maintained by the liver. Zinc shortage is caused by any change in the liver's parenchyma, and hepatocytes' releases of zinc are regulated differently. Zn2+ showed complete Zn interchange in hepatocytes in less than two days, according to throughput discoveries. 66 These components cause a brief metabolic dysregulation of zinc instead of metabolic activity, which results in a shortage of zinc in the plasma. Certain mediators and stressors can have similar characteristics to lipo- polysaccharides or pro-inflammatory cytokines. The expression of one or more genes is specifically disrupted by changes in zinc status. “It's possible that changes in zinc concentration cause the mRNA expression levels of metallothionein, retinol-binding protein, cholecystokinin, uroguanylin, endothelin, etc. to rise or fall.” Zinc plays a variety of tasks in the liver and, because of its importance in metabolism, it also affects how other organs' metabolisms evolve. [67]

The acute-phase protein metallothionein, which is mainly necessary for the absorption, distribution, and intracellular storage of zinc, has tight bonds with zinc. Additionally, metallothionein production rises as a result of increased zinc consumption. It has also been established that zinc and the cytokine interleukin-6 (IL-6) have nearby contacts, and that IL-6 plays a major role in controlling the genes of

acute-phase proteins.

"Apart from microbial growth regulation that enhances IL-6, zinc's role in the liver also creates acute phase proteins, in the gluconeogenesis decree, in the volatile substrates (nitrogen-monoxide) mechanism, or hydrophilic radicals." Hypozincemia, or low zinc with chronic acute-phase reactivity, is promoted by IL-6's involvement in the liver's Zip14 transporter. Hepatocytes are also linked to the beneficial properties of zinc transporters; yet, significant indulgence breaches continue. To date, IL-6 has demonstrated high activity for the Zip5 and Zip6 transporters (prostate, mammary gland, and steroid hormones) and leading activity for the bone development factor ZnT5. [68]

Zip-14 has a variety of roles in the provocative progressions of IL-6 development of hypozincemia. By altering the liver's hepcidin synthesis, IL-6 and Zip-14 have effects in inflammatory conditions that are comparable to those of serum iron (hypo-ferritinemia). "Zip- 14 also stimulates the uptake of zinc and non-transferrin bound iron (NTBI)." The increased NTBI concentration in hemochromatosis causes excess iron in several tissues, which increases the risk of cardiomyopathy, diabetes, hepatocellular carcinoma (HCC), and other conditions. Furthermore, Zip-14 interfered with the transport of iron, and it is hypothesised that the HFE gene causes hereditary hemochromatosis. Through hepatic restoration, the Zip- 14 transporter also interferes with zinc consumption. "Zip-14 mediating activity may represent a promising therapeutic target to support hepatic regeneration in chronic liver disease."

However, it also plays a significant part in lump growth, such as in HCC. According to a paper, malignant cells in HCC patients had down-regulated Zip-14, which reduces zinc and speeds up tumour growth. One could argue that the concentrated

ability of tumour cells to produce zinc is mediated by the Zip-14 transporter.[69]

Deficiency of Zinc in Liver Diseases

Worldwide, zinc insufficiency is becoming a more serious medical or health concern. Mostly identified around 1960, zinc deficiency is more common across all age groups and equally affects men and women. It can be brought on by inadequate dietary intake, decreased small intestine absorption, body needs, decreased zinc intake and loss through perspiration, urine, faeces, and other bodily fluids, as well as a number of hereditary conditions. It is connected to a number of illnesses, such as red cell diseases, malabsorption syndromes, and chronic liver disease. "The latest studies have used non-invasive high-throughput methods to identify nano-mechanical alterations in the liver or red blood cells, respectively, which could have a direct impact on human diseases. A number of conditions can lead to zinc shortage or change the metabolism of zinc in liver cirrhosis (Table 1). These include inadequate intake, changes in the metabolism of proteins and amino acids, decreased portosystemic shunts, hepatic extraction, poor absorption from alcohol, and the impact of cytokines and endotoxins, particularly IL-6."[65]

Table 1: "Zinc deficiency and associated conditions in liver diseases"

Causes of Liver Disease	Mechanism
Insufficient nutritional consumption	Protein and amino acids metabolism variabilities
Contracted hepatic abstraction	Porto-systemic shunts
Alcohol-induced defective absorption	Production of cytokines, primarily interleukin-6 (IL-6) Production of Endotoxins by Biological pathogens

Severe muscle waste has been reported to cause a significant loss of zinc in the urine.

In individuals with cirrhosis, ascites causes problems that lead to an increase in catabolism and a significant decrease in muscular activity. “Similar to condensing serum albumin levels and compact amount of albumin to fix zinc, the diuretic treatment of cirrhotic patients and the complication of ascites signals more than just an increased renal Zn elimination.”[70]

“Zinc deficiency has been associated with a number of clinical features in liver cirrhosis, including loss of body hair, testicular atrophy, appetite loss or poor appetite, immune abnormalities, altered taste and smell, reduced or altered metabolism of protein, thyroid hormones, and vitamin A, delayed wound healing, and decreased drug elimination ability.” The pathomechanisms of zinc deficiency in liver cirrhosis are numerous and varied. “Zinc deficiency can lead to oxidative tissue damage and/or control over certain signalling pathways in the liver. Additionally, oxidative pressure and related conditions such as vulnerability to inflammatory hepatitis, loss of acute phase defence in hepatitis, and variables for lipid oxidation may be impacted by the zinc deficiency.” Zinc shortage promotes oxidatively favourable transcription factors that can interfere with cellular life, function, and dissemination in redox state variation. This deficit affects liver function in a variety of ways, particularly the liver's capacity to repair itself. [65]

Reduced or deficient zinc can cause cellular and tissue damage due to the influence of oxidative stress. This is because it alters certain signalling cascades, which in turn impairs the configuration of enzymes, mitochondria, and ribosomes. Oxidative species production is triggered by a lack of Zn weakens the body's defences against viruses and deadly substances and increases the inflammatory parenchyma of the liver (hepatitis). The reductive oxidation of transcription factors that are in charge of the diversity of cellular activity is restricted by the shift in redox potential.

Oxidative tension may support endotoxemia, infections such as spontaneous peritonitis, and hormonal stress release in liver disorders.

Furthermore, the reflecting participation of immune disorders or their failures is associated with hepatic cirrhosis. Failure of the reticuloendothelial system, for instance, causes immune reconnaissance traits to be scarce or have little effect, and decreased liver protein synthesis complicates innate immunity and creates the recognition site, delaying the capacity of bacteria to undergo phagocytosis.[71]

Zinc Deficiency in Liver Cirrhosis Complications[65]

"Ascites is one of the most dangerous and potentially fatal complications of liver cirrhosis." By controlling how macro or micronutrients are absorbed, distributed, and used appropriately, the liver demonstrates a basic aspect of the nutrition directive. Consequently, a critical predictor indicator for overall mortality, liver transplant success, and lifespan value is protein-energy malnourishment in patients with advanced liver disease. "A decrease or reduction in branched amino acids (isoleucine, leucine, and valine) and an excess of plasma aromatic amino acids (phenylalanine, tyrosine, and tryptophan) are hallmarks of the catabolic state in cirrhosis." Furthermore, advanced undernourished muscle cessation revealed a reorganisation of amino acid and protein metabolism. They enhanced energy disbursement and repeatedly improved the hyperactive catabolic rate, and they reduced the clearance of ammonia from the muscles, liver, and muscles in cirrhotic individuals.

Ascites and hypo-albuminemia may result from supplementing with certain basic amino acids or a zinc mixture, according to several findings. This would increase the source of protein substrate and encourage the combining of proteins. It has been discovered that albumin is a multipurpose protein with immune-modulating,

antioxidant, and reclamation properties. It exhibits a final character in the distribution of metabolites, hormones, medications, and the transition of zinc and copper ions. About 80% of the zinc in plasma is carried by albumin, one of the primary transport proteins. It has been shown that severe zinc deficiency is associated with liver cirrhosis, which leads to anomalies in nitrogen metabolism. “Numerous biological processes, such as the stimulation of albumin and glycogenesis, the improvement of insulin confrontation, the stimulation of mitochondrial bioenergetics, the limitation of ROS production and hepatic cell apoptosis, and the enhancement of liver restoration, involve the twisting of branched change amino acids.” It has been suggested that branch chain amino acids (BCAAs) could help reduce CLD in randomised clinical studies. Regarding the capacity of BCAA-rich supplements to lower hypoalbuminemia, two processes have been implicated.

“Furthermore, ribosomal phosphorylation of the S6 protein in the liver of rats with CLD was induced by continuous dietary supplementation with BCAAs, according to another study. Consequently, supplementing with larger levels of albumin BCAAs can raise the osmotic pressure, which lowers extracellular fluid and may accelerate the development of ascites.” The depletion of BCAAs in muscle mass may be influenced by the zinc dietary supply. Consequently, the consumption of BCAAs may be used for albumin synthesis, which lowers albumin levels in the blood and lessens the severity of ascites. “Regardless of the degree of liver cirrhosis and its consequences, including diabetes mellitus, zinc stored in various organs, including as the liver, muscle, and bone, can be replenished.”

In a different study, Zn sulphate nutrients were used to repair malnourished infants with chromosomal damage and cytotoxic qualities in vitro. However, it should be noted that additional research with a large number of patients is necessary to

oversee the full implementation of reaching and sustaining clinical productivity in the treatment of liver cirrhosis.

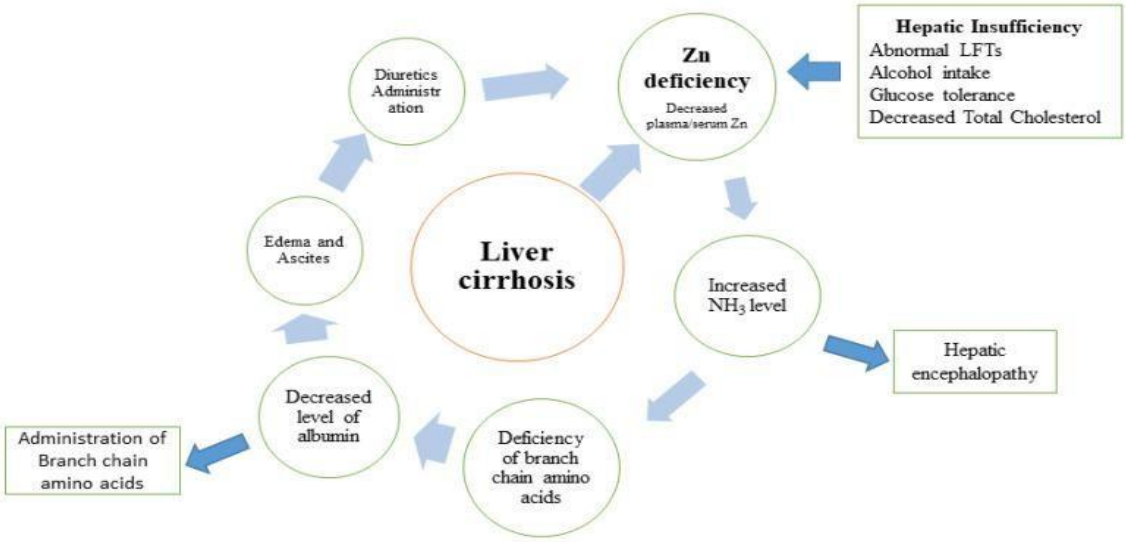
A reversible neuro-psychiatric phenomenon, hepatic encephalopathy (HE) can develop under severe situations such as acute and chronic liver diseases. Instances of HE involve about 70% of people with cirrhosis. Higher ammonia concentrations play a crucial part in the pathophysiology of HE, notwithstanding its diversity and heterogeneity.

Hyperammonemia causes astrocyte cell inflammation and related abnormalities that disrupt neuronal transmission and reduce the brain's ability to supply energy. Furthermore, oedema in the astrocytes increases oxidative and nitrosative pressure and affects the basic proteins in the brain.

Contagions, aberrant neutrophil activities, and the characteristics of pro-inflammatory cytokines are other elements of excessive ammonia that are intricate in the pathophysiology of HE. Because zinc deficiency disrupts the activity of urea cycle enzymes in the liver and skeletal muscle, it ruins nitrogen metabolism. In an experimental rat model of patients with cirrhosis and increasing liver disease, zinc deprivation is associated with changes in metabolic nitrogen. Since serum zinc levels are reduced in, HE patients and inversely correlated with blood ammonia levels, it is hypothesised that the reduced zinc may play a role in the pathophysiology of HE. Another case of a patient with severe HE and a zinc deficiency supports it as well. By lowering the amount of ammonia in the blood, the extended duration of zinc treatment improved the encephalopathy and survival. Only a small number of controlled trials have begun to examine zinc proficiency in the treatment of HE cases linked to liver cirrhosis. Overall, the results of a few controlled clinical investigations of zinc therapy in HE patients were marginal and uneven. According to one of the

intriguing claims, the exchange of zinc has a beneficial effect on the muscle spasms that patients with liver cirrhosis frequently experience.

Figure 9: Zinc deficiency and liver cirrhosis



"Hepatocellular carcinoma (HCC), a consequence of liver cirrhosis, is ranked as the third most prevalent type of cancer worldwide and the fifth most common cause of death from the disease." The primary illness risk factor for HCC development is liver cirrhosis. Although the exact process of hepatic carcinogenesis is unclear, many specifics have been explained. Signal transduction pathway engagement is known to slow the course of cancer and could be one of the objective constructions for systemic recovery. Nevertheless, there is a great deal of heterogeneity in HCC, and it is clear that the wide range of energies is required to represent the molecular genesis of HCC.

It is well established that chronic inflammatory effects and the spread of cancer are closely related. The genetic variability linked to long-term inflammatory exposure contributes to an increase in HCC cases. Aflatoxin and alcohol are examples of toxic sources, as are viral infections, among other inflammatory causes. Furthermore, metabolic disorders or imbalances, such as diabetes mellitus, can influence and spread long-term inflammatory reactions, which promotes the growth

of cancer. The carcinogenesis induced by infection is the focus of numerous diverse regulatory agents and signal pathways. Chronic inflammation causes early cellular death, telomere restriction, and genetic uncertainty as part of the cellular ageing mechanism. Hepatitis C propensity clearly illustrates the connection between long-term inflammatory exposure and virally-controlled immune abnormalities.

Immunological changes brought on by HCV-induced infections destroy hepatocytes, but developing new pathways at the same location keeps inflammation going, influences oxidative stress, and may harm DNA. At this point, HCC appears to move to hepatic expansion by developing persistent inflammation and increasing fibrosis. One of the vital trace elements with a variety of uses is zinc, and HCC is linked to low plasma concentrations of this element. Impurities, disruptions, anxiety, and malevolent pathways all raise plasma zinc levels. Reduced zinc meditations are correlated with elevated serum copper levels, and there is evidence linking elevated blood copper to the potential pathophysiology of HCC development. On the other hand, compared to the healthy liver parenchyma, the zinc concentration in HCC tissue was unusually low. About 18.5% of cases of HCC were found in a retrospective examination of patients with liver cirrhosis. Approximately 76.7% of these patients had zinc insufficiency. Zinc deficiency was found in 95% of chronic hepatitis C cases, while decreased zinc levels were seen in about 55% of instances of alcohol-induced cirrhosis. It is currently unclear if variations in zinc levels between serum and tissue promote the growth of tumours or, conversely, have an impact on the situation's malignant transformation.

“It has been proposed that these abnormalities may cause tumour growth by influencing Zn signal function, which guarantees the inhibitory or triggering properties on a broad variety of molecular assemblies, based on observations of

intracellular zinc levels in various malignancies. In addition, there are phosphates, caspase kinases, transcription factors, and receptors." As shown in the early studies on specific indicators of pancreatic and mammary cancer, a key component may accompany anomalies in the expression of several zinc transporters (Zip, ZnT). Throughout the development and progression of HCC, a prior study found a decrease in the Zip14 expression profile, which was correlated with a decrease in zinc concentrations.

REVIEW OF RELATED ARTICLES

Krishnakumar A et al (2024)[72] "By examining the prevalence of zinc deficiency in cirrhosis patients and evaluating its relationship to variables like alcohol consumption, albumin, prothrombin time, bilirubin, ascites, and the occurrence of hepatic encephalopathy, the current study aimed to confirm the relationship between serum zinc levels and the severity of cirrhosis." Investigate Males made up 88.6% of the study participants, while females made up 11.36%. The mean age was 52 years, and the disease burden was found to be higher among those aged 41 to 60 (66%) years. Additionally, a substantial difference in severity was observed between males and females. Furthermore, low serum zinc levels were substantially linked to patients with high Child-Pugh scores. About 75% of the cases developed ascites, which was significantly correlated with low serum zinc levels.

"Additionally, about 16% of the study participants developed hepatic encephalopathy with low serum zinc levels, and albumin levels were directly proportional to low serum zinc levels."

Nearly 72% of the patients had a positive history of alcohol use. Serum zinc levels were found to be significantly correlated with blood levels of sodium, prothrombin time, and total bilirubin.

Deep V et al (2023)[73] Patients with decompensated liver cirrhosis who were admitted to a tertiary care institution's medical intensive care unit were included in this prospective, observational study. They came to the conclusion that patients with decompensated cirrhosis of the liver have much lower serum zinc levels, and that these levels are linked to higher degrees of hepatic encephalopathy and a greater severity of the disease. Maintaining appropriate serum zinc levels may help individuals with decompensated liver cirrhosis avoid developing hepatic encephalopathy.

Rani P et al (2023)[74] Assessing serum zinc levels in liver cirrhosis patients and determining whether there is a relationship between the severity of the disease and serum zinc status were the goals of the current investigation. They came to the conclusion that patients with liver cirrhosis had decreased zinc levels. Patients with worsening illness severity had a more severe zinc deficit. Liver cirrhosis may develop as a result of low zinc levels. Zinc levels are therefore helpful in the prompt treatment of these patients as well as in preventing the development of hepatic encephalopathy and the worsening of cirrhosis.

A study conducted by **Azhar Satta et al in Saudi Arabia, March 2021**,[75] out of 220 patients, low Zinc levels were seen in 136 patients and concluded that serum zinc levels were less in 61.8% cirrhosis of liver patients.

Itaru Ozeki et al also studied in 2020,[76] Japan in 1,973 patients with chronic liver disease, which in 749 with cirrhosis of liver. In 555 patients low Zinc levels were seen which is 28.1% , which include 182 patients without liver cirrhosis and 373 (49.8%) with cirrhosis of liver and concluded that levels Zinc levels were common in patients with CLD.[4]

In a study by **Kazuhiro Katayama et al in 2018**,[77] Japan , out of 235 cirrhosis patients , blood zinc levels were less than 70 µg/dL in 88% of patients , concluded that low Zinc levels were prevalent in cirrhosis patients.

Kamani L et al (2018)[78] "This study's goal was to measure the zinc levels in the serum of patients with viral cirrhosis and contrast them with those of healthy, normal controls." This study included 45 participants in total. Thirteen individuals, or 28.9% of the total, had zinc insufficiency. Groups 1, 2, and 3 had mean zinc levels of 68.09±20.85, 50.69±15.86, and 92.91±17.18µg/dL, respectively. The three groups' mean zinc levels showed a highly significant difference (p=0.0001). The Child Pugh Score and the serum zinc level showed a negative relationship (r=-0.498). They came to the conclusion that serum zinc levels seemed to be lower in patients with advanced cirrhosis. Zinc supplementation may enhance the clinical outcome for patients with hepatic encephalopathy who have viral cirrhosis.

Sahar A. El-Nemr et al (2015)[79] observed in Zagazig University, Egypt. Out of Seventy-five patients with chronic HCV. The serum concentration of zinc decreased significantly in chronic HCV and has been implicated in liver disease progression.[5]

MATERIAL AND METHODS

- **Study design:** Cross-sectional study
- **Study area:** Inpatients and Outpatients of Department of General Medicine, Shri B M Patil Medical College and Research Centre, Vijayapura, Karnataka, India.
- **Study period:** Research study was conducted from May 2023 to December 2024.

Below is the work plan.

Table 2: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	% of allocation of study time	Duration in months
Understanding the problem, preparation of questionnaire.	5-10%	May 2023
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	June 2023 to May 2024
Analysis and interpretation	5-10%	June 2024 to August 2024
Dissertation write-up and submission	5-10%	September 2024 to December 2024

- **Sample size**: Using G*Power Ver 3.1.9.4 software for sample size calculation, The Correlation between Serum Zinc and Total bilirubin (r=0.222, p=0.0053)[80], this study requires a sample size of 85, to achieve a power of 98% for detecting a difference in Means: **Exact -** Correlation: Bivariate normal model with 5% level of significance.

Inclusion criteria:

All cases having liver cirrhosis as a diagnosis by clinical and USG abdomen of any etiology.

Exclusion criteria:

1. People who have received any zinc preparations orally previously.
2. History or evidence of inflammatory bowel disease.

METHODOLOGY:

Study Design and Setting

This observational study was conducted at BLDE (Deemed to be University) Shri B.M. Patil Medical College Hospital and Research Center, Vijayapura, from May 2023 to December 2024. The study included patients from both outpatient and inpatient departments who presented with clinical features, biochemical, and radiological evidence of liver cirrhosis.

Patient Selection and Assessment

Patients were recruited based on predetermined inclusion and exclusion criteria. A comprehensive medical history was obtained from all participants, followed by thorough clinical examination. The diagnosis of liver cirrhosis was confirmed through ultrasonographic examination. Detailed patient information was collected using a standardized proforma that included demographic data, clinical presentations, and risk factors for liver disease.

Laboratory Investigations

Blood samples were collected from all participants at the time of admission for various laboratory investigations. For serum zinc analysis, 3mL of blood was collected in plain tubes containing clot activator. These samples were incubated at room temperature for 30 minutes, followed by centrifugation at 3000 rpm for 10

minutes. The separated serum was analyzed using photometry to determine zinc levels.

"Routine investigations included complete blood count, random blood sugar, renal function tests, and electrocardiography. Specific investigations comprised liver function tests, blood albumin levels, prothrombin time, and international normalized ratio (INR). Viral markers including HBsAg and HCV were assessed using rapid diagnostic tests." All participants underwent abdominal ultrasonography for confirmation of cirrhosis and evaluation of portal hypertension.

Disease Severity Assessment

"The severity of liver cirrhosis was evaluated using the Child-Pugh scoring system, which assessed five parameters: hepatic encephalopathy, ascites, serum bilirubin, serum albumin, and prothrombin time."

"Based on the total score, patients were classified into three categories:

- Class A : 5-6 points , includes well-compensated cirrhosis
- Class B : 7-9 points , includes partially decompensated cirrhosis, and
- Class C : 10-15 points, severe decompensated cirrhosis."

Quality Control Measures

All laboratory tests were performed in accordance with standard operating procedures. The biochemistry laboratory participated in different quality control programs to confirm the accuracy of test results. Ultrasonographic examinations were performed by experienced radiologists using standardized protocols.

Data Collection and Management

Patient data was systematically collected using a structured proforma. This included demographic information, clinical findings, laboratory results, and Child-Pugh scores. To ensure data quality, all entries were verified by two independent

investigators. Confidentiality of patient information was maintained throughout the study period.

Standardization of Procedures

Blood collection and processing for zinc analysis followed a standardized protocol to minimize pre-analytical variations. Samples were processed within the recommended time frame, and appropriate quality control measures were implemented during the analytical phase. The assessment of clinical parameters for the Child-Pugh score was standardized among all participating physicians to ensure consistency in scoring.

STATISTICAL ANALYSIS

“The data was entered into an Excel sheet and analyzed using SPSS version 21. The results were displayed in tabular and graphical formats. The quantitative data were calculated using mean, median, standard deviation, and ranges, while the qualitative data were expressed as frequency and percentages. The significance of the mean was tested using the Student t test (Two Tailed), and a P value of less than 0.05 was deemed significant.”

RESULTS

The present cross sectional study was conducted among 85 patients having liver cirrhosis attending OPD and IPD in BLDE (Deemed to be University) Shri BM Patil Medical College hospital and research center, Vijayapura to compare zinc levels in liver cirrhosis and evaluate the severity using Child Pugh Score.

Following are the study findings:

Table 3: Distribution of patients according to age

Age (in years)	Frequency	Percentage
<30	06	7.1%
31-40	19	22.4%
41-50	29	34.1%
51-60	22	25.9%
>60	09	10.6%
Total	**85**	**100%**

The study included 85 patients with liver cirrhosis. The majority of patients fell in the middle-age groups, with 34.1% (29 patients) in the 41-50 years age group and 25.9% (22 patients) in the 51-60 years age group. Only 7.1% (6 patients) were under 30 years old, while 22.4% (19 patients) were between 31-40 years. The elderly population (>60 years) comprised 10.6% (9 patients). This distribution suggests that liver cirrhosis predominantly affected middle-aged adults in this study population.

Figure 10 **: Distribution of patients according to age**

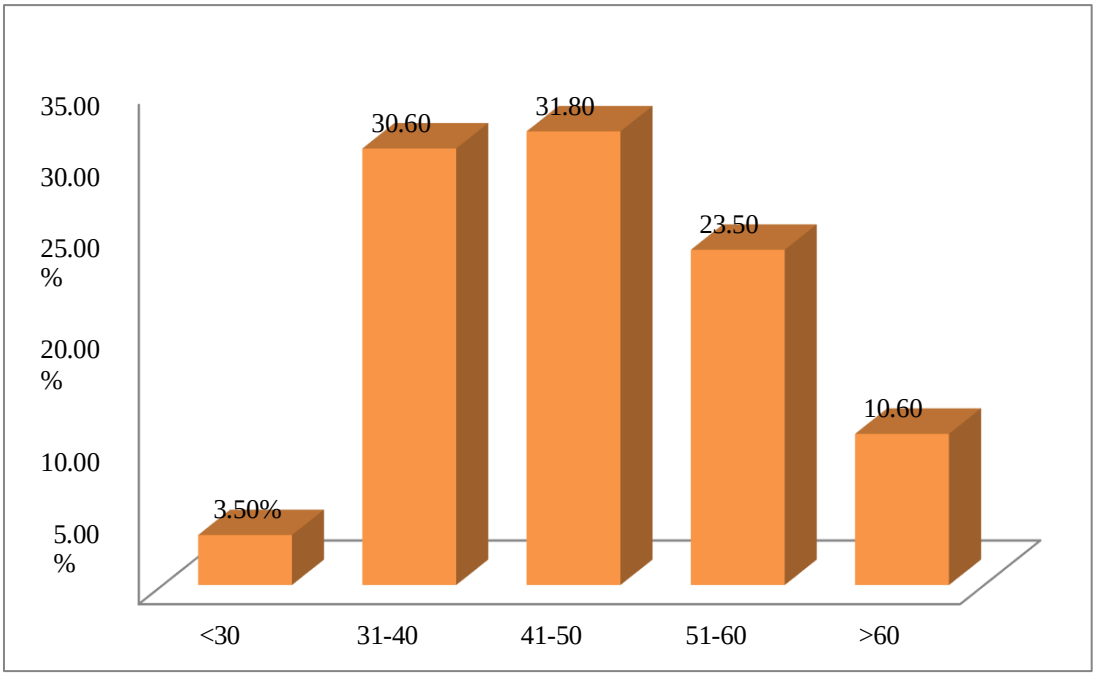


Table 4: Distribution of patients according to Gender

Gender	Frequency	Percentage
Female	4	4.7%
Male	81	95.3%
Total	**85**	**100%**

There was a striking gender disparity in the study population. Males constituted an overwhelming majority at 95.3% (81 patients), while females represented only 4.7% (4 patients). This significant male predominance could be related to the primary etiology of cirrhosis in this population.

Figure 11**: Distribution of patients according to Gender**

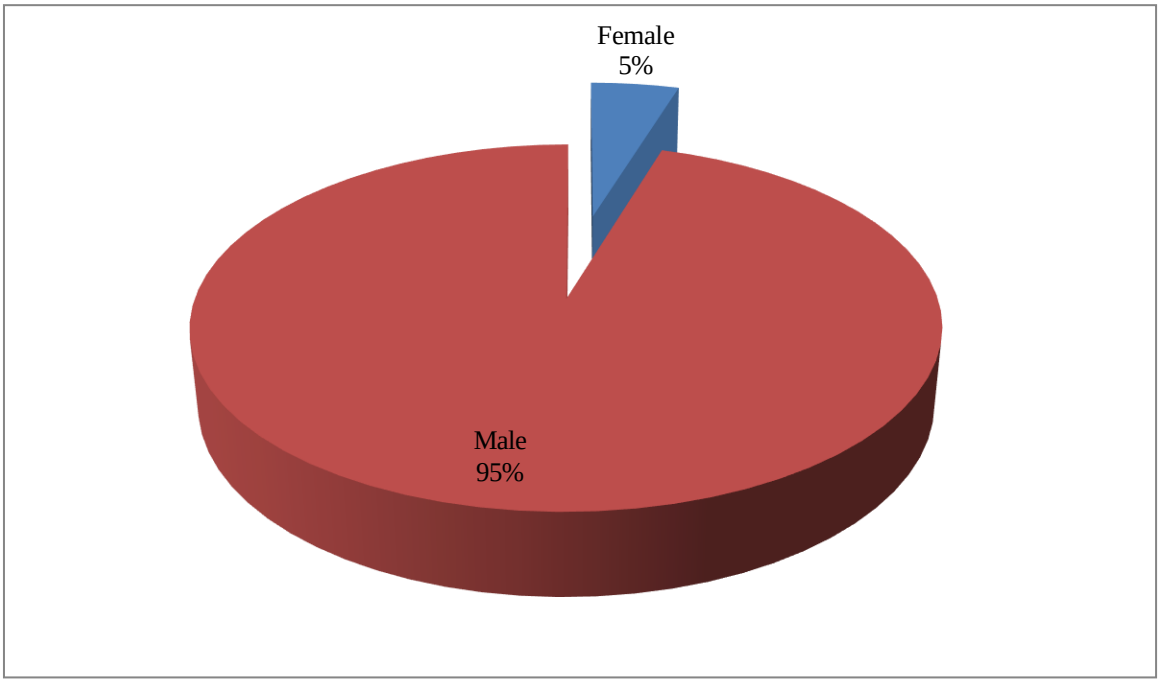


Table 5: Distribution of patients according to Etiology

Etiology	Frequency	Percentage
Alcohol	76	89.4%
Hepatitis B	05	5.9%
Hepatitis C	04	4.7%
Total	**85**	**100%**

Alcohol was overwhelmingly the primary cause of liver cirrhosis in this study, accounting for 89.4% (76 patients). Viral causes were much less common, with Hepatitis B responsible for 5.9% (5 patients) and Hepatitis C for 4.7% (4 patients). This distribution strongly correlates with the male predominance noted earlier, as alcoholic liver disease is more common in males.

Figure 12**: Distribution of patients according to Etiology**

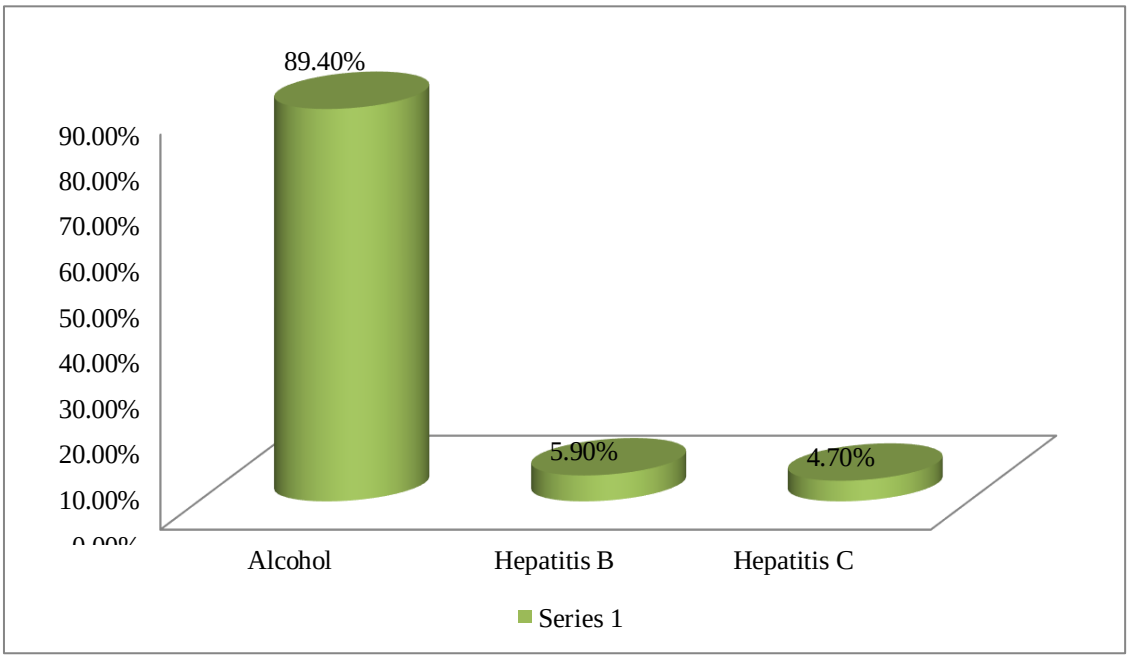


Table 6: Distribution of patients according to Alcohol Consumption

Alcohol Consumption	Frequency	Percentage
<60gms/day	11	14.5%
60+ gms/day	65	85.5%
Total	**76**	**100%**

Alcohol was overwhelmingly the primary cause of liver cirrhosis in this study, accounting for 89.4% (76 patients). Among them 11(14.5%) consumed less than **<60gms/day** whereas 65 (85.5%) consumed more than **60gms/day** of alcohol.

Figure 13**: Distribution of patients according to Alcohol Consumption**

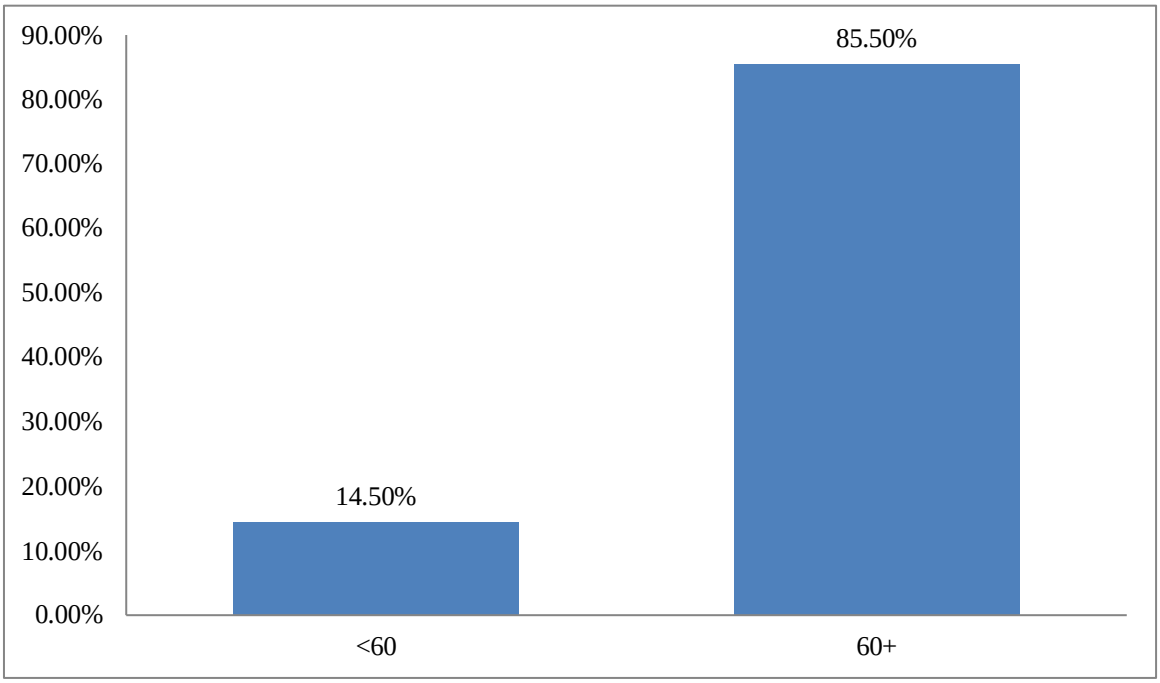


Table 7: Distribution of patients according to Child Pugh Score

Child Pugh Score	Frequency	Percentage
Class A	4	4.7%
Class B	24	28.2%
Class C	57	67.1%
Total	**85**	**100%**

The Child Pugh Score, which measures the severity of liver cirrhosis, showed that most patients had advanced disease. Class C (most severe) comprised 67.1% (57 patients), followed by Class B at 28.2% (24 patients), and only 4.7% (4 patients) in Class A (least severe). This indicates that the majority of patients presented with advanced liver disease.

Figure 14**: Distribution of patients according to Child Pugh Score**

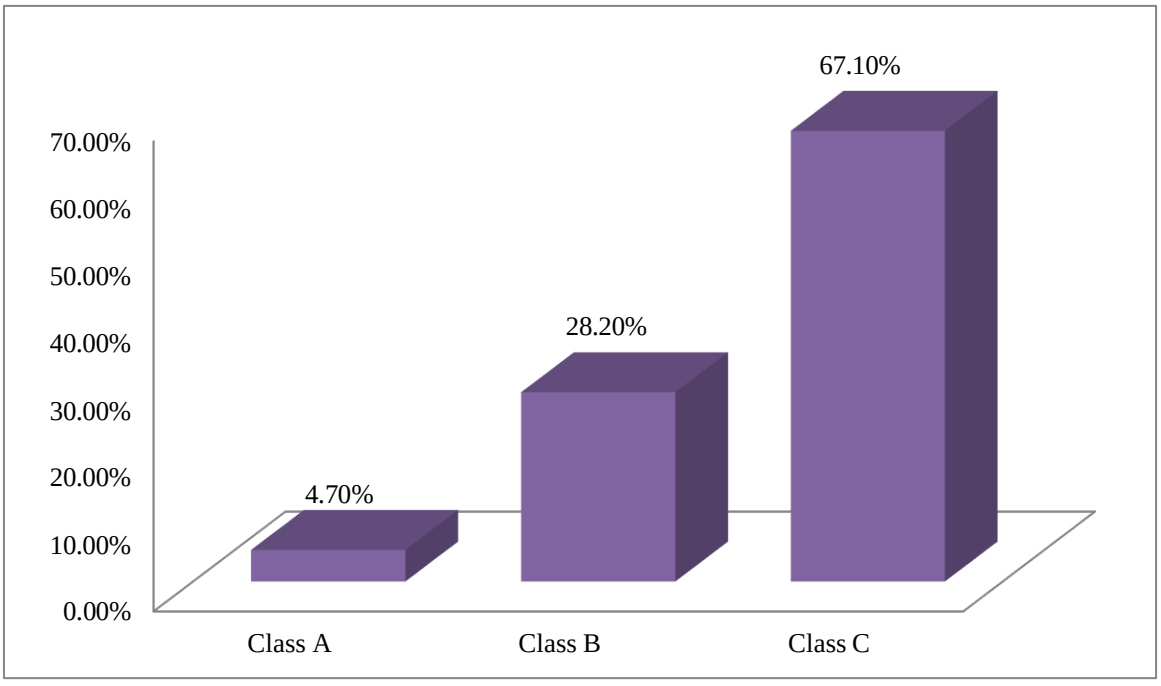


Table 8: Distribution of patients according to Severity of Ascitis

Ascitis	Frequency	Percentage
Mild	5	5.9%
Moderate	27	31.8%
Severe	53	62.4%
Total	**85**	**100%**

Ascitis (fluid accumulation in the abdomen) was predominantly severe, affecting 62.4% (53 patients). Moderate ascitis was present in 31.8% (27 patients), while only 5.9% (5 patients) had mild ascitis. This distribution mirrors the Child Pugh Score findings, confirming the advanced nature of disease in most patients.

Figure 15**: Distribution of patients according to Severity of Ascitis**

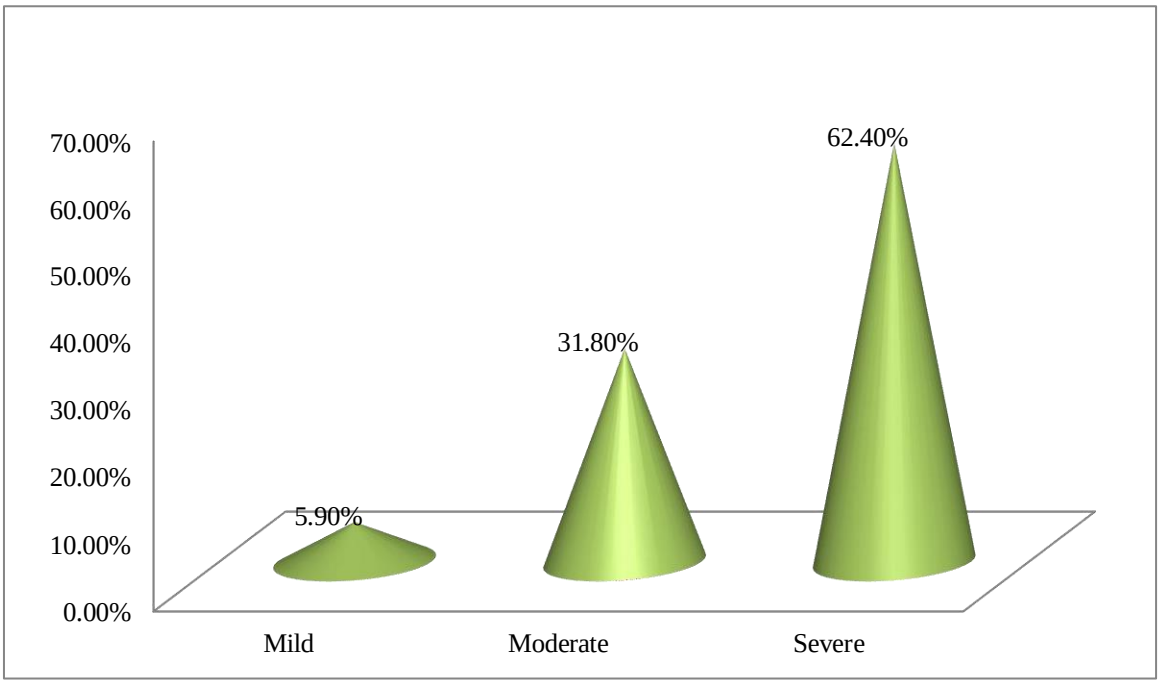


Table 9: Distribution of patients according to Zinc Levels

Zinc	Frequency	Percentage
Zinc deficiency (<51)	83	97.6%
Normal (52-286)	2	2.4%
Total	**85**	**100%**

An overwhelming majority of patients (97.6%, 83 patients) had zinc deficiency (<51mcg/dl), while only 2.4% (2 patients) had normal zinc levels (52-286mcg/dl). This suggests a strong correlation between liver cirrhosis and zinc deficiency.

Figure 16**: Distribution of patients according to Zinc Levels**

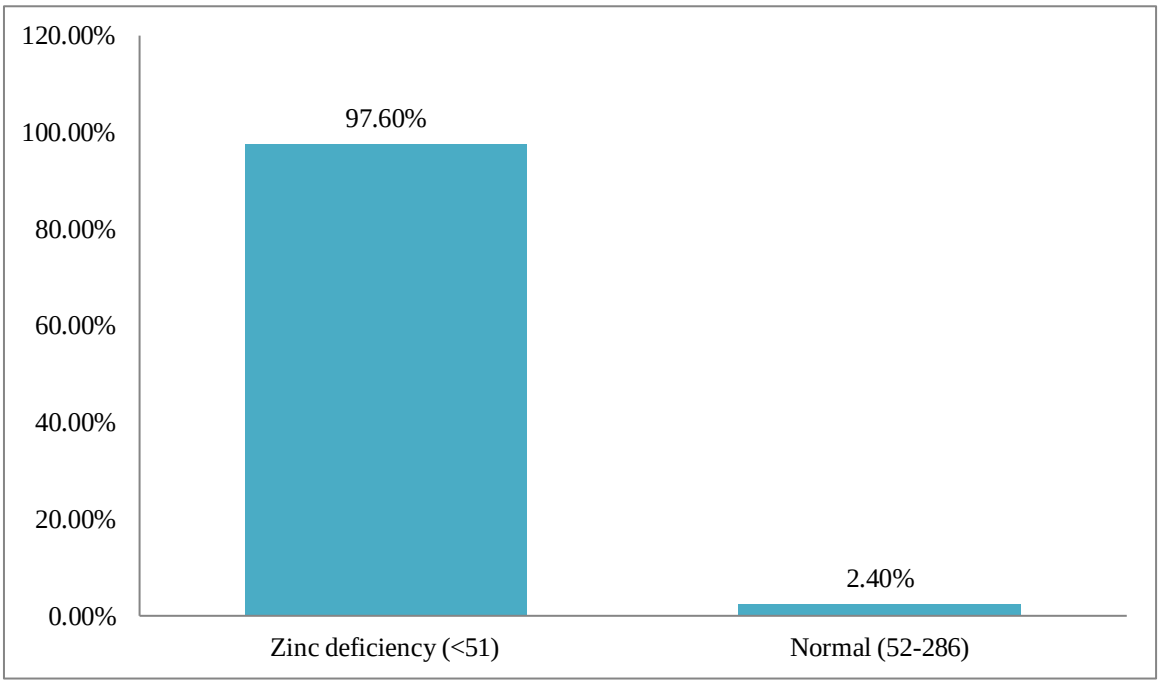


Table 10: Distribution of patients according to Albumin Levels

Albumin	Frequency	Percentage
Reduced (<3.3)	83	97.6%
Normal (3.4-5.4)	2	2.4%
Total	**85**	**100%**

The albumin distribution exactly matched the zinc level distribution, with 97.6% (83 patients) showing reduced levels (<3.3) and only 2.4% (2 patients) having normal levels (3.4- 5.4). This parallel suggests a possible relationship between zinc and albumin levels in cirrhotic patients.

Figure 17**: Distribution of patients according to Albumin Levels**

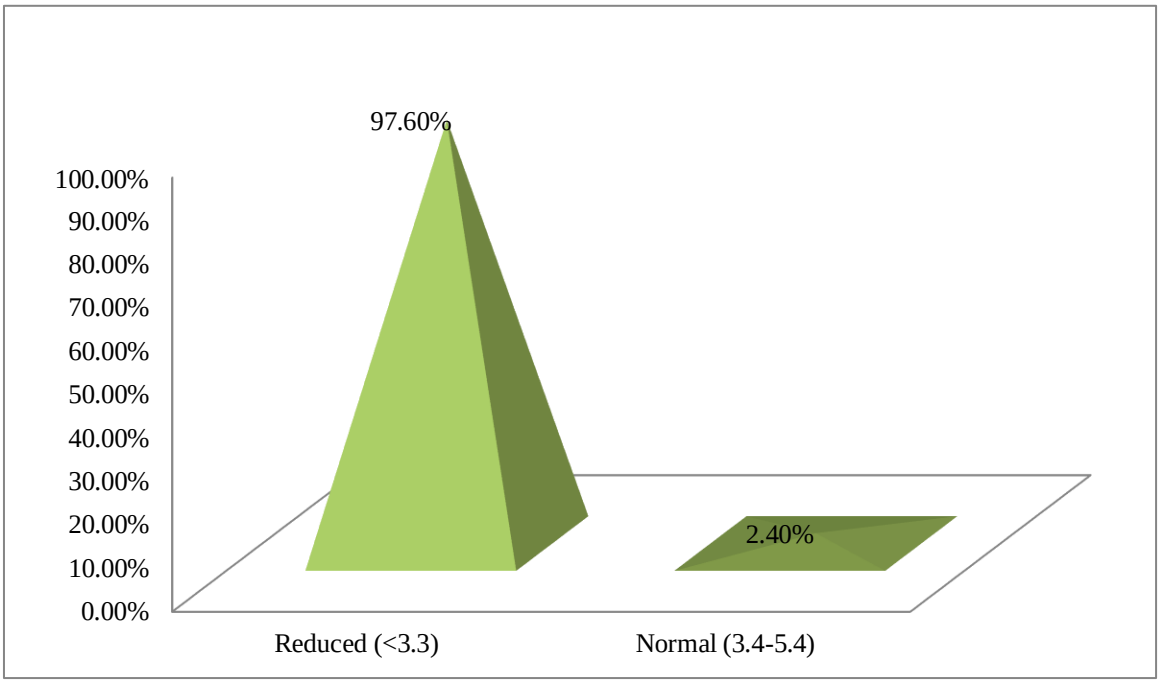


Table 11: Distribution of patients according to Zinc Levels with Child Pugh Scores

Zinc	CLASS A	CLASS B	CLASS C
Zinc deficiency (<51)	3 (75%)	23 (95.8%)	57 (100%)
Normal (52-286)	1 (25%)	1 (4.2%)	0
Total	**4 (100%)**	**24 (100%)**	**57 (100%)**
P value	**0.005**		

This important cross-tabulation shows a significant relationship (p=0.005) between zinc deficiency and disease severity. Zinc deficiency was present in 75% of Class A patients, 95.8% of Class B patients, and 100% of Class C patients. This demonstrates that zinc deficiency becomes more prevalent as liver disease severity increases.

Figure 18**: Distribution of patients according to Zinc Levels with Child Pugh Scores**

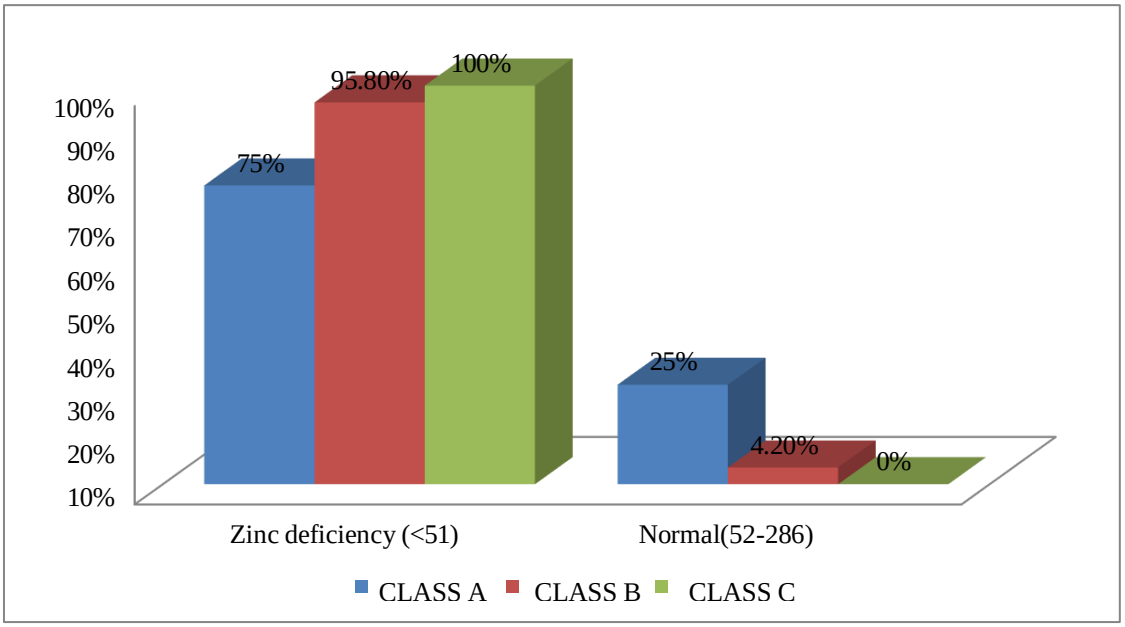


Table 12: Comparison of mean Zinc Levels according to Child Pugh Score

Zinc	CLASS A	CLASS B	CLASS C	P value
Mean + SD	50.4 + 4.31	42.32 + 4.86	37.02 + 3.68	<0.001

The analysis shows a significant ($p<0.001$) inverse relationship between zinc levels and disease severity. Mean zinc levels decreased from Class A (50.4±4.31) to Class B (42.32±4.86) to Class C (37.02±3.68), indicating that zinc levels drop as liver disease worsens.

Figure **19: Comparison of mean Zinc Levels according to Child Pugh Score**

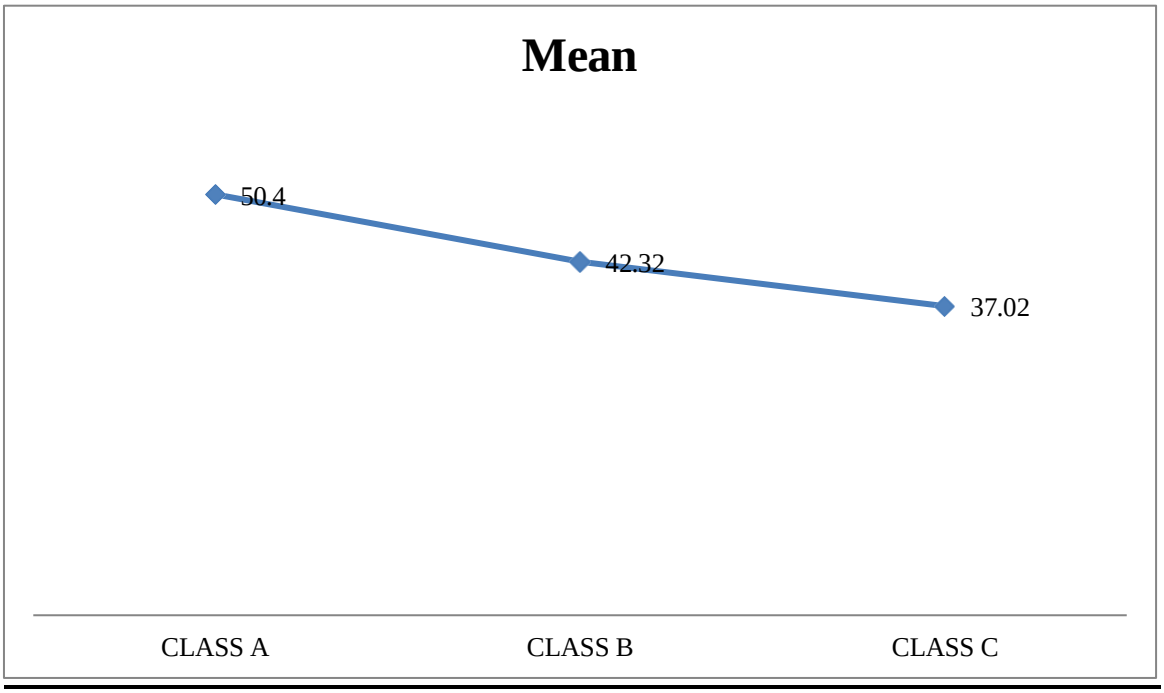


Table 13: Distribution of patients according to outcome

Outcome	Frequency	Percentage
Alive	72	84.7%
Death	13	15.3%
Total	**85**	**100%**

The mortality rate in the study was 15.3% (13 patients), while 84.7% (72 patients) survived. This provides important prognostic information about the study population.

Figure 20**: Distribution of patients according to outcome**

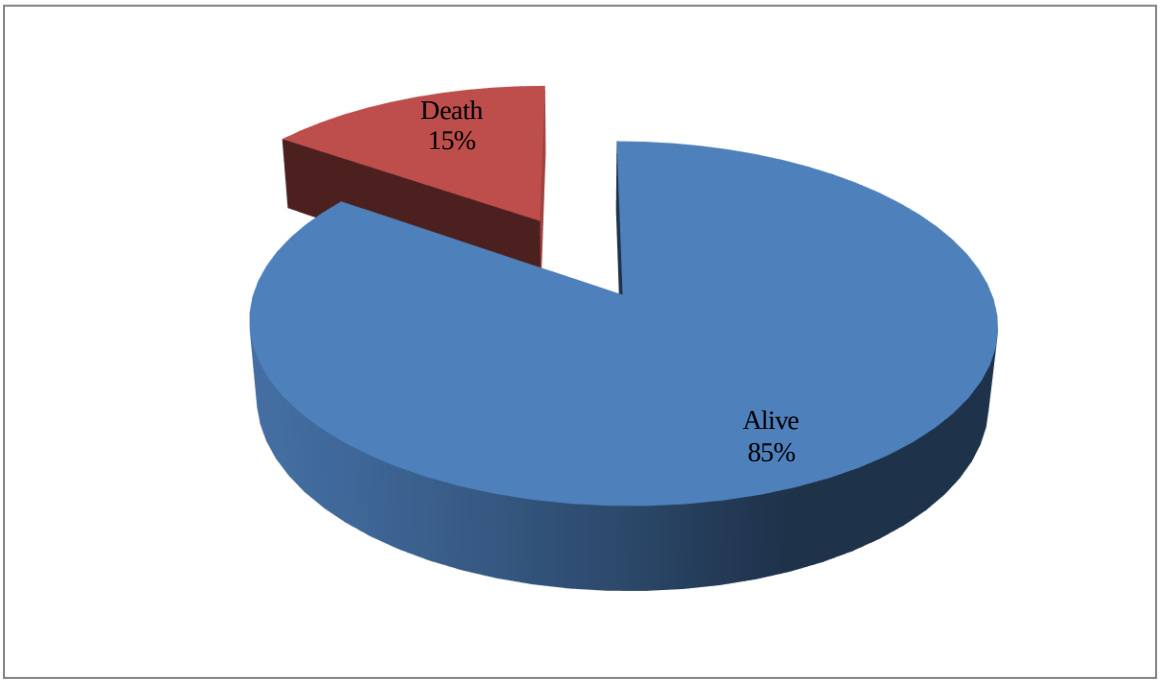


Table 14: Distribution of Zinc Levels

Variable		Zinc deficiency (83)	Normal (2)	P value
Age	**<30**	3 (3.5%)	0	0.029
	31-40	26 (31.3%)	0	
	41-50	27 (32.5%)	0	
	51-60	20 (24.1%)	0	
	>60	07 (8.4%)	02 (100%)	
Gender	**Female**	4 (4.8%)	0	0.75
	Male	79 (95.2%)	2 (100%)	
Etiology	**Alcohol**	74 (89.2%)	2 (100%)	0.21
	Hepatitis B	5 (6%)	0	
	Hepatitis C	4 (4.8%)	0	

Age distribution showed a significant relationship with zinc levels (p=0.029), with all patients under 60 showing zinc deficiency, while 2 patients >60 had normal levels. Gender distribution showed no significant relationship with zinc levels (p=0.75). Etiology showed no significant relationship with zinc levels (p=0.21), though zinc deficiency was present across all etiologies.

Table 15: Correlation of serum zinc with child pugh score and serum albumin

Serum Zinc	Correlation co-efficient	P value
Child pugh score	-0.576	**<0.001**
Serum Albumin	0.326	**0.002**

The correlation between serum zinc and child pugh score showed the correlation co- efficient (r) as -0.576, which was statistically significant (p<0.001) The negative correlation coefficient (r = -0.576) indicates an inverse relationship between serum zinc levels and Child- Pugh score in patients with liver cirrhosis. The strength of this correlation (-0.576) is considered moderate to strong. This means that as the Child-Pugh score increases (indicating worsening liver function/more severe cirrhosis), the serum zinc levels decrease. The correlation we found between serum zinc and serum albumin (r=0.326, p=0.002) was statistically significant. This positive correlation suggests that as serum albumin levels decrease, serum zinc levels tend to decrease as well.

Figure 21a: Correlation between serum zinc and child pugh score

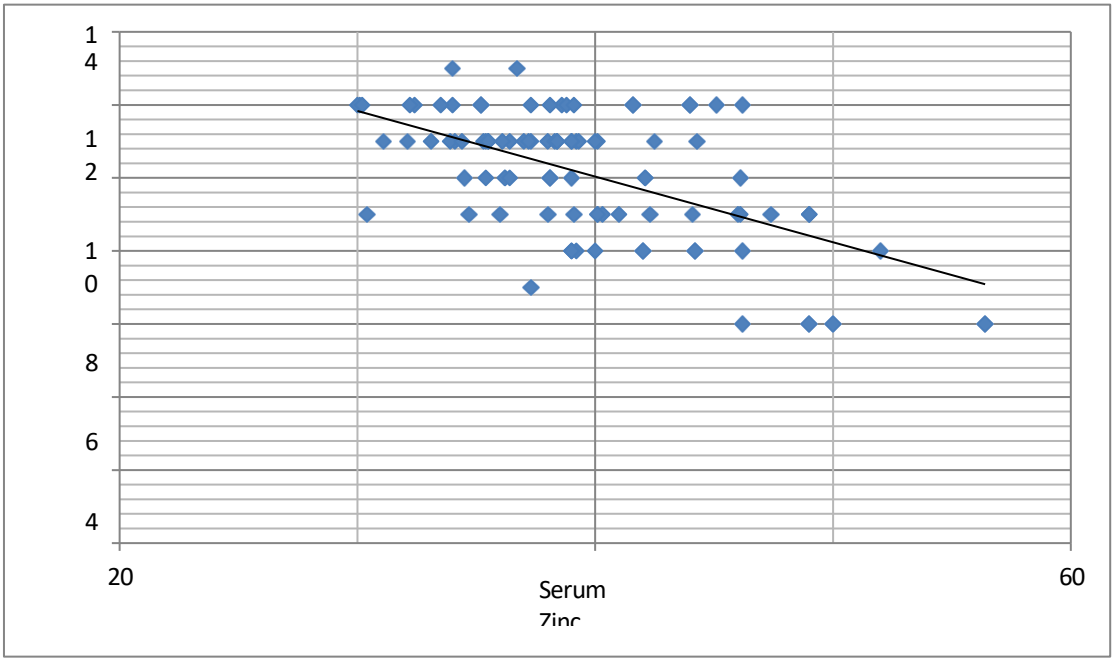
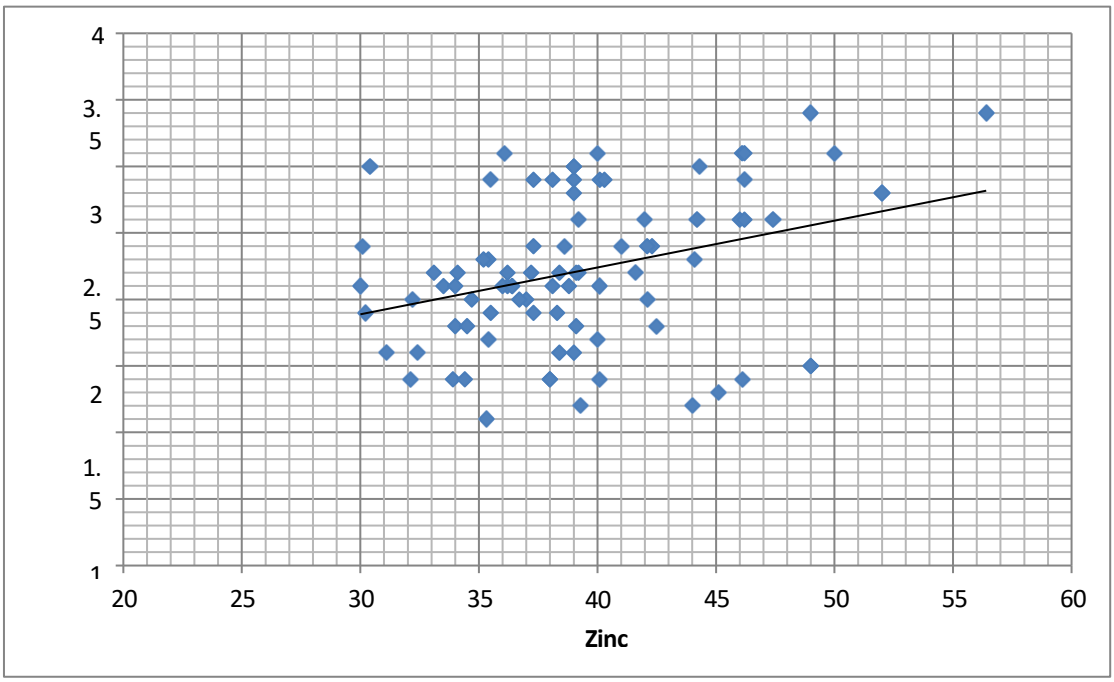


Figure 21b: Correlation between serum albumin and serum zinc



DISCUSSION

Liver cirrhosis represents the final common pathway for a wide spectrum of chronic liver diseases, characterized by fibrosis, architectural distortion, and the formation of regenerative nodules. This progressive condition leads to hepatic dysfunction and portal hypertension, manifesting with complications such as ascites, hepatic encephalopathy, and esophageal varices. Within the intricate pathophysiology of liver cirrhosis, micronutrient imbalances have emerged as significant contributors to disease progression and clinical manifestations. Zinc, an essential trace element involved in over 300 enzymatic reactions, has garnered particular attention given its critical role in protein synthesis, immune function, DNA synthesis, and antioxidant defense mechanisms. The liver plays a central role in zinc homeostasis, and the disruption of hepatic function in cirrhosis can significantly impact zinc metabolism. This study was undertaken to evaluate the relationship between serum zinc levels and liver cirrhosis severity as measured by the Child-Pugh classification system, with the aim of better understanding the clinical implications of zinc deficiency in this patient population and potentially identifying therapeutic targets to improve patient outcomes.

Demographic and Clinical Profile

Our cross-sectional study conducted among 85 cirrhotic patients at BLDE University's Shri BM Patil Medical College Hospital revealed striking demographic patterns. The age distribution demonstrated a predominance of middle-aged adults, with 34.1% falling within the 41-50 years age group and 25.9% in the 51-60 years range. This observation aligns with findings from Sajja KC et al., who reported a similar age distribution pattern with the majority of cirrhotic patients falling within the fourth and fifth decades of life.[81] The middle-age predominance likely reflects the

natural history of liver diseases, particularly alcoholic liver disease, which typically requires years of exposure before progressing to cirrhosis.

A remarkable gender disparity was observed in our study population, with males constituting 95.3% of the cohort compared to only 4.7% females. This pronounced male predominance exceeds the generally reported male-to-female ratios in cirrhosis. Mohan et al. documented a male-to-female ratio of 4:1 in their study of cirrhotic patients in South India[82], while international data from Mokdad et al. suggested a global male predominance with ratios varying from 2:1 to 3:1 depending on geographical regions.[83] The extraordinarily high male percentage in our study can be primarily attributed to the etiology profile, where alcohol was the predominant cause (89.4%), with viral hepatitis accounting for only a small fraction (Hepatitis B: 5.9%, Hepatitis C: 4.7%).

The overwhelming contribution of alcohol to cirrhosis etiology in our study (89.4%) significantly exceeds the proportions reported in other Indian studies. Sharma et al. reported alcohol as the etiology in 64% of cirrhotic patients in North India[84]. The particularly high alcoholic etiology in our sample may reflect regional drinking patterns, socioeconomic factors, or referral patterns to our institution. This finding underscores the critical importance of alcohol control measures in reducing the burden of liver cirrhosis in this specific population.

Disease Severity Assessment

The Child-Pugh classification has remained a cornerstone in assessing the severity of liver cirrhosis for decades. Our study revealed that the majority of patients presented with advanced disease: 67.1% were categorized as Child-Pugh Class C (most severe), while 28.2% fell into Class B, and only 4.7% in Class A (least severe). This preponderance of advanced disease mirrors findings from several Indian studies.

Deep V et al. reported that 58.2% of their cirrhotic cohort presented with Child-Pugh Class C[85], and similarly, Kumar D et al. found that 52% of patients in their study had advanced cirrhosis (Child-Pugh C) at presentation.[86]

The high proportion of patients with advanced disease can be attributed to multiple factors. First, the predominantly alcoholic etiology in our cohort is associated with poor treatment adherence and continued hepatotoxic insults. Second, there is often a significant delay in seeking medical attention, with many patients presenting only after developing complications. Patel KM et al. documented that of 667 patients with cirrhosis or HCC, 133 (20%) had a missed CLD diagnosis, and 243 (36%) had a delayed CLD diagnosis.[87] Third, the largely rural and semi-urban catchment area of our institution may contribute to delayed healthcare access due to geographical, financial, or awareness barriers.

The severity distribution was further reflected in the ascites profiles, with 62.4% of patients presenting with severe ascites, 31.8% with moderate ascites, and only 5.9% with mild ascites. This closely parallels the Child-Pugh classification distribution, as ascites is one of the parameters assessed in this scoring system. The high incidence of severe ascites underscores the advanced nature of liver dysfunction in our patient population and aligns with data from Mahale et al., who reported Ascites is the most common cause of decompensation in cirrhosis, as 5% to 10% of patients with compensated cirrhosis per year develop this complication.[88]

Zinc Deficiency in Liver Cirrhosis

Our study revealed a strikingly high prevalence of zinc deficiency among cirrhotic patients, with 97.6% exhibiting levels below the normal threshold (<51 µg/dL). This exceeds the prevalence reported in several comparable studies. Sengupta S et al. found zinc deficiency in 83% of cirrhotic patients[89], while Grungreiff et al.

reported a prevalence of 83.9% in their European cohort.[90] The higher prevalence in our study may be attributed to multiple factors, including nutritional status, the predominance of alcoholic etiology, and the advanced stage of liver disease in our patient population.

Interestingly, we observed a significant inverse relationship between zinc levels and disease severity as measured by the Child-Pugh classification ($p<0.001$). Mean zinc levels progressively decreased from Child-Pugh Class A (50.4±4.31 μg/dL) to Class B (42.32±4.86 μg/dL) to Class C (37.02±3.68 μg/dL). This gradient of zinc deficiency across disease severity classes has been documented in multiple studies. Sengupta S et.al.[89] reported that the zinc deficiency was significantly higher in patients with Child–Pugh B or C cirrhosis than in those with Child–Pugh A, or in those with MELD score 15 or higher; in fact, more than 90 % of these subgroups of patients were found to be zinc deficient. Katayama et al. demonstrated that zinc levels declined proportionally with worsening Child-Pugh scores, reporting the correlation co-efficient of 0.469 ($p<0.001$).[91] Similarly, Stamoulis et al. found a significant negative correlation between serum zinc concentrations and Child-Pugh scores ($r = -0.65$, $p<0.001$).[92]

Our cross-tabulation analysis further reinforced this relationship, showing that zinc deficiency was present in 75% of Child-Pugh Class A patients, 95.8% of Class B, and 100% of Class C patients ($p=0.005$). This progressive increase in the prevalence of zinc deficiency with worsening liver function suggests that zinc depletion either contributes to or results from the pathophysiological processes that drive disease progression in cirrhosis.

Pathophysiology of Zinc Deficiency in Cirrhosis

The remarkably high prevalence of zinc deficiency in our cirrhotic population warrants a detailed examination of the underlying pathophysiological mechanisms. Zinc homeostasis is disrupted in liver cirrhosis through multiple pathways, creating a complex picture of deficiency that worsens with disease progression.

First, dietary intake of zinc is often compromised in cirrhotic patients due to anorexia, altered taste perception, and dietary restrictions often imposed to manage complications such as ascites and hepatic encephalopathy. Lactulose, commonly prescribed for hepatic encephalopathy, can further reduce zinc absorption through its chelating effects. Gopal et al. demonstrated that cirrhotic patients consumed approximately 40% less dietary zinc compared to healthy controls.[93]

Second, intestinal absorption of zinc is impaired in cirrhosis. Portal hypertension leads to intestinal edema and altered gut mucosal integrity, affecting the absorption of micronutrients. Mohammad MK et al. documented a 30% reduction in zinc absorption in cirrhotic patients compared to healthy controls using zinc isotope studies.[94] Additionally, alcohol, the predominant etiology in our cohort, directly damages intestinal mucosa and reduces zinc absorption even before cirrhosis develops.

Third, increased zinc losses occur through several routes in cirrhosis. Hepatorenal syndrome and diuretic therapy enhance urinary zinc excretion. Soomro et al. found that urinary zinc excretion was 2.8 times higher in cirrhotic patients compared to controls.[95] Gastrointestinal bleeding, a common complication in advanced cirrhosis, represents another route of zinc loss.

Each unit of blood contains approximately 1 mg of zinc, and recurrent bleeding episodes can substantially deplete zinc stores.

Fourth, albumin synthesis is reduced in cirrhosis, affecting zinc transport in circulation.

Our study found a striking parallel between zinc and albumin deficiency, with both showing 97.6% prevalence in our cohort. This is not coincidental, as approximately 80% of circulating zinc is bound to albumin. Sengupta et al. demonstrated a strong positive correlation ($r=0.73$, $p<0.001$) between serum zinc and albumin levels in cirrhotic patients.[89] The reduced albumin not only affects zinc transport but also its bioavailability to tissues.

Fifth, chronic inflammation in cirrhosis increases the production of cytokines like interleukin-6, which upregulates hepatic production of metallothionein. This protein sequesters zinc in the liver, reducing its availability in circulation. Murata K et al. found that metallothionein levels were elevated in cirrhotic patients and inversely correlated with serum zinc levels.[96]

Finally, oxidative stress, a key feature in the pathogenesis of liver cirrhosis, depletes antioxidant reserves including zinc-dependent enzymes like superoxide dismutase. This creates a vicious cycle where zinc deficiency exacerbates oxidative damage, which further drives disease progression. Prasad et al. demonstrated that oxidative stress markers were significantly higher in zinc-deficient cirrhotic patients compared to those with normal zinc levels.[97]

Clinical Implications of Zinc Deficiency

The clinical implications of zinc deficiency in cirrhosis extend far beyond its role as a biomarker of disease severity. Zinc deficiency directly contributes to many of the clinical manifestations and complications seen in cirrhotic patients, potentially accelerating disease progression and worsening prognosis.

Hepatic encephalopathy (HE) has been strongly linked to zinc deficiency.

Zinc is essential for the proper functioning of urea cycle enzymes, particularly ornithine transcarbamylase, which detoxifies ammonia in the liver. In zinc deficiency, ammonia metabolism is compromised, increasing the risk of HE. Takuma et al. conducted a placebo- controlled trial that demonstrated zinc supplementation reduced the incidence of HE episodes by 45% over a 6-month period compared to standard treatment alone.[98] Similarly, Chavez- Tapia et al. in their meta-analysis found that zinc supplementation significantly improved psychometric test performance in cirrhotic patients with minimal hepatic encephalopathy.[99]

Immune dysfunction is another significant consequence of zinc deficiency in cirrhosis. Zinc is crucial for both innate and adaptive immune responses, including neutrophil function, natural killer cell activity, and T-cell maturation. The increased susceptibility to infections observed in cirrhotic patients may be partly attributed to zinc deficiency. Mohammad et al. reported that cirrhotic patients with zinc deficiency had a 2.4-fold higher risk of developing spontaneous bacterial peritonitis compared to those with normal zinc levels.[100] This is particularly relevant given that infections are a leading cause of mortality in cirrhosis.

Reduced wound healing and tissue repair capabilities associated with zinc deficiency may contribute to the development of pressure ulcers, prolonged recovery from procedures, and poor surgical outcomes in cirrhotic patients. Zinc is essential for collagen synthesis, fibroblast proliferation, and epithelialization. Lin PH et al. demonstrated that zinc-deficient cirrhotic patients had significantly delayed wound healing ranging from membrane repair, oxidative stress, coagulation, inflammation and immune defense, tissue re-epithelialization, angiogenesis, to fibrosis/scar formation. With huge demands for improved wound care.[101]

Taste and appetite disturbances are common in cirrhosis and are exacerbated by zinc deficiency. Zinc is required for the function of gustin, a protein essential for normal taste perception. Madden et al. found that zinc supplementation improved taste acuity and dietary intake in cirrhotic patients, potentially addressing the malnutrition that often complicates the disease.[102]

Skeletal manifestations, including osteopenia and osteoporosis, are increasingly recognized complications of cirrhosis. Zinc deficiency contributes to bone disease through its effects on osteoblast activity and regulation of parathyroid hormone. Mikolasevic et al. reported that zinc-deficient cirrhotic patients had significantly lower bone mineral density compared to those with normal zinc levels, independent of other risk factors.[103]

The relationship between zinc deficiency and mortality in cirrhosis has been examined in several studies. In our cohort, we observed a 15.3% mortality rate during the study period. Though we did not specifically analyze the relationship between zinc levels and mortality, several studies have demonstrated this association.

Zinc Supplementation in Cirrhosis: Therapeutic Implications

Given the high prevalence of zinc deficiency in our study (97.6%) and its association with disease severity, zinc supplementation emerges as a potential therapeutic intervention in liver cirrhosis. Several studies have evaluated the efficacy of zinc supplementation in addressing various complications of cirrhosis.

Katayama et al. conducted a randomized controlled trial comparing zinc supplementation (80 mg/day) to placebo in 79 cirrhotic patients for 6 months. They reported significant improvements in Child-Pugh scores in the zinc group compared to placebo (mean decrease: 2.1 vs. 0.4 points, $p<0.001$), primarily driven by improvements in ascites, serum albumin, and encephalopathy.[104] Similarly, Takuma

et al. demonstrated that zinc supplementation (225 mg/day) for 3 months significantly improved ammonia clearance and psychometric performance in cirrhotic patients with minimal hepatic encephalopathy.[105]

Infection risk, a major concern in cirrhosis, may also be modifiable through zinc supplementation. Mohammad et al. found that cirrhotic patients receiving zinc supplementation (50 mg/day) for 12 months had a 35% reduction in infectious complications compared to standard care.[106] This effect was more pronounced in patients with Child-Pugh Class B and C, suggesting that those with more advanced disease may derive greater benefit from zinc repletion.

Hepatocellular regeneration and fibrosis progression, key determinants of disease trajectory in cirrhosis, may be influenced by zinc status. Experimental models have demonstrated that zinc supplementation promotes hepatocyte proliferation and reduces fibrogenic activity. Matsumura et al. reported that zinc supplementation attenuated fibrosis progression in a 24-week clinical trial of 48 cirrhotic patients, as assessed by serial transient elastography measurements and serum fibrosis markers.[107]

Nutritional parameters may also improve with zinc supplementation. Madden et al. demonstrated that cirrhotic patients receiving zinc (50 mg/day) for 3 months showed significant improvements in appetite, dietary intake, and lean body mass compared to placebo.[108] These effects likely result from improved taste perception, enhanced protein synthesis, and reduced inflammatory catabolism.

The optimal dosing, duration, and formulation of zinc supplementation in cirrhosis remain subjects of debate. Grungreiff et al. suggested that zinc doses of 50-75 mg/day are typically required to normalize zinc status in cirrhotic patients, with therapy generally needed for at least 3-6 months.[109] Zinc acetate and zinc gluconate are preferred formulations due to better tolerability compared to zinc sulfate.

Prolonged supplementation appears safe, with minimal risk of toxicity due to intact homeostatic mechanisms for zinc excretion in most cirrhotic patients.

Monitoring response to zinc supplementation should include both clinical parameters and serum zinc levels. However, interpretation of serum zinc can be challenging due to confounding factors like inflammation and hypoalbuminemia. Stamoulis et al. suggested that erythrocyte zinc concentration might provide a more accurate assessment of zinc status in cirrhotic patients, being less affected by acute-phase responses.[110]

While our study did not evaluate zinc supplementation, the findings strongly support the rationale for zinc replacement in cirrhotic patients, particularly those with advanced disease.

Future prospective studies should address whether early zinc supplementation can alter disease progression or improve long-term outcomes in cirrhosis.

Limitations and Future Directions

Our study has several limitations that warrant consideration. First, the cross-sectional design precludes establishing causal relationships between zinc deficiency and disease severity. It remains unclear whether zinc deficiency is merely a consequence of advanced liver disease or if it actively contributes to disease progression. Longitudinal studies with serial measurements of zinc levels and disease parameters would better elucidate this relationship.

Second, the overwhelming predominance of alcoholic etiology (89.4%) and male gender (95.3%) in our cohort limits the generalizability of our findings to more diverse cirrhotic populations. Comparative studies across different etiologies could provide insights into whether the relationship between zinc deficiency and disease severity varies by underlying cause.

Third, our study measured only serum zinc, which may not accurately reflect total body zinc status, particularly in the setting of inflammation and hypoalbuminemia. Assessment of erythrocyte zinc, hair zinc, or urinary zinc excretion might provide a more comprehensive evaluation of zinc homeostasis in cirrhosis.

Fourth, we did not assess dietary zinc intake or absorption, factors that significantly influence zinc status. Detailed nutritional assessments coupled with zinc absorption studies could help differentiate between poor intake, impaired absorption, and increased losses as causes of zinc deficiency in individual patients.

Fifth, while we documented a 15.3% mortality rate during the study period, we did not analyze the specific relationship between zinc levels and mortality or other clinical outcomes. Prospective studies examining zinc levels as predictors of specific complications, quality of life, and survival would enhance our understanding of the prognostic significance of zinc deficiency.

Future research directions should include interventional studies of zinc supplementation with clearly defined clinical endpoints beyond simple normalization of zinc levels. These might include improvements in hepatic synthetic function, reduction in complication rates, enhancement of quality of life, and survival benefits. The optimal timing, dosing, and duration of zinc supplementation need to be established through well-designed clinical trials.

Additionally, exploration of the molecular mechanisms linking zinc to hepatocyte function, fibrogenesis, and portal hypertension could identify novel therapeutic targets. The interplay between zinc and other micronutrients in cirrhosis, particularly copper and selenium, also warrants investigation, as imbalances rarely occur in isolation.

Conclusion

Our study demonstrates an extraordinarily high prevalence of zinc deficiency (97.6%) among cirrhotic patients, with a significant inverse relationship between zinc levels and disease severity as measured by the Child-Pugh classification. The progressive decrease in mean zinc levels from Child-Pugh Class A (50.4±4.31 μg/dL) to Class B (42.32±4.86 μg/dL) to Class C (37.02±3.68 μg/dL) suggests that zinc depletion parallels the deterioration of liver function.

The striking parallel between zinc and albumin deficiency (both 97.6%) highlights the intertwined nature of protein synthesis impairment and zinc homeostasis disruption in cirrhosis.

The demographic and clinical profile of our cohort, characterized by middle-aged male predominance and overwhelming alcoholic etiology, underscores the substantial burden of alcohol-related liver disease in our population. The advanced nature of disease at presentation, with 67.1% in Child-Pugh Class C, emphasizes the need for earlier detection and intervention strategies.

The findings from this study have important clinical implications. Zinc assessment should be considered in the routine evaluation of cirrhotic patients, particularly those with advanced disease or specific complications like hepatic encephalopathy. Zinc supplementation emerges as a potentially beneficial adjunctive therapy, though optimal protocols require further investigation.

In conclusion, zinc deficiency is nearly universal in liver cirrhosis and correlates significantly with disease severity. Recognition of this association may enhance our understanding of cirrhosis pathophysiology and open avenues for targeted nutritional interventions that could potentially modify disease outcomes.

CONCLUSION

The present study unequivocally establishes a significant relationship between zinc deficiency and liver cirrhosis, with a remarkable prevalence of 97.6% zinc deficiency among the studied cirrhotic patients. More importantly, a clear inverse correlation was demonstrated between serum zinc levels and the severity of liver cirrhosis as assessed by the Child-Pugh classification. As liver function deteriorated from Child-Pugh Class A to Class C, mean zinc levels progressively decreased, with all patients in Class C showing zinc deficiency.

This study also highlights the demographic and clinical profile of cirrhotic patients in our region, characterized by a predominance of middle-aged males and alcoholic etiology. The high proportion of patients presenting with advanced disease (Child-Pugh Class C: 67.1%) underscores the need for earlier detection and intervention strategies, including consideration of nutritional status and micronutrient deficiencies.

The parallel deficiency of zinc and albumin observed in our study (both 97.6%) supports the intricate relationship between protein synthesis, zinc transport, and overall liver function. This association may have therapeutic implications, as interventions targeting zinc status could potentially influence multiple aspects of hepatic function and cirrhosis-related complications.

While our cross-sectional study cannot establish causality, the findings strongly suggest that zinc assessment should be incorporated into the routine evaluation of cirrhotic patients. Zinc supplementation emerges as a potential adjunctive therapy, particularly for patients with advanced disease who demonstrate the most profound deficiency. Future prospective interventional studies are needed to determine whether zinc replenishment can modify disease progression, reduce complications, or improve

quality of life and survival in cirrhotic patients.

In conclusion, zinc deficiency is nearly universal in liver cirrhosis, correlates with disease severity, and may represent both a marker of advanced disease and a modifiable factor in the complex pathophysiology of cirrhosis. Recognition of this relationship provides new avenues for comprehensive care strategies in the management of liver cirrhosis.

SUMMARY

INTRODUCTION

Liver cirrhosis represents the final common pathway for chronic liver diseases, characterized by extensive fibrosis and hepatocyte dysfunction. Zinc, an essential micronutrient with critical roles in protein synthesis, enzymatic reactions, and antioxidant defense, has been implicated in liver pathophysiology. However, the relationship between zinc deficiency and cirrhosis severity remains incompletely characterized in the Indian population. This study aimed to evaluate serum zinc levels in patients with liver cirrhosis and correlate them with disease severity as measured by the Child-Pugh classification.

AIMS AND OBJECTIVES

Objectives:

1. To compare zinc levels in liver cirrhosis.
2. To evaluate the severity of cirrhosis using Child Pugh score.

MATERIAL AND METHODS

This hospital-based cross-sectional study was conducted among 85 patients with liver cirrhosis attending the outpatient and inpatient departments of BLDE University's Shri BM Patil Medical College Hospital. Detailed clinical evaluation, biochemical investigations including serum zinc levels, and Child-Pugh scoring were performed. Zinc deficiency was defined as serum levels below 51 μg/dL. Statistical analysis included descriptive statistics, chi-square tests, and ANOVA to assess relationships between variables.

RESULTS

- This cross-sectional study conducted among 85 patients with liver cirrhosis at BLDE University's Shri BM Patil Medical College Hospital yielded the following key results:
- The demographic analysis revealed a predominance of middle-aged adults, with 34.1% of patients falling in the 41-50 years age group and 25.9% in the 51-60 years range. There was a striking gender disparity, with males constituting 95.3% of the cohort compared to only 4.7% females.
- Regarding etiology, alcohol was overwhelmingly the primary cause of liver cirrhosis (89.4%), with viral causes accounting for much smaller proportions (Hepatitis B: 5.9%, Hepatitis C: 4.7%).
- Disease severity assessment using the Child-Pugh classification showed that the majority of patients presented with advanced disease: 67.1% were categorized as Class C (most severe), 28.2% as Class B, and only 4.7% as Class A (least severe). This distribution was mirrored in the ascites profiles, with 62.4% having severe ascites, 31.8% moderate ascites, and 5.9% mild ascites.
- The central finding of the study was the extraordinarily high prevalence of zinc deficiency, affecting 97.6% of patients. A significant inverse relationship was observed between zinc levels and disease severity. Mean zinc levels progressively decreased from Child-Pugh Class A (50.4±4.31 μg/dL) to Class B (42.32±4.86 μg/dL) to Class C (37.02±3.68 μg/dL), with $p<0.001$. Zinc deficiency was present in 75% of Class A patients, 95.8% of Class B patients, and 100% of Class C patients ($p=0.005$).
- Albumin levels showed a distribution identical to zinc levels, with 97.6% of patients having reduced levels (<3.3 g/dL) and only 2.4% having normal levels.

This parallel suggests a close relationship between zinc and albumin metabolism in liver cirrhosis.

- The mortality rate in the study cohort was 15.3% (13 patients), while 84.7% (72 patients) survived. Analysis of zinc deficiency across different variables showed a significant relationship with age ($p=0.029$), but no significant associations with gender ($p=0.75$) or etiology ($p=0.21$).
- These findings collectively demonstrate that zinc deficiency is nearly universal in liver cirrhosis and correlates significantly with disease severity, suggesting potential diagnostic and therapeutic implications for zinc assessment and supplementation in the management of cirrhotic patients.

CONCLUSION:

This study demonstrates an extraordinarily high prevalence of zinc deficiency in liver cirrhosis with a significant inverse correlation with disease severity. The progressive decline in zinc levels with worsening Child-Pugh scores suggests that zinc deficiency may be both a marker of advanced disease and potentially a contributor to disease progression. These findings support the incorporation of zinc assessment into the routine evaluation of cirrhotic patients and suggest that zinc supplementation could be considered as an adjunctive therapy, particularly in advanced disease.

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APPENDIX –I

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 890/2022-23 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinized the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "COMPARISON OF ZINC LEVELS IN LIVER CIRRHOSIS AND EVALUATING THE SEVERITY USING CHILD PUGH SCORE".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.VIDYADHARI KAKUMANU

NAME OF THE GUIDE: **DR.PRAKASH G. MANTUR, PROFESSOR, DEPT. OF GENERAL MEDICINE.**

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail:office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

ANNEXURE II

CONSENT FORM

BLDEDU'S SHRI B. M. PATIL MEDICAL COLLEGEHOSPITAL

AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - **"COMPARISON OF ZINC LEVELS IN LIVER CIRRHOSIS AND EVALUATING THE SEVERITY USING CHILD PUGH SCORE"**

PRINCIPAL INVESTIGATOR - **Dr. VIDYADHARI KAKUMANU**

+91 8978382688

P.G. GUIDE NAME - Dr. PRAKASH.G.MANTUR

PROFFESSOR

DEPARTMENT OF MEDICINE

All aspects of this consent form are explained to the patient in the language understood by him/her.

INFORMED PART PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator inthis study.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are

associated with the usual course of treatment.

BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records andwill be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special writtenpermission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. **Dr. VIDYADHARI KAKUMANU** is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. **VIDYADHARI KAKUMANU** may terminate my participation in the study after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to the purpose of the research, the procedures required and the possible risks and benefitsto the best of my ability in patient's own language.

_____ _____

Dr. VIDYADHARI KAKUMANU Date

(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **Dr. VIDYADHARI KAKUMANU** has explained to me the purpose of research, the study procedures that I willundergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate asa subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE –III

BLDE (DU)

SHRI. B M PATIL MEDICAL COLLEGE VIJAYAPURA,

KARNATAKA

SCHEME OF CASE TAKING

Informant:

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Past Occupation:

Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past History:

Personal History:

Family History:

Treatment History:

General Physical Examination

Height:

Weight:

Body Mass Index:

Vitals

PR:

BP.:

RR:

Temp

Eyes

Cyanosis

Clubbing

Abdominal girth

SYSTEMIC EXAMINATION

CENTRAL NERVOUS SYSTEM:

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

PER ABDOMEN:

INVESTIGATIONS

1. Radiological investigations:

USG ABDOMEN AND PELVIS

HAEMATOLOGY –

1) Hemoglobin	gm. %
2) Total WBC counts	Cells/mm^3
3) Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
Platelet count	

2. BIOCHEMISTRY

1) RANDOM BLOOD SUGAR - mg/dl
2) SERUM ZINC LEVELS - U / mL
3) RENAL FUNCTION TEST :

CREATININE	
UREA	
SODIUM	
POTASSIUM	

4) HBsAg(RAPID)
5) HCV(RAPID)
6) Prothrombin Time
7) International normalized ratio
8) Liver function test

TOTAL BILIRUBIN	
DIRECT BILIRUBIN	
INDIRECT BILIRUBIN	
ALBUMIN	
SGOT	
SGPT	
ALBUMIN	

CTP

CLASS A

CLASS B

CLASS C

CONCLUSION:

Date:-

Signature:-

Final diagnosis:

DR. PRAKASH G. MANTUR

ANNEXURE-IV

MASTER CHART

S NO	PATIENTS NAME	IP NO.	AGE/SEX	SR.ZINC	ASCITIS	VIRALS	SR. BIL	SR ALBUMIN	CHID PUGH SCORE	STATUS	ALCOHOL (gm/day)	ALCOHOL HISTORY(YEARS)
1	VISHAL KISHOR	178019	MALE/30	47.4	MODERATE	NONE	4.4	2.6	CLASS B 9	ALIVE	110	9
2	BHIMAPPA HARIJAN	305349	MALE/58	40	MODERATE	NONE	2.5	3.1	CLASS B 8	DEAD	80	15
3	KAMALAPPA YALLAPPA	151600	MALE/70	39.2	SEVERE	NONE	7.1	2.6	CLASS C 11	DEAD	100	20
4	ARJUN NAVI	176847	MALE/59	30.1	SEVERE	NONE	3.2	2.4	CLASS C 12	ALIVE	40	15
5	MUTTAPPA	202433	MALE/30	46.2	MODERATE	NONE	2.1	2.9	CLASS B 8	ALIVE	120	10
6	ANIL KUMAR PAMPANAVAR	207165	MALE/45	49	MODERATE	NONE	2.1	1.5	CLASS B 9	ALIVE	80	15
7	RAVI D BIRADAR	208323	MALE/52	33.1	SEVERE	NONE	5.4	2.2	CLASS C 11	ALIVE	70	10
8	RAFIQ BEPARI	217808	MALE/45	42.5	SEVERE	NONE	8	1.8	CLASS C 11	ALIVE	120	20
9	SIDDARAYA KANNUR	184245	MALE/58	30	SEVERE	NONE	6.8	2.1	CLASS C 12	ALIVE	100	15
10	LAXMAN JANGAPPA KANNUR	231747	MALE/58	41	MODERATE	NONE	1.6	2.4	CLASS B 9	ALIVE	80	15
11	NAGAPPA BIRADAR	145492	MALE/56	34.1	SEVERE	NONE	5.4	2.2	CLASS C 11	ALIVE	120	12

12	HUSANAPPA MAHANINGAPPA	349290	MALE/55	49	MILD	NONE	1.9	3.4	CLASS A 6	ALIVE	60	20
13	RAMESH LALU RATHOD	227946	MALE/48	36.4	SEVERE	NONE	4	2.1	CLASS C 11	ALIVE	100	18
14	UMAKANTH D CHAVAN	256515	MALE/38	39	SEVERE	NONE	2.6	1.6	CLASS C 10	ALIVE	140	16
15	CHANDRASHEKAR ANGADI	256709	MALE/52	35.4	SEVERE	NONE	3.4	1.7	CLASS C 11	ALIVE	120	20
16	GOPAL V KULKARNI	258446	MALE/60	34	SEVERE	NONE	2.1	1.8	CLASS C 12	ALIVE	100	25
17	BASU HARISHCHANDRA	258525	MALE/40	42.1	SEVERE	NONE	2	2	CLASS C 10	ALIVE	80	18
18	ABDUL HAMID TAMBOLI	259912	MALE/36	36.2	SEVERE	NONE	2.5	2.1	CLASS C 10	ALIVE	100	18
19	NANA SAHEB PATIL	419878	MALE/32	35.4	SEVERE	NONE	6.2	2.3	CLASS C 10	ALIVE	160	12
20	MACHANTAPPA GADDI	209146	MALE/62	38	SEVERE	NONE	5	1.4	CLASS C 9	ALIVE	120	20
21	SUMITRA BASAVARAJ	160965	FEMALE/45	39.3	SEVERE	HCV	9.1	1.2	CLASS C 11	DEAD	NILL	NILL
22	SHEKAPPA PAWAR	091883	MALE/42	38.4	SEVERE	NONE	3.7	1.6	CLASS C 11	ALIVE	100	16
23	NAMDEV RATHOD	267936	MALE/56	49	SEVERE	NONE	6.3	1.5	CLASS B 9	ALIVE	70	20
24	ABDUL RAJAK UKALI	273152	MALE/55	40.1	SEVERE	HBSAG	3.4	1.4	CLASS C 11	ALIVE	NILL	NILL
25	SUDHEER KUMAR	273162	MALE/38	42	MODERATE	NONE	4.1	2.6	CLASS B 8	ALIVE	50	16
26	SHIVAKUMAR	273285	MALE/48	44	SEVERE	NONE	3.9	1.2	CLASS C 12	ALIVE	100	15
27	BASAWARAJ G BIRADAR	274882	MALE/55	40.1	MODERATE	NONE	5.3	2.9	CLASS B 9	DEAD	80	20
28	PARASHURAM YALLAPA	261703	MALE/36	46	MODERATE	NONE	2.9	2.6	CLASS B 9	ALIVE	80	12
29	MANJUNATH NANUDU RAO	270757	MALE/38	35.3	SEVERE	NONE	4.1	1.1	CLASS C 11	ALIVE	110	10
30	KRISHANAPPA M VABASE	136457	MALE/58	38.6	SEVERE	NONE	5.2	2.4	CLASS C 12	ALIVE	50	20
31	MALLAPPA HUGAR	386524	MALE/50	38.1	MODERATE	NONE	3.4	2.9	CLASS C 12	ALIVE	120	20
32	DRAKSHAYANI C SIRADNI	151340	FEMALE/54	42.3	MODERATE	HBSAG	5.4	2.4	CLASS B 9	ALIVE	NILL	NILL
33	MATHARABA	323829	MALE/46	33.9	SEVERE	NONE	8	1.4	CLASS C 11	ALIVE	100	18
34	MAHANTAGOUDA BIRADAR	340522	MALE/58	44.1	MODERATE	NONE	5	2.3	CLASS B 9	ALIVE	40	18
35	RAMESH BENKANAHALLI	341378	MALE/45	32.4	SEVERE	NONE	7.5	1.6	CLASS C 12	DEAD	110	20
36	APPASH DODDAMANI	354163	MALE/36	39.2	MODERATE	NONE	3.2	2.2	CLASS B 8	ALIVE	80	16

37	GAJANAN SALUNKE	106926	MALE/49	33.5	SEVERE	NONE	7.1	2.1	CLASS C 12	ALIVE	110	14
38	GUTTAPPA YAMANAPPA	349058	MALE/60	34.7	SEVERE	NONE	4.6	2	CLASS C 9	ALIVE	100	22
39	RAVINDRA NAGALINGAPPA	335577	MALE/62	37.3	SEVERE	NONE	9.7	1.9	CLASS C 11	ALIVE	80	20
40	RAHUL ANIL	373712	MALE/27	35.5	MILD	NONE	2.5	2.9	CLASS C 11	ALIVE	80	8
41	DYAMAWWA MALLAPA	207172	FEMALE/65	32.2	SEVERE	HCV	2.4	2	CLASS C 12	ALIVE	NILL	NILL
42	MALLIKARJUN SUTAGI	225199	MALE/35	46.2	MODERATE	NONE	1.9	2.6	CLASS B 8	ALIVE	50	15
43	MAHESH VITTAL	258411	MALE/33	39	MODERATE	NONE	2.4	3	CLASS B 9	ALIVE	60	10
44	ANIL HANMANTH TALWAR	258348	MALE/45	40.3	MODERATE	NONE	2.2	2.9	CLASS B 9	ALIVE	100	10
45	PRAKASH R CHAVAN	258390	MALE/48	39	MODERATE	NONE	2	2.9	CLASS B 8	ALIVE	70	11
46	SIDDARAM HIREMETH	358675	MALE/52	39.1	SEVERE	HBSAG	2.8	1.8	CLASS C 9	ALIVE	NILL	NILL
47	BHIMA RAO	135693	MALE/39	34.4	SEVERE	NONE	5.4	1.4	CLASS C 11	ALIVE	110	10
48	HANAMANTHRAY GOWDA	117696	MALE/62	38.8	SEVERE	NONE	3.2	2.1	CLASS C 12	ALIVE	100	20
49	RAJU SURESH JADHAV	405358	MALE/48	50	MILD	NONE	1.6	3.1	CLASS A 6	ALIVE	50	10
50	IRAPPA SABU ARATAL	071284	MALE/50	38	SEVERE	NONE	4.4	1.4	CLASS C 11	ALIVE	110	11
51	ABHIMANYU GOUNDI	295521	MALE/51	40.1	SEVERE	NONE	5.4	2.1	CLASS B 9	ALIVE	90	12
52	SANJIV	2024/1060	MALE/35	52	MODERATE	NONE	3.1	2.8	CLASS B 8	DEAD	70	9
53	BASAVARAJ NAVI	289615	MALE/42	36	MODERATE	NONE	4.4	2.1	CLASS B 9	DEAD	100	14
54	BASSAPPA HALAPPAGAR	405347	MALE/62	39	MODERATE	NONE	3.4	3	CLASS C 11	DEAD	130	20
55	ASHOK NAYAK	135760	MALE/39	45.1	SEVERE	NONE	3.9	1.3	CLASS C 12	ALIVE	110	14
56	THIPPANA THALAVAR	283662	MALE/37	46.1	SEVERE	NONE	11	1.4	CLASS C 10	ALIVE	110	12
57	ANNARAYA KONALLI	099785	MALE/45	34.5	SEVERE	NONE	13.4	1.8	CLASS C 10	ALIVE	120	14
58	CHANABASAPPA	112253	MALE/68	37	SEVERE	HCV	21	2	CLASS C 11	DEAD	NILL	NILL
59	KAREPPA NINGAPPA	280454	MALE/49	40	SEVERE	NONE	4.6	1.7	CLASS C 11	ALIVE	100	18
60	SHARANAPPA KADEKAPA	282095	MALE/30	39.1	SEVERE	NONE	6.9	2.2	CLASS C 12	ALIVE	110	9
61	BASAVARAJ BHIMARAJA	077200	MALE/43	34	SEVERE	NONE	2.8	2.1	CLASS C 13	ALIVE	110	9

62	SACHIN SHARANAPPA	370491	MALE/30	32.1	SEVERE	NONE	6.3	1.4	CLASS C 11	ALIVE	120	10
63	SHIVANAND JANIWAR	261419	MALE/50	56.4	MILD	NONE	2.2	3.4	CLASS A 6	ALIVE	40	11
64	ASHOK ANNAPPA	380492	MALE/44	38.3	MODERATE	NONE	5	1.9	CLASS C 11	ALIVE	90	12
65	BHIMARAYA BASAPPA	263810	MALE/66	38.4	SEVERE	NONE	6.4	2.2	CLASS C 11	DEAD	140	14
66	RAGHAVENDRA KOPPAD	271991	MALE/40	41.6	SEVERE	NONE	3.4	2.2	CLASS C 12	ALIVE	100	14
67	SADASHIV TOTAD	283675	MALE/53	36.2	SEVERE	NONE	3	2.2	CLASS C 10	ALIVE	100	20
68	PRASAD K GOBBUR	035557	MALE/27	46.1	MODERATE	NONE	3.3	3.1	CLASS B 9	ALIVE	80	12
69	MAHADEVAPPA GUDDODAGI	050224	MALE/45	30.4	MODERATE	NONE	3.2	3	CLASS B 9	ALIVE	80	15
70	SANGANNA BIRADAR	297963	MALE/60	35.5	SEVERE	NONE	4	1.9	CLASS C 11	DEAD	130	20
71	SURESH NAIKODI	200550	MALE/45	36.7	SEVERE	NONE	4.9	2	CLASS C 13	ALIVE	120	10
72	RENASIDDA PUJARI	098781	MALE/45	36.1	MODERATE	NONE	3.5	3.1	CLASS C 11	ALIVE	110	15
73	SANTOSH JEVERGI	262755	MALE/45	37.3	MODERATE	HBSAG	2.4	2.9	CLASS B 7	DEAD	NILL	NILL
74	MAHANTESH BASAVARAJ	2024/2954	MALE/45	39	MODERATE	NONE	4	2.8	CLASS B 8	ALIVE	90	12
75	YALLAPA WALIKAR	2024/4038	MALE/44	31.1	SEVERE	NONE	8	1.6	CLASS C 11	ALIVE	100	12
76	BOURAWWA PUJARI	2024/4316	FEMALE/47	36.4	SEVERE	HCV	12.1	2.1	CLASS C 10	ALIVE	NILL	NILL
77	RAJASHEKAR NIMBAL	2024/4633	MALE/52	35.2	SEVERE	NONE	6.2	2.3	CLASS C 12	ALIVE	100	10
78	SABU BAJANIRI	2024/5353	MALE/56	30.2	SEVERE	NONE	5.6	1.9	CLASS C 12	ALIVE	110	20
79	MALLAPPA BENKI	2024/5471	MALE/40	42.1	SEVERE	NONE	6.2	2.4	CLASS C 10	ALIVE	100	20
80	RAMESH SHIVAPPA	2024/2354	MALE/40	37.2	SEVERE	HBSAG	6	2.2	CLASS C 11	DEAD	NILL	NILL
81	MAHAMMAD RAFIQ	2024/2428	MALE/40	44.2	MODERATE	NONE	7.4	2.6	CLASS B 8	ALIVE	60	10
82	KASHINATH KONDAPPA	356933	MALE/80	46.2	MILD	NONE	1.3	3.1	CLASS A 6	ALIVE	40	20
83	MASTEPPA BABALADDI	234094	MALE/42	44.3	MODERATE	NONE	7.5	3	CLASS C 11	ALIVE	110	10
84	DEVINRAPPA DODDAMANI	289285	MALE/45	38.1	SEVERE	NONE	7	2.1	CLASS C 10	ALIVE	100	16
85	SHIVASHANKAE GOLAPPA	375020	MALE/34	37.3	SEVERE	NONE	3.1	2.4	CLASS C 12	ALIVE	110	9