"CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORE IN CIRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE"

By:

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Dissertation submitted to the

Sri Devaraj Urs Academy of Higher Education and Research,

Tamaka, Kolar, Karnataka,

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF MEDICINE (M.D.)

IN

GENERAL MEDICINE

Under The Guidance Of

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The Institutional Ethics Committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has examined and unanimously approved the synopsis entitled **"Correlation of serum prolactin level to child pugh score in cirrhosis of liver in assessing the severity of the disease"** being investigated by **DR. VEMANAMANDA SUJITHA**, Dr. Srinivas S V in the Department of Medicine at Sri Devaraj Urs Medical College, Tamaka, Kolar. **Permission is granted by the Ethics Committee to start the study.**

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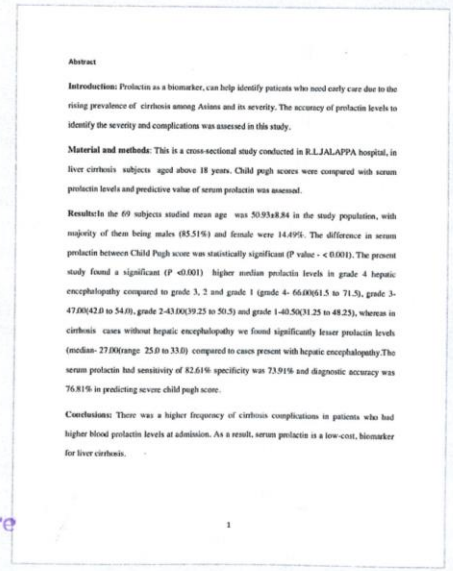

Abstract

Introduction: Prolactin as a biomarker, can help identify patients who need early care due to the rising prevalence of cirrhosis among Asians and its severity. The accuracy of prolactin levels to identify the severity and complications was assessed in this study.

Material and methods: This is a cross-sectional study conducted in R.L.JALAPPA hospital, in liver cirrhosis subjects aged above 18 years. Child pugh scores were compared with serum prolactin levels and predictive value of serum prolactin was assessed.

Results: In the 69 subjects studied mean age was 50.93±8.84 in the study population, with majority of them being males (85.51%) and female were 14.49%. The difference in serum prolactin between Child Pugh score was statistically significant (P value - < 0.001). The present study found a significant (P <0.001) higher median prolactin levels in grade 4 hepatic encephalopathy compared to grade 3, 2 and grade 1 (grade 4- 66.00(61.5 to 71.5), grade 3-47.00(42.0 to 54.0), grade 2-43.00(39.25 to 50.5) and grade 1-40.50(31.25 to 48.25), whereas in cirrhosis cases without hepatic encephalopathy we found significantly lesser prolactin levels (median- 27.00(range 25.0 to 33.0) compared to cases present with hepatic encephalopathy.The serum prolactin had sensitivity of 82.61% specificity was 73.91% and diagnostic accuracy was 76.81% in predicting severe child pugh score.

Conclusions: There was a higher frequency of cirrhosis complications in patients who had higher blood prolactin levels at admission. As a result, serum prolactin is a low-cost, biomarker for liver cirrhosis.

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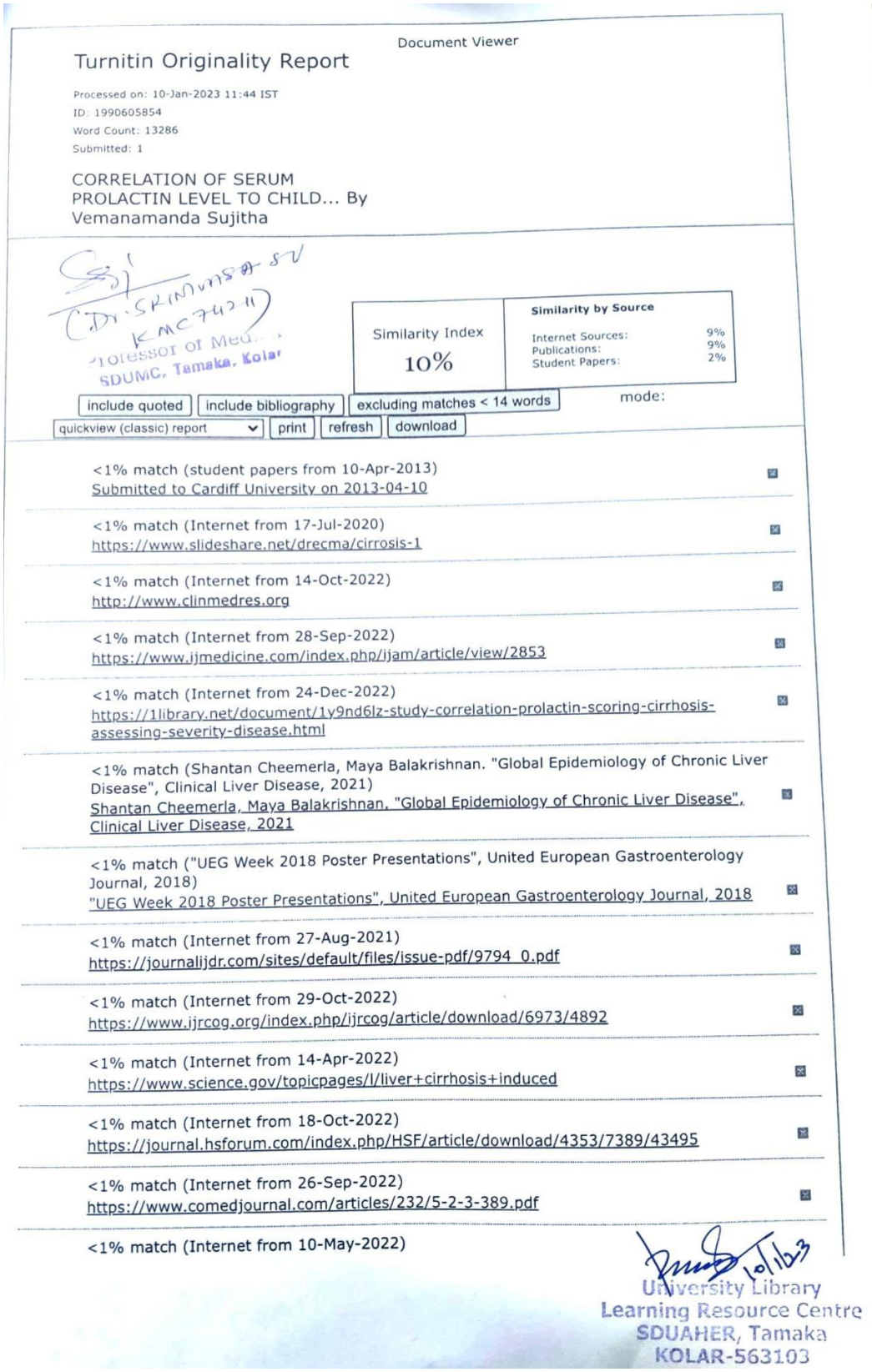

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Dr **VEMANAMANDA SUJITHA**

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ABBREVIATIONS

Glossary	Abbreviations
NAFLD	Non-Alcoholic Fatty Liver Disease
HSC	Hepatic Stellate Cells
LSEC	Liver Sinusoidal Endothelial Cells
CPT	Child-Pugh Turcotte
MELD	Model of End-stage Liver Disease
INR	International Normalized Ratio
NO	Nitric Oxide
TIDA	Tuberoinfundibular
THDA	Tuberohypophyseal
PHDA	Periventricular Hypophyseal
DHEA	Dihydroepiandrosterone
PCOS	Polycystic Ovarian Syndrome
HE	Hepatic Encephalopathy
IQR	Interquartile Range
ROC	Receiver Operative Curve

ABSTRACT

Introduction: Prolactin as a biomarker, can help identify patients who need early care due to the rising prevalence of cirrhosis among Asians and its severity. The accuracy of prolactin levels to identify the severity and complications was assessed in this study.

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INTRODUCTION

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Cirrhosis is characterized by nodule formation surrounded by dense fibrosis resulting in distortion of hepatic vascular architecture which eventually leads to portal hypertension and hepatic dysfunction. Previously cirrhosis was considered as end stage liver disease which could be treated only with liver transplantation. But recent findings indicate wide variation in occurrence of one year mortality in cirrhosis from 1 to 57% and is directly dependent on occurrence of decompensating events.[1] Cirrhosis is usually asymptomatic until it reaches complicated stage. Cirrhosis can be compensated which is a benign form or decompensated which is associated with condictions like jaundice, ascites, hepatic encephalopathy and will have poor prognosis.[2] The treatment focus for decompensated cirrhosis is management of complications and it usually requires liver transplantation. Patients with symptomatic cirrhosis will benefit by treating the underlying disease that caused it[3]. It helps in fibrosis regression, improves portal hypertension which is the main cause for future decompensation.[4] But the treatment requires early diagnosis which is very challenging and rarely accomplished. It is estimated that three out of four patients with liver cirrhosis show decompensation on initial diagnosis.[5] There will not be linear progression of liver disease to cirrhosis, it is rather influenced by many diseases specific, host-specific and environmental factors. In non-alcoholic fatty liver disease (NAFLD), the risk of cirrhosis can be estimated with biopsy and histopathological studies. The predicted time for development of cirrhosis is 4.2 years when there are marked inflammatory changes and 13 % with no marked inflammatory changes. Around15% of patients with non-alcoholic etiology can develop cirrhosis within 10 years on disease onset.[6]

The leading causes around the world are hepatitis C infection and increased alcohol intake whereas in developing countries cirrhosis is mainly caused due to hepatitis B virus infection.

Initial stages of cirrhosis are asymptomatic making its early diagnosis and assessment difficult. The disorder is widely undiagnosed until complicated which leaves with liver transplantation as the only treatment option.[7] Late diagnosis is considered as main reason for mortality associated with liver cirrhosis. Portal hypertension is considered the main culprit leading to advanced cirrhosis. [8] Adding to the high risk of mortality, it also causes increased healthcare costs due to hospitalization, and reduced quality of life. [9]

Biopsy is usually considered as gold standard for diagnosis and staging Cirrhosis. But biopsy can have sampling errors, high interobserver variability leading to 33 to 50% diagnostic errors in cirrhosis due to heterogeneity.[10] Liver biopsy has many other disadvantages including its invasive and painful nature, post procedure complications and high cost.[11] Imaging modalities like ultrasonography were considered to be useful in detecting morphological characteristics of liver cirrhosis but may appear completely normal without any morphological changes.[12] Ultrasonography can diagnose cirrhosis, but its specificity is not 100%.

Among non-invasive diagnostic and grading tests for liver cirrhosis Child Pugh scoring system is used for prediction of mortality. This scoring system requires assessment of many parameters and has certain limitations. The scoring system has only ten different scores which does not grade severity of cirrhosis accurately. The prothrombin time which is one of the parameters of Child Pugh scoring system varies greatly in testing.[13] Recent studies show levels of prolactin help to diagnose cirrhosis and predict its severity. Measuring levels of prolactin in blood is an easy to perform, cost effective test.[14]

Liver is a major organ involved in metabolism, detoxification and protein synthesis.[15] The production of prolactin hormone by pituitary gland is controlled by dopamine.[16] Decreased

dopamine levels stimulate the pituitary gland and increases the prolactin levels.[14] The increased circulating oestrogen owing to reduced excretion by the liver itself has an inhibitory effect on dopamine secretion, thereby stimulating prolactin secretion.[15] Liver dysfunction leads to increase in circulating concentrations of aromatic amino acids which increase synthesis of false neurotransmitters like octopamine and phenyl ethanolamine.[16] These neurotransmitters inhibit dopamine release leading to increased production of prolactin.[17]

Need for the study:

India contributed 18.3% of two million global liver disease related deaths in 2015 [18]. In past four decades the burden of mortality due to liver cirrhosis is progressively increasing in India due to cultural lifestyle transition, increased alcohol consumption, fatty diet, lack of exercise.[19] In the year 2016 chronic liver diseases and cirrhosis accounted for 2.1% of all deaths in India. Alcohol and viral hepatitis are two major causes of liver cirrhosis. The alcohol consumption in India doubled between 2005 to 2016.[20] Cirrhosis is eleventh leading cause of death globally. The global burden has been estimated to be 20.7/100, 000 in 2015 which is a 13% increase from 2000.[21] Cirrhosis incidence has increased in Europe and Asia from 2000 to 2015 and has been reduced in some countries like Japan due to vaccinations and successful treatment for liver infections. But its incidence is increasing in other countries of the world due to increased obesity, comorbidities and alcohol intake.[22] Alcoholic males above the age of 50 with comorbidities like diabetes are at a higher risk of developing cirrhosis. Based on above facts this study aims to correlate prolactin levels to Child Pugh class in assessing severity of cirrhosis. This will help to establish efficacy of serum prolactin level in assessing severity at an early stage facilitating easy diagnosis and treatment.

AIMS AND OBJECTIVES

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1. To evaluate the diagnostic and prognostic significance of serum prolactin concentration in determining the severity of liver cirrhosis as identified through Child Pugh Score.
2. To evaluate the efficacy of serum prolactin concentration in indicating complications associated with cirrhosis of liver.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Cirrhosis is an end stage of chronic liver disease. It is a diffuse process of fibrosis and nodular formation leading to distortion of normal architecture of the entire liver.[23]

Epidemiology:

Cirrhosis is eleventh and fifteenth leading cause of death and morbidity in the world. A study conducted in 2016 showed that 2.2% of deaths globally were caused by cirrhosis.[24] The global burden has been estimated to be 20.7/100, 000 in 2015 which is a 13% increase from 2000.[21] Theincidence rates in Europe is 26.0/100, 000, and 16.5/100, 000 in East Asia to 23.6/100, 000 in Southeast Asia.[21] The global burden has been estimated to be 20.7/100, 000 in 2015 which is a 13% increase from 2000.

Deaths from cirrhosis due to viral hepatitis increased during the period between 1980 and 2010, but recent advances in screening and treatment protocols along with vaccination programms helped to bring the mortality rates owing to viral hepatits down[25].

In males the leading causes of cirrhotic deaths were hepatitis and C (31·5% and 25.5% respectively) and alcohol accounted for 27·3%. In females, deaths caused by hepatitis B (24·0%) and alcohol-related liver disease (20·6%) were lower than in males [26].

Table 1: Etiology of Deaths due to Cirrhosis in Men and Women [26]

Etiology	Men	Women
Hepatitis B	31.5%	24.0%
Hepatitis C	25.5%	26.7%
ALD	27.3%	20.6%
NASH/NAFLD	7.7%	11.3%
Other*	8%	17.3%

The source of cirrhosis can usually be determined by acquiring adequate history of the patient, liver function tests and histologic stuides. In Asia the most common cause of cirrhosis is Hepatitis B infection while in the western countries increased alcohole consumption and hepatitis C infection were most common.[23] Comorbidities like diabetes, hypertension, obesityalong with non-modifiable risk factors like male gender and age above of 50yrs were associated with increased risk of cirrhosis.[27]

Pathophysiology:

Multiple cell types of liver and their role in pathogenesis of liver cirrhosis:

Hepatic stellate cells (HSC): These cells are found in space of Disse in liver. The main function of these cells are that they are main sources of vitamin A[28].HSCs undergo transition to active state when they are subjected to continuous infections and inflammation. The transition of HSC cells to active state progress to cirrhosis. It is also main cause for collagen deposition [29]. HSCs activation results in cell proliferation and migration, contraction, generation collagen and other extracellular matrix resulting in liver fibrosis.[30]

Liver sinusoidal endothelial cells (LSEC): These cells form sinusoidal wall also called as endothelium. These cells constitute fenestrae on surface of endothelium.[31] which measure around 150nm in diameter and acts as a dynamic filter between sinusoids and parenchymal cells [32]. Chronic alcohol abuse results in decrease in number of fenestrae[33] initiating perisinusoidal fibrosis by alteration of retinol metabolism. LSECs secrete cytokine IL-33 which activates HSCs and promotes fibrosis.[34]

Kupffer cells: Kupffer cells form the reticuloendothelial system and factors like viruses, alcohol, high fat diet activate KCs which produce harmful soluble mediators and destroy hepatocytes[40, 35] KCs cause activation of HSCs and fibrosis. KCs also increase portal pressure by releasing thromboxane A2 [36]

Hepatocytes: These are primary liver parenchymal cells which target the hepatotoxic agents. [37] In liver injury there will be apoptosis of hepatocytes which leads to tissue inflammation, fibrogenesis and eventually cirrhosis.

Genetic predisposition for cirrhosis:

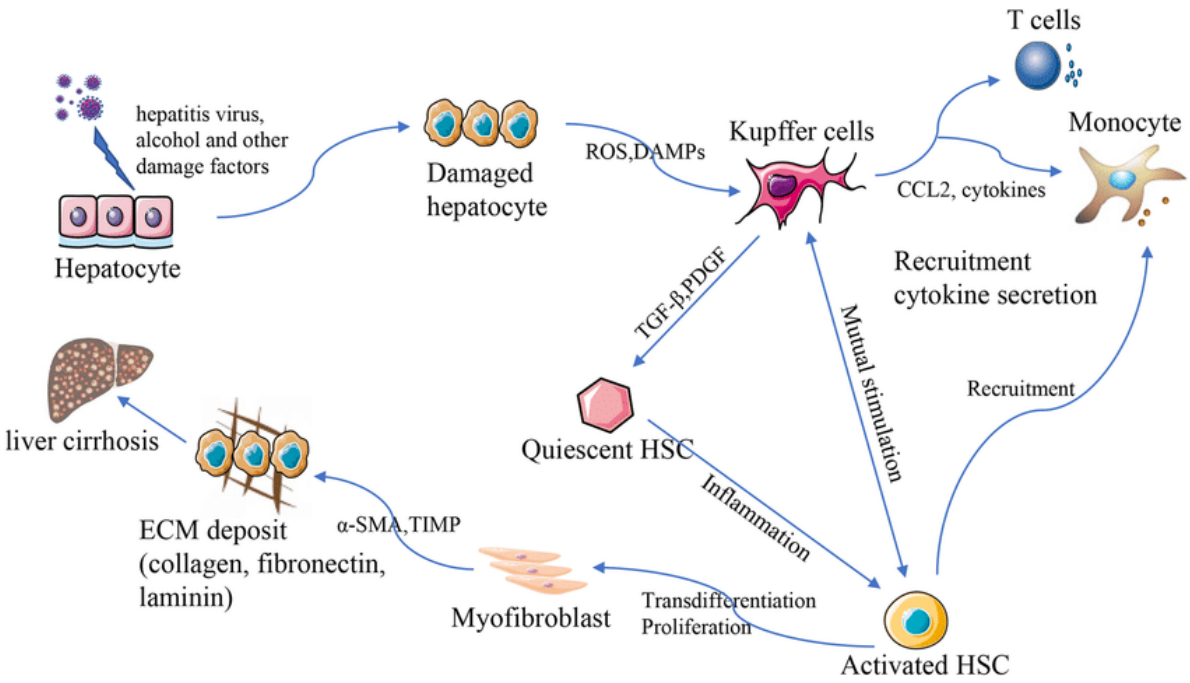
It is noticed that individuals with similar risk factors like HCV or alcohol abuse have variable rate of development of cirrhosis.[44] Certain genetic polymorphisms are found to increase risk of fibrosis progression.[45] Altered gene expressions for protein synthesis and storage[46], enzyme activity[47], inflammation[48], coagulation cascade[49], fibrogenesis [50] can all contribute to the disease process.

Clinical presentation:

Most of the patients of cirrhosis are asymptomatic and undiagnosed . Many of these people never seek medical attention, and cirrhosis that has been misdiagnosed is nevertheless regularly discovered through autopsies.[38]

The progression of the disease depends on the causative factors and management of the underlying cause. Alcohol consumption increases the rate of cirrhotic activity in the liver . After decompensation, death without transplant can reach 85% over a 5-year period.[23]

Figure 1: Pathogenesis of liver cirrhosis[39]



Diagnosis:

Imaging:

Imaging studies are less sensitive in detecting cirrhosis. The altered echotexture of liver, thin hepatic central vein, enlarged spleen and caudate lobe of liver combined with an apparent cause can increase the specificity of these imaging studies.[40] However the severity of the disease is seldom predicted[41]. Biopsy is considered the best modality in diagnosing and staging of the disease which not only identifies fibrosis, inflammation, ballooning which are hallmarks for cirrhosis but also help with grading and prognostic evaluation.[55] However, biopsy had disadvantages like it being an invasive procedure, higher cost, increased risk of bleeding and inter observer variability.[56]

Complications:

Ascites, Hepatic encephalopathy, Oesophageal varices, spontaneous bacterial peritonitis are the common co

mplications associated with liver cirrhosis.[42]

Table 2: Complication associated with cirrhosis- prevention and treatment:

Complication	Prevention	Treatment
Variceal bleeding [43]	Non selective beta blockers Variceal band ligation	*Acute:* Blood products Vasocontrictors Sclerotherapy Band Ligation
Ascites [44]	Low Na diet	TIPSS Surgical Shunts *Chronic:* TIPS Diuretics Ascitic tap Shunts
Renal dysfunction [45]	Avoid hypovolemia	Hepatorenal syndrome*:* vasopressors
Hepatic encephalopathy [42]	Avoid precipitants	Treatment of infections, dyselectrolytemia Rifaximin treatment Secondary prophylaxis with an antibiotic.
Spontaneous bacterial peritonitis [46]	Treat ascites	

Treatment:

Pharmacological reversal of cirrhosis:

Cirrhosis regresses by elimination of firbrogenic trigger due to dynamic processes of firborgenesis and fibrolysis.[47] The therapeutic treatment for reversal of cirrhosis is classified as primary and secondary. The aim of primary approach is to treat the underlying disease[48] while secondary approach focuses on mechanism of fibrogenesis. Reversal of cirrhosis by restoration of liver parenchyma is possible with combination of antifibrotic therapy and

hepatocyte renewal.[49] Hepatocyte transplantation improves liver function and reverses advanced fibrosis.[50]

Prognostic markers in liver cirrhosis:

Several prognostic scores have been formulated over the years for predicting the severity and mortality in cirrhosis. Etiology, course, comorbidities and complications of the disease have been considered in formulating these scores enabling improved management of the patient. Child-Pugh Turcotte (CPT) classification and Model of End-stage Liver Disease (MELD) scores, are the most commonly used scores[51].

Child Pugh Turcotte (CPT) classification

The child Pugh scoring system developed by Child and Turcotte is used for prediction of severity of liver cirrhosis. The Child Pugh score includes ascites, hepatic encephalopathy, international normalized ratio (INR), total bilirubin and albumin[67].

Table 3: Child Pugh Turcotte (CPT) classification

POINTS	**1**	**2**	**3**
Encephalopathy	Absent	Grade 1 - 2	Grade 3-4
Ascites	Absent	mild	moderate
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	< 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.2	> 2.2 [23]
SCORE		**5-6 POINTS**	**7-9 POINTS**	**10-15 POINTS**
Life expectancy (years)		15-20	4-14	1-3

The survival rate at 1 year for Child Pugh class A, B, and C are 100, 80, and 45 percent, respectively [52].

The following markers can be used to along with Child -Pugh and MELD scores to determine an accurate prognosis.

C reactive protein: It is an acute phase reactant which indicates the degree of inflammation[53].

Vitamin D:

The preservation of the body's phosphate homeostasis depends on vitamin D (calciferol). It comes from the skin and food. 7-dehydrocholesterol found in the skin is converted into 25-OH vitamin D3 in the presence of UV-B rays. A recent study found that there is increased deaths in patients with vitamin D levels < 6 ng/mL[54].

Copeptin:

In cirrhotic patients, overproduction of nitric oxide (NO) promotes compensatory systems, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and arginine vasopressin, to restore appropriate blood volume. AVP levelsincrease as the liver function declines, suggesting that this biological marker may be useful in predicting outcomes. However, it is challenging to measure and is not frequently available. Equimolar amounts of copeptin and AVP are released into the serum. Copeptin being a more stable protein than AVP, it can be measured and can be used as a marker of inflammation[55].

Von Willebrand factor antigen:

The ability of the vascular endothelium to emit vasoactive compounds, such as NO plays a crucial part in the regulation of vascular tone (vasoconstrictors). Abnormal vascular reactivity in cirrhotic individuals is caused by endothelial dysfunction, which also contributes to portal

hypertension by raising intrahepatic vascular resistance and portal flow However, routine use of this test is not practical.

Prolactin:

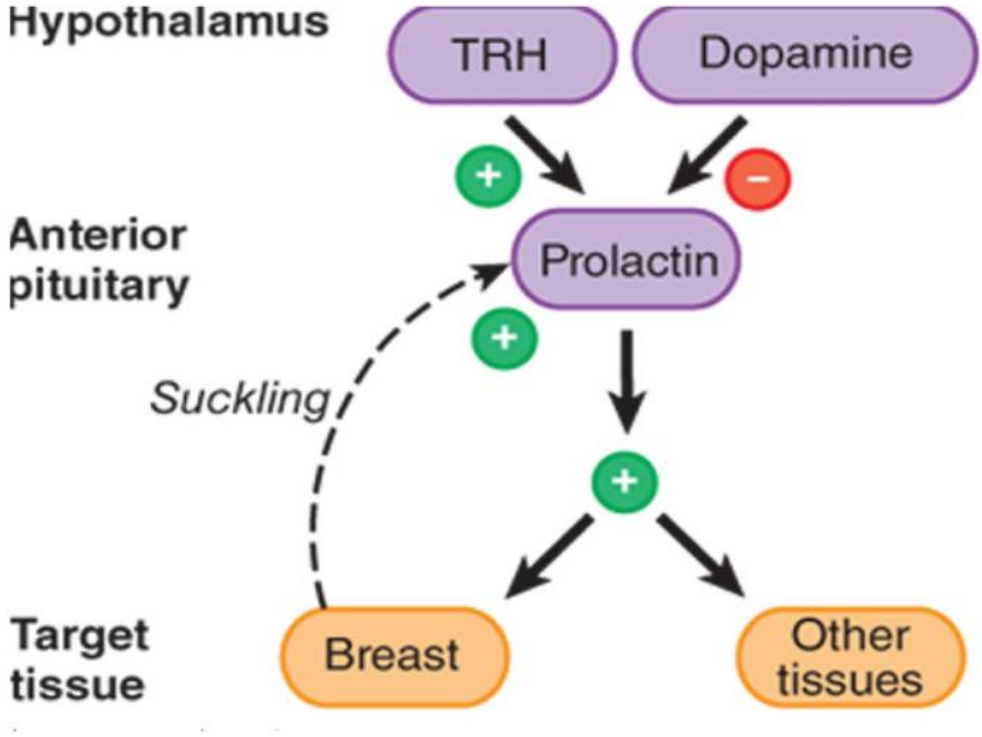
Prolactin hormone made up of 199 amino acids from prolactin prohormone. Prolactin is synthesized by anterior pituitary gland under dopamine mediated hypothalamic regulation. It can also be secreted by central nervous system, mammary glands and the immune system. Initiation of prolactin secretion by these tissues will be triggered by nipple stimulation, light olfaction and stress. Prolactin synthesis is also stimulated by other factors including thyrotropin releasing hormone, oestrogen and dopamine antagonists (antipsychotics). The levels of prolactin are usually low in males and non-lactating, non-pregnant females [56]. Anterior region of pituitary gland is responsible for secretion of various hormones including prolactin. The lactotrophs of anterior pituitary gland secrete prolactin and these increase during pregnancy. Thyrotropin releasing hormone and dopamine released by hypothalamus modulate lactotrophic activity. Dopamine acts on lactotrophic cells through D2- receptors which modulate intracellular signalling and inhibiting prolactin synthesis. Dopamine inhibits prolactin synthesis in non-pregnant and non-lactating females. Prolactin also has negative feedback effect on its production. Nipple stimulation stimulates sensory nerves in the nipple which carry signals through spinal cord to arcuate nucleus and inhibit dopamine release and promote prolactin synthesis.

Prolactin belongs to cytokine family of proteins. It has four antiparallel alpha helices and strong structural homology with growth hormone and placental lactogen. Post-translational modifications like phosphorylation, glycosylation, sulfation and deamidation result in formation of numerous variants of prolactin.

Regulation of prolactin secretion:

Dopamine is the principal factor responsible for the inhibition of prolactin synthesis and secretion.[57] The neurons which regulate Prolactin secretionare divided into: the tuberoinfundibular (TIDA), tuberohypophyseal (THDA), and periventricular hypophyseal (PHDA) dopaminergic neurons.[58] Dopamine regulates or inhibits prolactin secretion by inhibiting the calcium inflow needed for depolarisation of the membrane. It also inhibits adenylate cyclase which will diminish the prolactin gene expression.[59]

Figure 2: Regulation of prolactin secretion[60]



Biological functions of prolactin:

Lactotrophic function:

Prolactin's primary function is to maintain breastfeeding after delivery and encourage the production of milk. The growth of the lactotrophs is stimulated by rising oestrogen output in pregnant women, which raises prolactin secretion.Prolactin stimulates mammary gland growth and postpartum lactation.[61]

Reproductive effects:

Effects on other hormones:

Prolactin improves glucose homeostasis by increasing β-cell mass under certain conditions such as pregnancy, whereas hyperprolactinaemia due to a pituitary gland adenoma exacerbates insulin resistance.[62] Prolactin also enhances dihydroepiandrosterone (DHEA), cortisol and aldosterone secretion by the adrenal cortex cells.[63]

Effects on immune system:

It acts as a cytokine which stimulates immune system at lower levels while inhibiting at higher levels.[64]

Hyperprolactinaemia

An rise in circulating prolactin levels is referred to as hyperprolactinaemia, which typically causes reproductive issues in both sexes, particularly anovulatory infertility in females. There are three different types of hyperprolactinaemia: functional/physiological, factitious/ analytical, and pathological. The significant rise in prolactin that is found during nursing and pregnancy is called physiological hyperprolactinaemia. It's typical to experience functional hyperprolactinaemia brought on by therapeutic drugs that block dopamine release or its activity in the pituitary. [65]

Polycystic ovarian syndrome (PCOS), chronic renal failure, hepatic cirrhosis, epilepsy, chest trauma, primary hypothyroidism, Cushing's disease, and Addison's disease are among the conditions that frequently cause hyperprolactinaemia.[66]

Estimation of prolactin:

Hormonal and radiological tests are the two main ones used to diagnose hyperprolactinemia. The diagnosis of hyperprolactinaemia can be made with just one serum prolactin test that is

over the upper limit of normal and acquired without undue venepuncture stress. At least two to three hours after emerging from sleep, a fasting blood sample should be taken. Women have longer reference intervals than males for any particular assay.[61]

Relevant studies:

Animesh, D., et al.[67] studied serum Prolactin levels in 70 patients in comparision with Child Pugh Score. This a study of 70 patients showed that serum prolactin level correlated with the Child Pugh score in predicting the severity of the diseaseand patients with higher levels had increased complications like hepatic encephalopathy, esophageal varices.

Vikash Singh., et al.[68]compared serum prolactin levels in cirrhosis patients with Child Pugh score and concluded that prolactin not only can indicate the severity and prognosis of the disease but can also predict mortality.

Prashant, P., et al.[69] assessed the correlation of prolactin to the Child-Pugh Score and found that prolactin level can also be used for predicting mortality in patients with liver cirrhosis.

Debnath, A., et al.[67]assessed serum Prolactin level in Cirrhosis and deduced that it can be used in prediction of complications of the disease.

Sakhnani, D, R., et al.[70] assessed the relation between serum prolactin levels and the severity of the liver cirrhosis. The study concluded that Serum Prolactin levels showed positive correlation with Modified Child Pugh Score and Fibroscan in predicting the severity of disease.

Dr. Rajasekhara Pandian, T, K., et al.[71] conducted a study to correlate Child Pugh scoring which is used to determine the severity of cirrhosis and serum marker Prolactin. The study concluded that Serum prolactin levels are comparable with child Pugh score in prediction of severity and complications of cirrhosis. Prolactin levels can be used as negative prognostic marker.

Prabhu, P, P., et al.[72]evaluated the prognostic efficacy of serum prolactin and the ability of the same to predict severity and complications of cirrhosis in comparision to Child Pugh Score.It was observed that it can predict the complications of cirrhosis and can be used to assess the prognosis and hence can be used as a prognostic marker.

Balakrishnan, H, C., et al.[73]studied serum prolactin levels in cirrhosis of liver. This study shows that prolactin is a low cost blood marker that can predict the severity and increased occurrence of complications of cirrhosis of liver.

Metwally, R., et al.[74] study found that Prolactin can be used as a negative prognostic marker in liver cirrhosis as it increases exponentially with increased severity particularly in patients with hepatic encephalpathy and ascites.

Khalil, F, M., et al.[75] concluded that PRL level increases significantly with severity of liver disease particularly in patients with ascites and hepatic encephalopathy and can be considered as a negative prognostic marker.

Jha, S, K., et al.[76]deduced that prolactin has a significant correlation with grades of heaptic encephalopathy.

Giri, R., et al.[77] assessed and evaluated the serum prolactin level in hepatic encephalopathy (HE) patient. The higher the levels of serum prolactin the greater the severity and can be used in cirrhosis patients to determine the prognosis of the disease .It was found to be much higher in patients with complications like esophageal varices and hepatic encephalopathy .

Lacunae in Literature:

Biomarker diagnostic tests like prolactin levels for assessment of severity of liver cirrhosis are easy to perform and cost effective. Statistically empowered sample study sets are essential for judicious diagnostic biomarker selection. This study will fill that necessity by correlating serum prolactin levels with Child Pugh score for diagnosis and assessment of severity of liver cirrhosis.

MATERIALS AND METHODS

MATERIALS AND METHODS

SOURCE OF DATA: This study was conducted in R.L.JALAPPA hospital in patients who fulfill inclusion and exclusion criteria from outpatients and inpatients of R.L.JALAPPA hospital

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

1.Patients > 18 years

2.Patients with cirrhosis of liver

Exclusion criteria:

1.Cranial surgery

2.Pituitary or hypothalamic disease

3.Chronic renal failure

4.Seizure disorders

5.Chest wall trauma

Sampling size: The sample size was calculated using G*Power software version 3.1.9.7.and it came to be 69 subjects.

Methodology

Patients of chronic liver disease coming to the department of internal medicine fulfilling the inclusion and exclusion criteria were included in study. Informed written consent was taken

from all subjects. A carefully formulated proforma was used to collect the data. All patients were examined carefully.

Investigations:

- CBC
- RFT
- SERUM ELECTROLYTES
- Serum prolactin levels
- LFT
- Urine routine
- HCV
- HbsAg
- PT/apTT/INR
- USG abdomen

STATISTICAL METHODS:

Ascites, Hepatic Encephalopathy Grade, Varices, Spontaneous bacterial peritonitis, Child Pugh Score etc., were Primary outcomes. Prolactinbeing the secondary outcome. Descriptive analysis was carried out for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram, cluster bar chart. For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Kruskal Wallis Test (P Value) (>2 groups). Chi square test was used for comparison of two groups. The utility of

Serum Prolactin in predicting Severity of Child Pugh Score was assessed by Receiver Operative curve (ROC) analysis. area under the ROC curve along with its 95% CI and p value are presented. Basing on the ROC analysis, it was decided to consider 39.5 as the cut off value. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test with the decided cut off values along with their 95% CI were presented.

P value of <0.05 was considered as statistically significant.

Data was analyzed by using coGuide software.[78]

RESULTS

RESULTS

Table 4: Descriptive analysis of age (years) in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Age (years)	50.93±8.84	51.00	33.00	66.00	48.84	53.01

The mean age (years) was 50.93±8.84 with minimum age being 33 and maximum age 66 (95% CI 48.84 to 53.01). (Table 4)

Table 5: Descriptive analysis of gender in the study population (N=69)

Gender	Frequency	Percentage
Male	59	85.51%
Female	10	14.49%

59 **(**85.51%) participants were male and remaining 10 (14.49%) participants were female. (Table 5 & Figure 3)

Figure 3: Pie chart of gender in the study population (N=69)

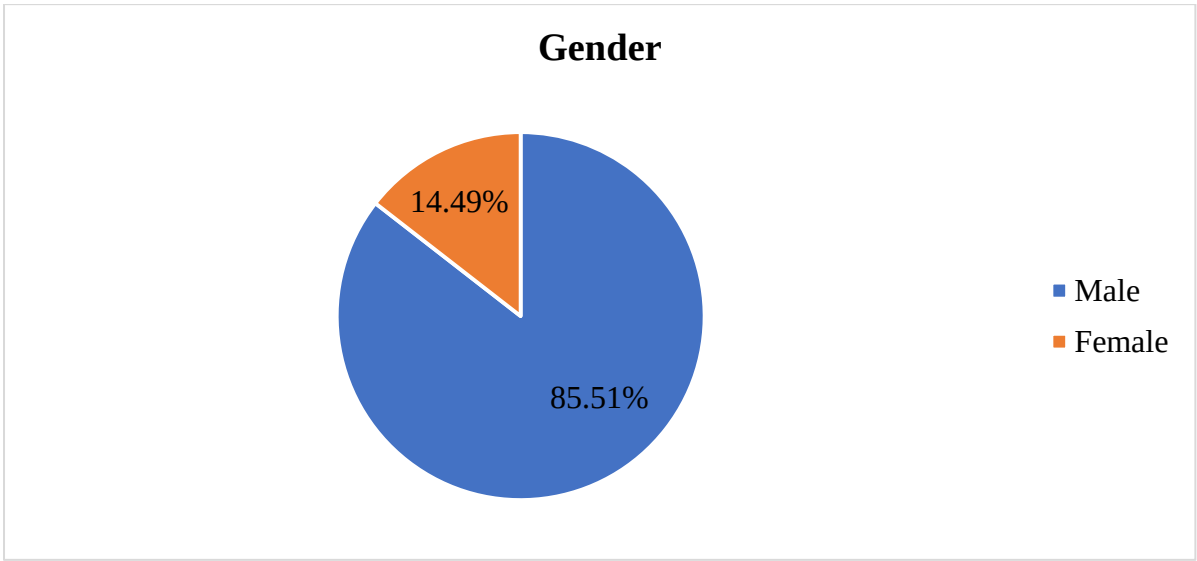


Table 6: Descriptive analysis of prolactin in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Prolactin	39.70±13.95	38.00	22.00	77.00	36.40	42.99

The mean prolactin was 39.70±13.95 in the study population, minimum level was 22 and maximum level was 77 in the study population (95% CI 36.40 to 42.99).

Table 7: Descriptive analysis of total bilirubin (mg/dl) in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Total bilirubin (mg/dl)	4.96±2.06	4.20	2.90	12.00	4.47	5.45

The mean total bilirubin (mg/dl) was 4.96±2.06, ranging from 2.90 to 12 (95% CI 4.47 to 5.45). (Table 7)

Table 8: Descriptive analysis of albumin (g/dl) in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Albumin (g/dl)	3.28±0.85	3.20	1.70	5.20	3.08	3.48

The mean albumin (g/dl) was 3.28±0.85 in the study population, Ranged between 1.70 g/dl to 5.20 g/dl (95% CI 3.08 to 3.48). (Table 8)

Table 9: Descriptive analysis of prothrombin time (sec)in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Prothrombin time (sec)	19.09±4.89	18.00	11.00	30.00	17.93	20.24

The mean prothrombin time (sec) was 19.09±4.89 in the study population, Ranged between 11 sec to 30 sec (95% CI 17.93 to 20.24). (Table 9)

Table 10: Descriptive analysis of international normalised ratio in the study population (N=69)

Name	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
International normalised ratio	1.83±0.50	1.80	1.00	3.40	1.72	1.95

The mean international normalised ratio was 1.83±0.50 in the study population, Ranged between 1 to 3.40 (95% CI 1.72 to 1.95). (Table 10)

Table 11: Descriptive analysis of ascites in the study population (N=69)

Ascites	Frequency	Percentage
Mild	18	26.09%
Moderate	13	18.84%
Severe	7	10.14%
Absent	31	44.93%

Among the study population, 18 (26.09%) participants had mild ascites, followed by moderate, severe had 13 (18.84%) and 7 (10.14%). (Table 11 & Figure 4)

Figure 4: Bar chart of ascites in the study population (N=69)

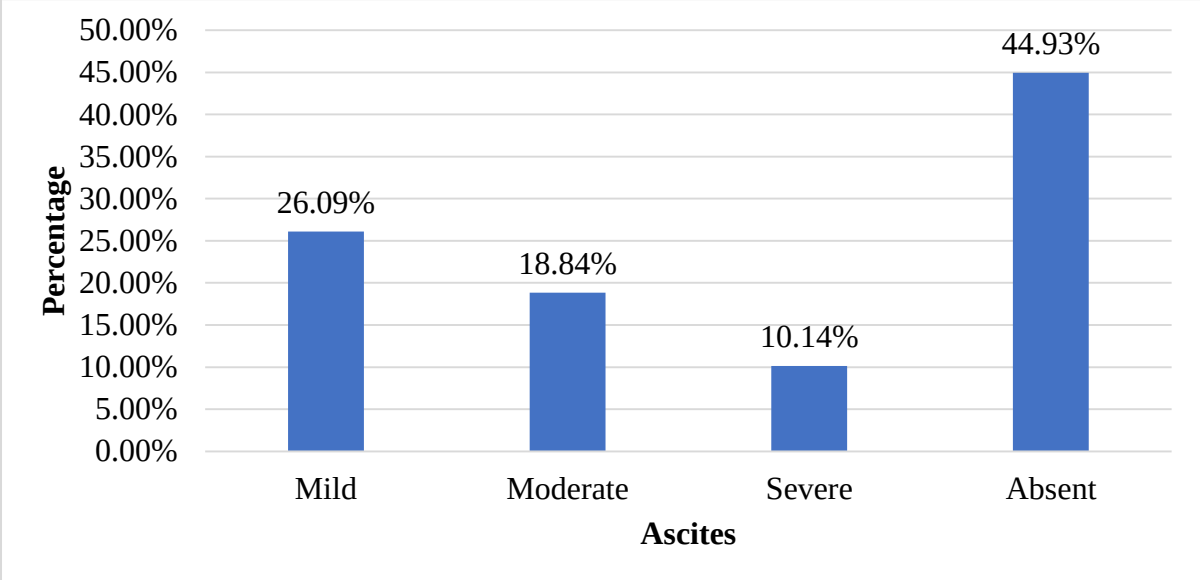


Table 12: Descriptive analysis of hepatic encephalopathy grade in the study population (N=69)

Hepatic Encephalopathy Grade	Frequency	Percentage
Grade 1	10	14.49%
Grade 2	6	8.70%
Grade 3	13	18.84%
Grade 4	7	10.14%
None	33	47.83%

Among the study population, 10 **(**14.49%) participants had hepatic encephalopathy grade 1, 6 (8.70%) had grade 2, 13 (18.84%) had grade 3, 7 (10.14%) had grade 4. (Table 12 and Figure 5)

Figure 5: Bar chart of hepatic encephalopathy grade in the study population (N=69)

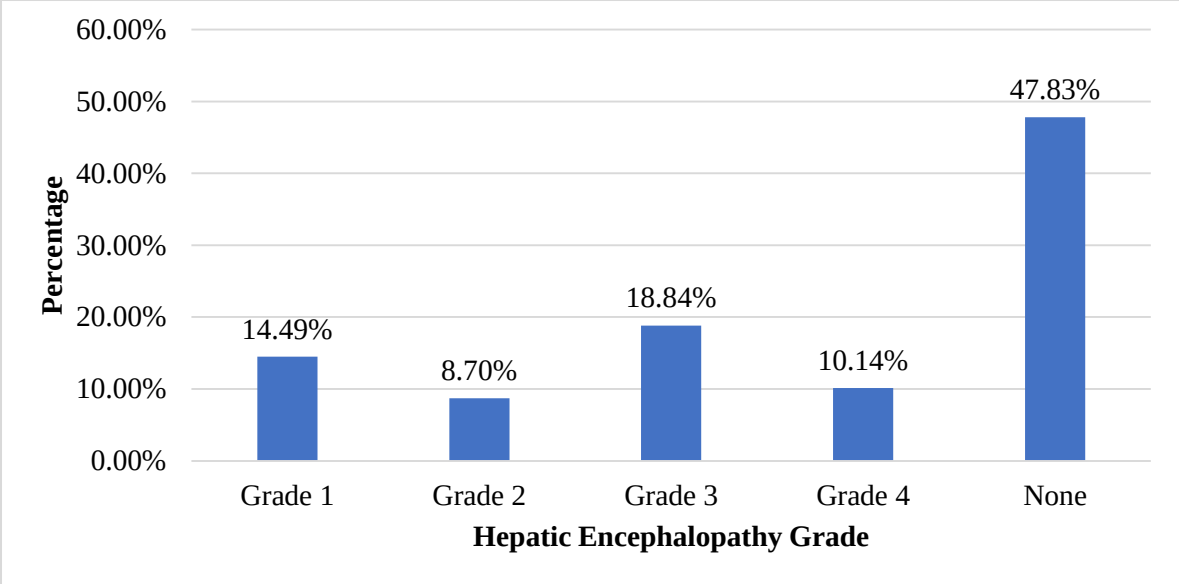


Table 13: Descriptive analysis of child pugh score in the study population (N=69)

Child Pugh Score	Frequency	Percentage
Class A	23	33.33%
Class B	23	33.33%
Class C	23	33.33%

Among the study population, class A, class B and class C all the child pugh score were with equal distribution as 23 **(**33.33%) each. (Table 13 and Figure 6)

Figure 6: Pie Chart of child pugh score in the study population (N=69)

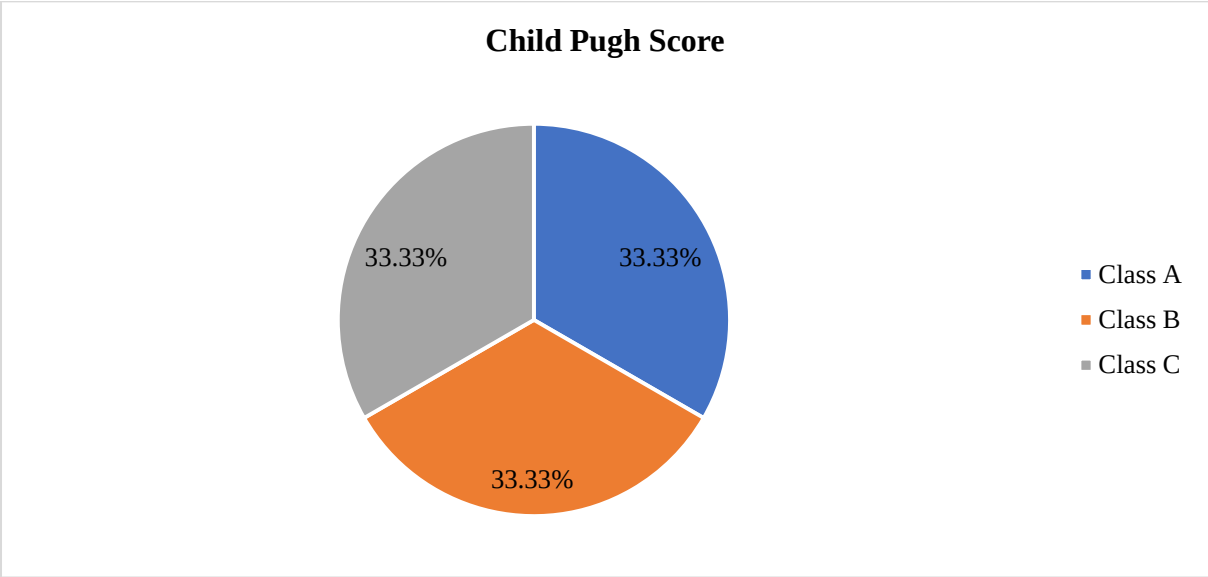


Table 14: Descriptive analysis of child pugh score in the study population (N=69)

Name	Mean ± S. D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Child pugh score	8.74±3.11	9.00	5.00	15.00	8.01	9.47

The mean child pugh score was 8.74±3.11 ranging between 5 to 15 (95% CI 8.01 to 9.47). (Table 14)

Table 15: Descriptive analysis of etiology in the study population (N=69)

Etiology	Frequency	Percentage
Alcohol	46	66.67%
Nash	7	10.14%
Viral	16	23.19%

Among the study population, 46 (66.67%) participants were with etiology as alcohol, 7 (10.14%) were with nash and 16 (23.19%) were with viral etiology. (Table 15 & Figure 7)

Figure 7: Bar chart of etiology in the study population (N=69)

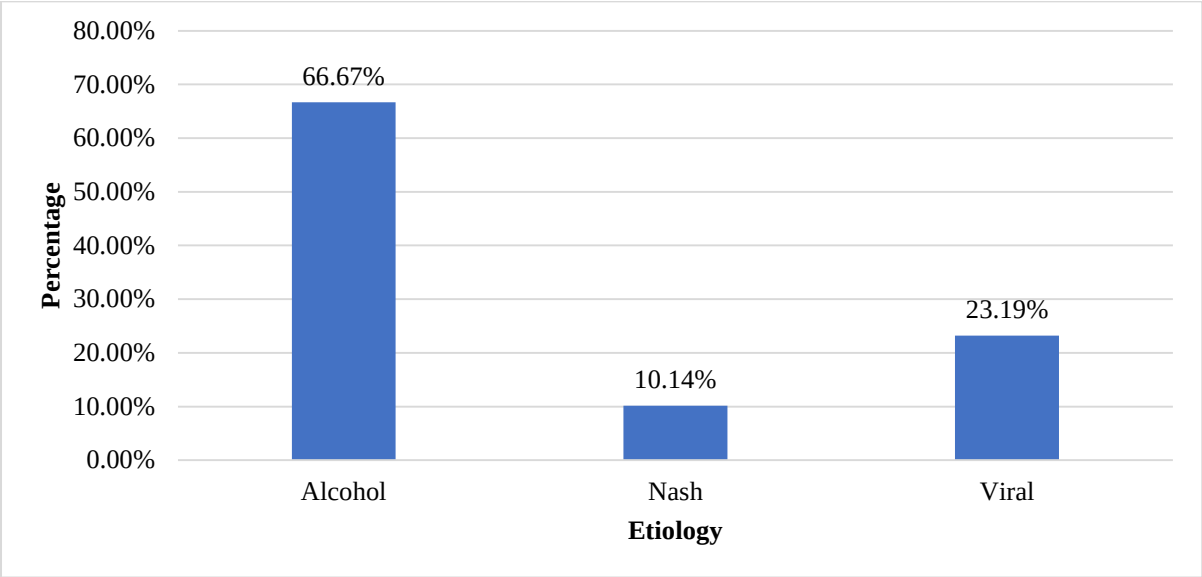


Table 16: Descriptive analysis of varices in the study population (N=69)

Varices	Frequency	Percentage
Yes	7	10.14%
No	62	89.86%

In this study, 7 (10.14%) participants had varices. (Table 16 and Figure 8)

Figure 8: Bar Chart of varices in the study population (N=69)

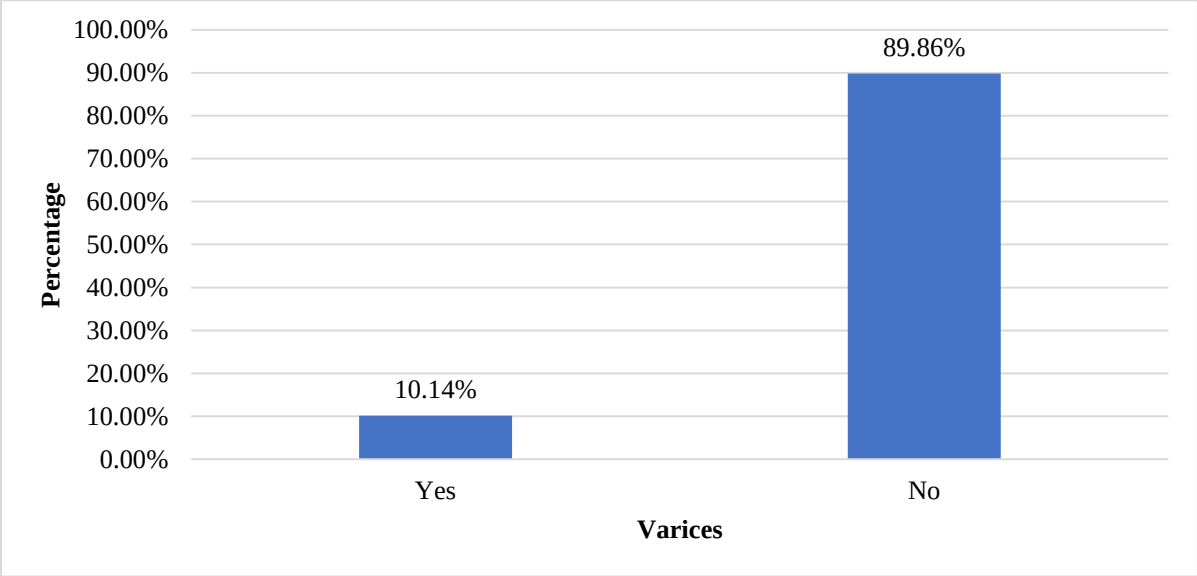


Table 17: Descriptive analysis of Spontaneous bacterial peritonitis in the study population (N=69)

Spontaneous bacterial peritonitis	Frequency	Percentage
Yes	7	10.14%
No	62	89.86%

Among this population, 7 (10.14%) participants had spontaneous bacterial peritonitis. (Table 17 and Figure 9)

Figure 9: Pie Chart of spontaneous bacterial peritonitis in the study population (N=69)

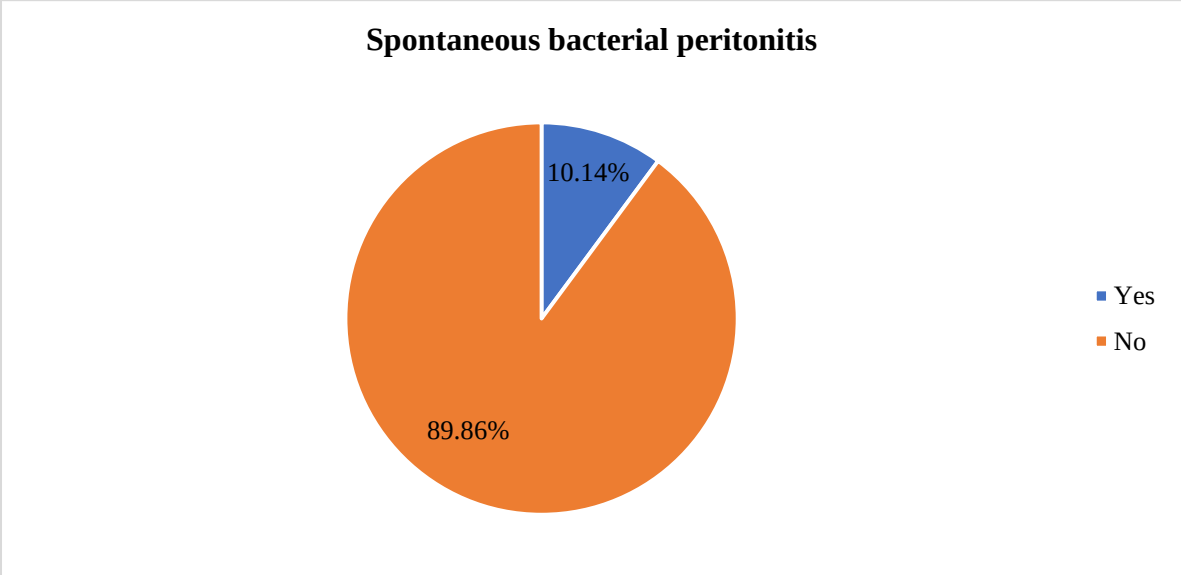


Table 18: Comparison of prolactin with ascites in the study population (N=69)

Parameter	Ascites (Median (IQR))				Kruskal Wallis Test (P Value)
	Mild (N=18)	Moderate (N=13)	Severe (N=7)	Absent (N=31)	
Prolactin	43.50(40.0 to 48.75)	52.00(40.0 to 58.0)	58.00(44.0 to 68.5)	27.00(25.0 to 30.0)	<0.001

The median prolactin of mild samples was 43.50(40.0 to 48.75), it was 52.00(40.0 to 58.0) in moderate, it was 58.00(44.0 to 68.5) in severe and it was 27.00(25.0 to 30.0) in absent of ascites. The median difference of prolactin across ascites was statistically significant with a P value of <0.001. (Table 18 & Figure 10)

Figure 10: Boxplot of comparison of prolactin with ascites in the study population (N=69)

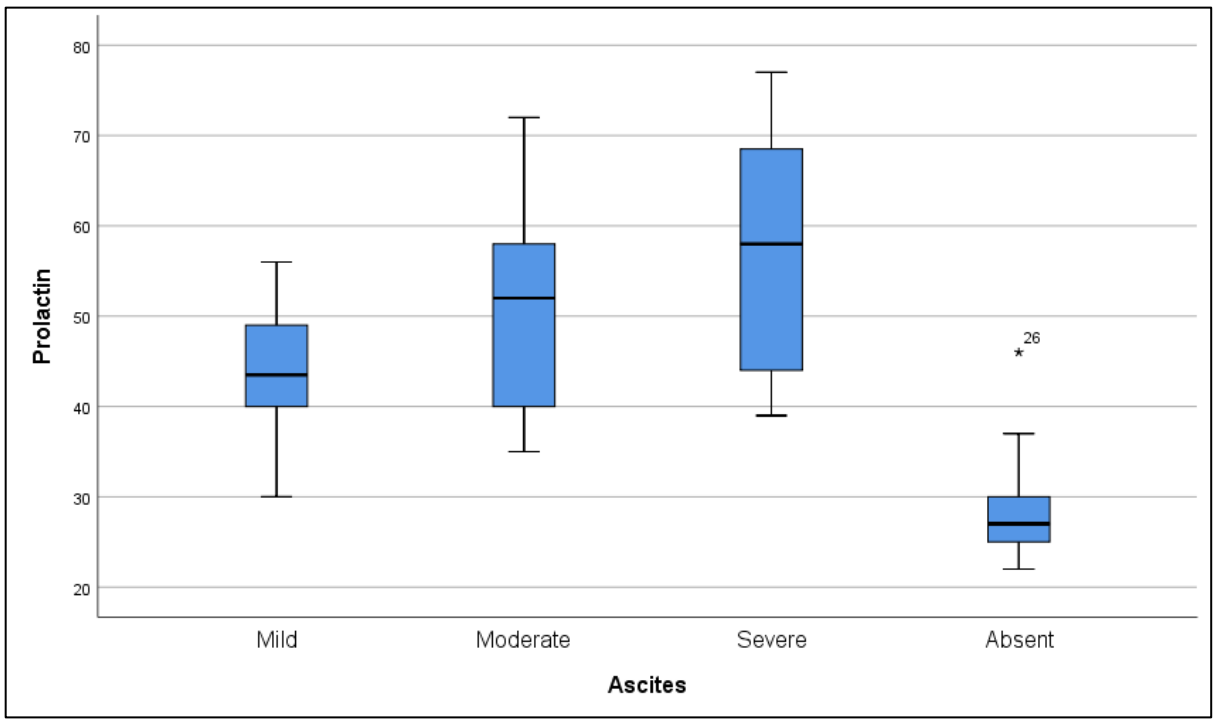


Table 19: Comparison of prolactin with hepatic encephalopathy grade in the study population (N=69)

Parameter	Hepatic Encephalopathy Grade (Median (IQR))					Kruskal Wallis Test (P Value)
	Grade 1 (N=10)	Grade 2 (N=6)	Grade 3 (N=13)	Grade 4 (N=7)	None (N=33)	
Prolactin	40.50(31.25 to 48.25)	43.00(39.25 to 50.5)	47.00(42.0 to 54.0)	66.00(61.5 to 71.5)	27.00(25.0 to 33.0)	<0.001

The median prolactin of hepatic encephalopathy grade 1 samples was 40.50(31.25 to 48.25), it was 43.00(39.25 to 50.5) in grade 2, it was 47.00(42.0 to 54.0) in grade 3, it was 66.00(61.5 to 71.5) in grade 4 and it was 27.00(25.0 to 33.0) in absent hepatic encephalopathy grade. The median difference of prolactin across hepatic encephalopathy grade was statistically significant with a P value of <0.001. (Table 19 and Figure 11)

Figure 11: Boxplot of comparison of prolactin with hepatic encephalopathy grade in the study population (N=69)

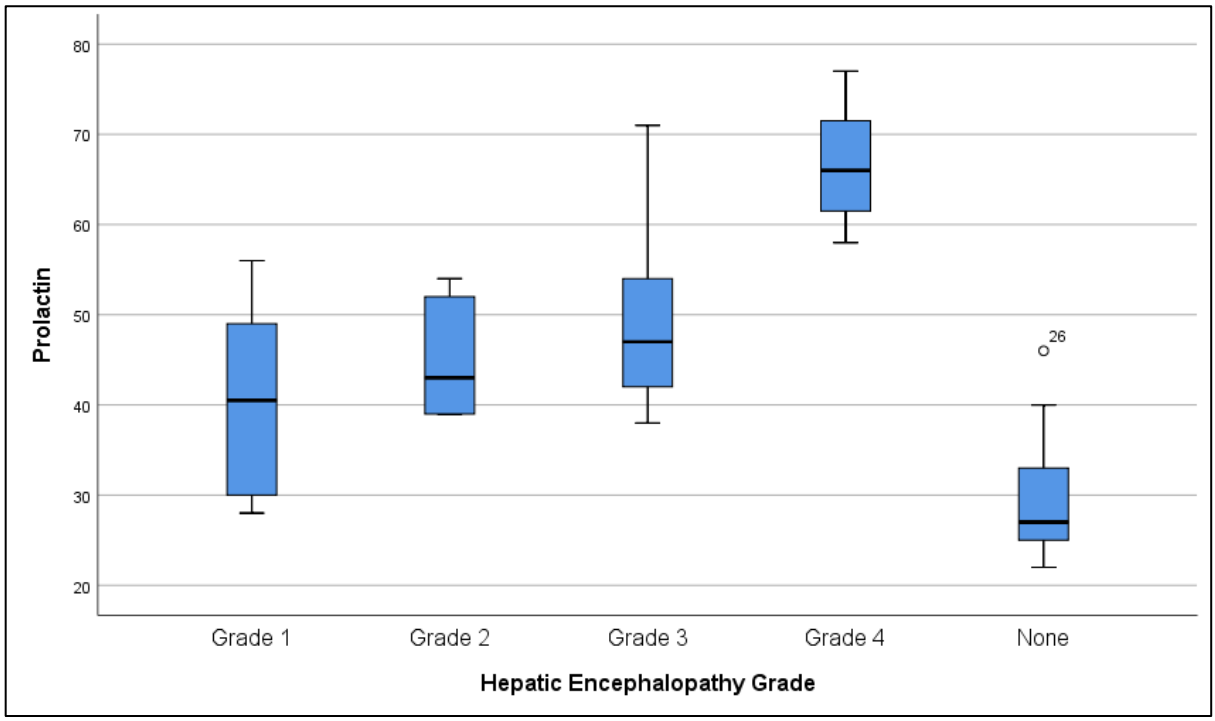


Table 20: Comparison of prolactin with varices in the study population (N=69)

Parameter	Varices		Mann Whitney U Test (P Value)
	Yes (N=7)	No (N=62)	
Prolactin	46.00(44.0 to 50.0)	35.00(27.0 to 46.75)	0.0108

The median prolactin was 46.00(44.0 to 50.0) in varices and it was 35.00(27.0 to 46.75) in no varices. The median difference of prolactin between varices was statistically significant with a P value of 0.0108. (Table 20 & Figure 12)

Figure 12: Boxplot of comparison of prolactin with varices in the study population (N=69)

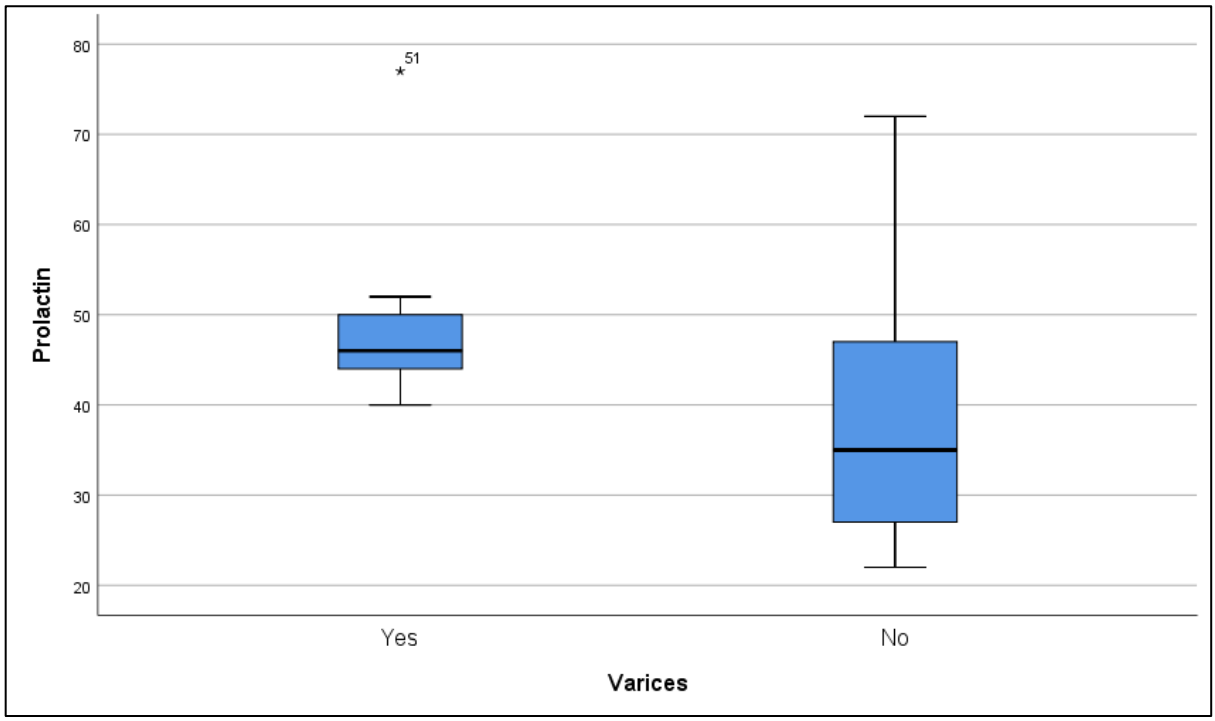


Table 21: Comparison of prolactin with spontaneous bacterial peritonitis in the study population (N=69)

Parameter	Spontaneous bacterial peritonitis		Mann Whitney U Test (P Value)
	Yes (N=7)	No (N=62)	
Prolactin	46.00(39.5 to 64.5)	36.00(27.0 to 46.75)	0.0147

The median prolactin was 46.00(39.5 to 64.5) in spontaneous bacterial peritonitis and it was 36.00(27.0 to 46.75) in no spontaneous bacterial peritonitis. The median difference of prolactin between spontaneous bacterial peritonitis was statistically significant with a P value of 0.0147. (Table 21 & Figure 13)

Figure 13: Boxplot of comparison of prolactin with spontaneous bacterial peritonitis in the study population (N=69)

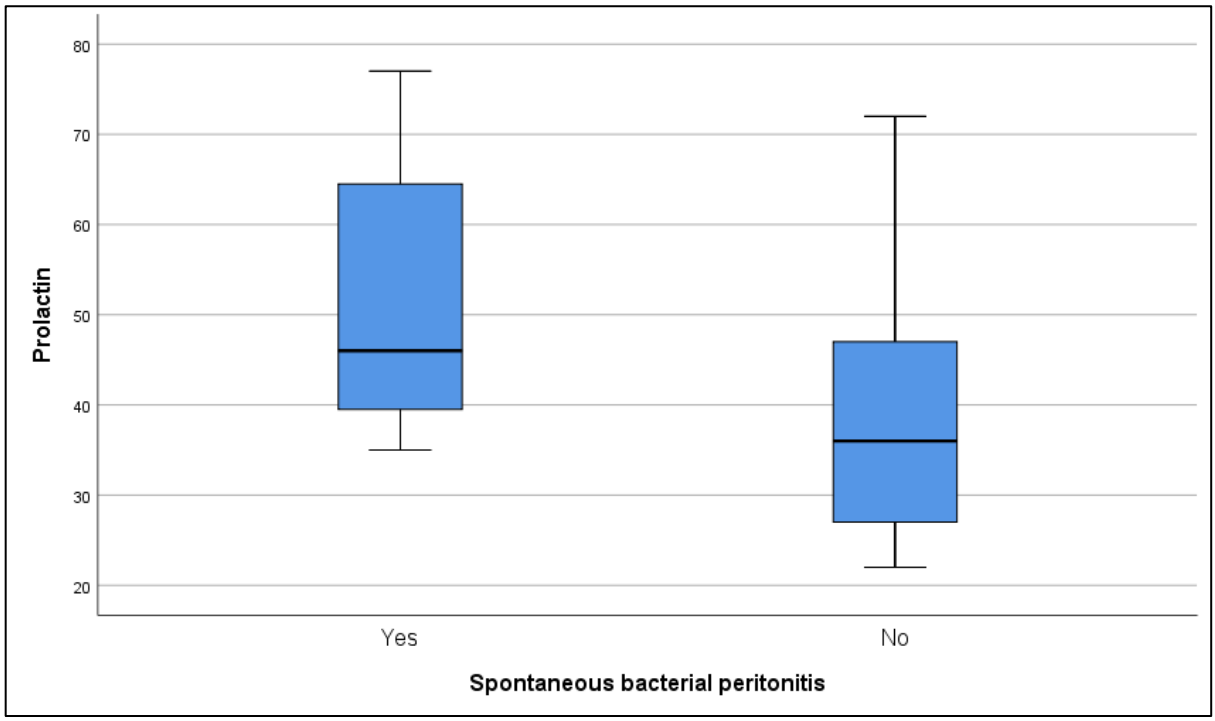
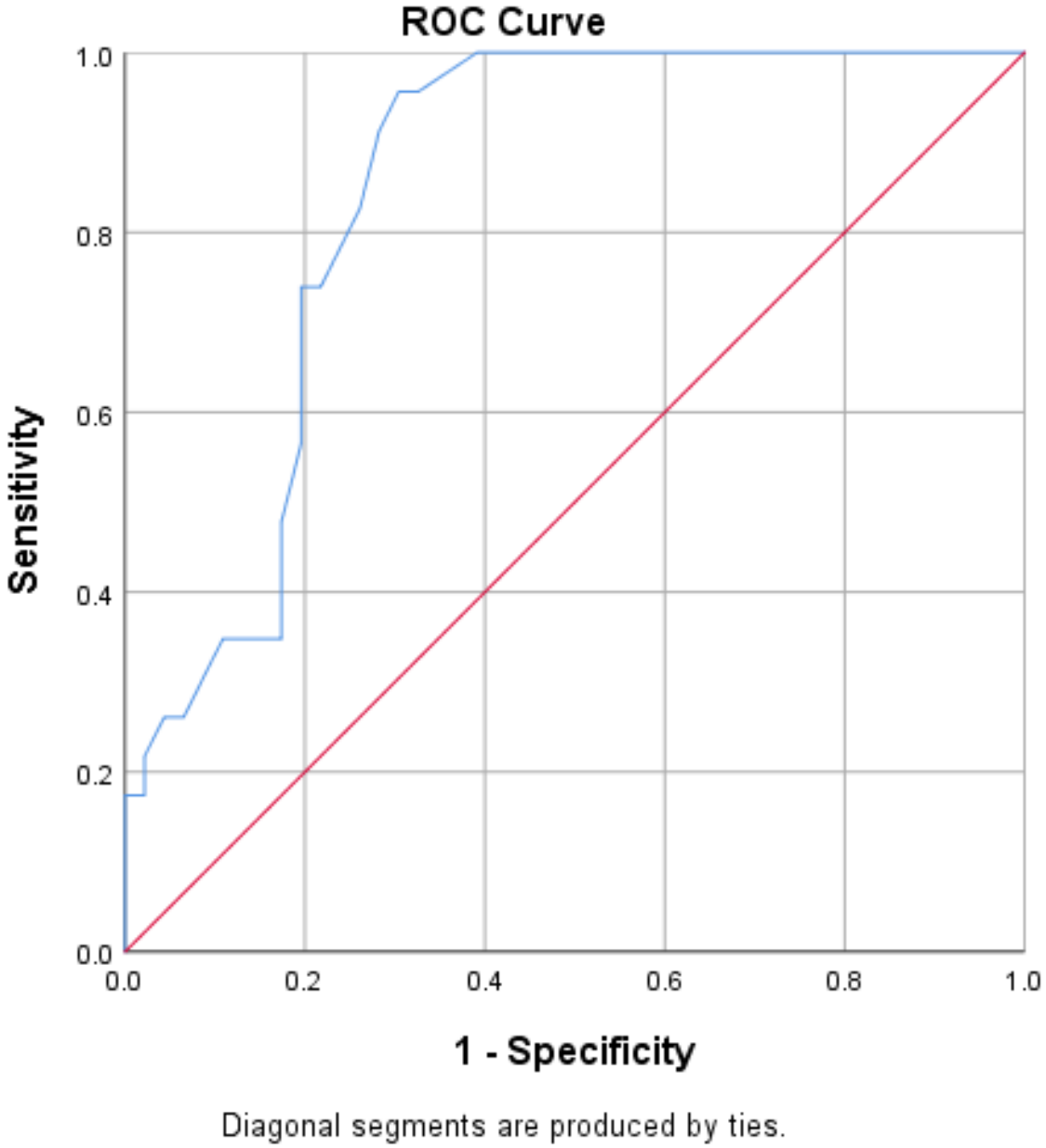


Figure 14: Receiver operating curve for serum prolactin in predicting severity (N=285)



Variable	Area under the curve	Std. Error[a]	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Serum Prolactin	0.845	0.046	0.000	0.755	0.934

Table 22: Comparison of serum prolactin with child pugh score in the study population (N=69)

Serum Prolactin	Child Pugh Score		Chi square	P value
	Severe (N=23)	Mild To Moderate (N=46)		
High (>=39.5)	19 (82.61%)	12 (26.09%)	19.798	<0.001
Low (<39.5)	4 (17.39%)	34 (73.91%)		

In sever child pugh score, 19 (82.61%) participants were high serum prolactin and 4 (17.39%) were low serum prolactin. In mild to moderate child pugh score, 12 (26.09%) participants were high serum prolactin and 34 (73.91%) were low serum prolactin. The difference inserum prolactin between child pugh score was statistically significant with a P value of <0.001. (Table 22 & Figure 15)

Figure 15: Cluster bar chart of comparison of serum prolactin with child pugh score in the study population (N=69)

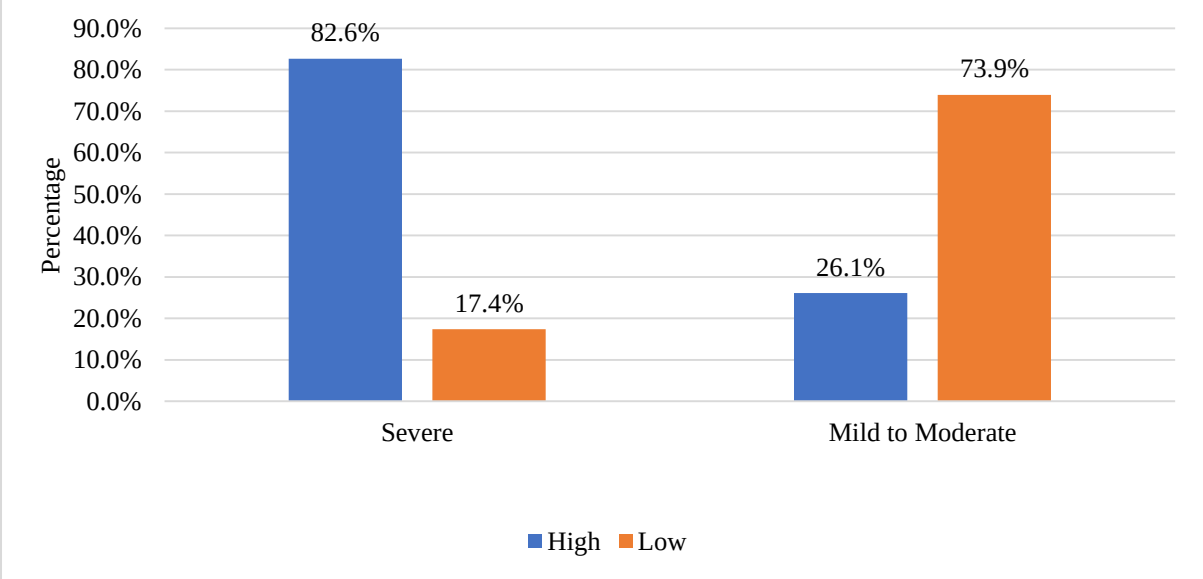


Table 23: Predictive validity of serum prolactin in predicting severe child pugh score in the study population (N=69)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	82.61%	61.22%	95.05%
Specificity	73.91%	58.87%	85.73%
False positive rate	26.09%	14.27%	41.13%
False negative rate	17.39%	4.95%	38.78%
Positive predictive value	61.29%	42.19%	78.15%
Negative predictive value	89.47%	75.20%	97.06%
Diagnostic accuracy	76.81%	65.09%	86.13%

The serum prolactin had sensitivity of 82.61% (95% CI 61.22% to 95.05%) in predicting severe child pugh score. Specificity was 73.91% (95% CI 58.87% to 85.3%), false positive rate was 26.09% (95% CI 14.27% to 41.13%), false negative rate was 17.39% (95% CI 4.95% to 38.78%), positive predictive value was 61.29% (95% CI 42.19% to 78.15%), negative predictive value was 89.47% (95% CI 75.20% to 97.06%), and the total diagnostic accuracy was 76.81% (95% CI 65.09% to 86.13%). (Table 23)

DISCUSSION

DISCUSSION:

Cirrhosis of the liver is linked to a number of endocrine system abnormalities, which are considered to be primarily brought on by the diseased liver's inefficient hormone clearance. It is now understood that altered secretion and feedback mechanisms are also part of the pathophysiology of impaired hormonal function in liver cirrhosis.[73]

Prolactin is one such hormone in this regard. The current theory on human prolactin is that it is a pituitary-derived hormone whose synthesisis regulated by dopamine and whose biological activities are solely related to breastfeeding and reproductive processes.[79]

There has been much discussion over the prolactin levels in individuals with hepatic impairment. The decrease in dopamine levels is the primary cause of the elevation of prolactin.[14] Dopamine-mediated hypothalamic inhibition and the stimulatory effects of circulating oestrogens are the primary regulators of prolactin release. These oestrogens operate directly on the anterior pituitary and dopamine production from the hypothalamus to increase prolactin release.[14]

A shift in the kind of amino acids entering the central nervous system results from decompensated liver function. The fake neurotransmitters may prevent the release of dopamine, which would lead to hyperprolactinemia.[17] Prognostic measures like the Child Pugh scoring system do not offer us an indication of the likelihood of complications due to the rising occurrence of the condition, particularly among Asian nations. [73] Therefore, a key tool in early management in such circumstances is the use of a biomarker, which can predict the severity and complications.

Age and gender

The present study was a cross-sectional study with 69 subjects. The mean age of the study population was 50.93±8.84 in the study population, with majority of them were males (85.51%) and female were 14.49%. A similar study by Balakrishnan, C, et al. [73] involving 60 patients, also found male predominance (83%) and female only 17%, were between the ages of 40 and 50. Hepatitis B infection (9%), followed by alcoholic liver disease (73%) were the two most frequent causes of cirrhosis in this research. [73] A comparable research conducted on 70 patients by Velissaris D et al.[14] where 26 subjects had cirrhosis and remaining were enrolled as controls, the mean age of the cirrhosis subjects was 64.6 ± 9.5 years with a 2:1 male to female ratio. Six individuals had cirrhosis of the liver and thirteen had viral hepatitis out of a total of 60 patients with liver disease who tested positive for HBsAg.[14] A recent study by Animesh, D et al. [80] involved 70 subjects with mean age 47 ±13 years, male predominance (ratio:4:1). Punekar, P et al.[81] involved 60 subjects with mean age of 44.9±12.8 years and male predominance (86.7%) and female 13.3%.

Aetiology and complications of liver cirrhosis

In the present study we found Ascites: Mild ascites in 26.9%, moderate ascites in 18.84% and severe inn 18.84%; hepatic encephalopathy: grade 1 in 14.49%, grade 2 in 8.7%, grade3 in 18.84% and grade 4 in 10.14%. Majority (66.67%) of the study population found alcohol as the main aetiology for cirrhosis followed by viral in 23.19% and NASH in 10.14%. Complications: Varices was found in 10.14% and spontaneous bacterial peritonitis was observed in 10.14% of the study population. Animesh, D et al. [80] study found majority of them had Ascites (98.5%), and portal hypertension (90%) followed by oesophageal varices in 62.85%, upper GI haemorrhage in 44.3% patients, and hepatic encephalopathy (grades 1-4) was present in 50 (71.42%) patients. [80] Punekar, P et al.[81] also found alcohol (55%) as major

etiology followed by hepatitis in 18.3%. Similarly, Balakrishnan et al. [73] found 73% having alcoholic cause followed by 9% and 5% positive for hepatitis B and C. Alcohol was found to be major etiology in the present study in other similar studies. However, in contrast a Hong et al[82], found hepatitis B virus (56%) to be the most frequent etiology.

Punekar, P et al[81] observed 13.3% to have varices, 78.3% had gross ascites, 11.7% had moderate ascites, hepatic encephalopathy grade 2 was found in 15% and grade 4 in 33% .Animesh, D et al. [80] found ascites in 98.5%, portal hypertension in 90%, varices in 62.85%, GI bleeding in 44.3% and hepatic encephalopathy grade1-IV in 71.42%. However, in our study the proportion of dtusy population with complications were less in comparison to these studies. [80, 81]

Biochemical analysis

In the present study the mean prolactin was 39.70±13.95, meantotal bilirubin (mg/dl) was 4.96±2.06 in the study population, the mean albumin (g/dl) was 3.28±0.85, the mean prothrombin time (sec) was 19.09±4.89, the mean international normalised ratio was 1.83±0.50. Khalil, F et al[83] study found mean prolactin levels to be with 18.76±9.14 ng/ml, the mean albumin level was 3.08±0.85 g/dl, the mean total bilirubin level 2.6±1.3 mg/dl, mean Prothrombin time 8.9±5.54 sec.

Child pugh score and serum prolactin

In the present study the distribution of class A, class B and class C was equal with 33.33% each in each class. The mean child pugh score was 8.74±3.11 in the study population. According to Khalil et al.[83] the mean child pugh score was 9.16±3.16.

Punekar, P et al[81] study observed from a total of 60 patients, 60% were categorised as having Class B, while 31.7% had a Child-Pugh Class C and only 8.3% individuals were Class A . Velissaris et al.[14] study found class A in 24.3%, class B in 22.9% and class C in 42.9% . In another study by Jha, S et al[76] found class A in 34.3%, class B in 22.9% and class C in 42.9%. Balakrishnan, C et al. [73] found 10% in class A, 40% in Class B and 50% in Class C. In the present study, severe child pugh score, 82.61% participants had high serum prolactin and 17.39% showed low serum prolactin. In mild to moderate child pugh score, 26.09% participants had high serum prolactin and 73.91% had low serum prolactin. The difference in the levels of serum prolactin when compared to child pugh score was statistically significant with a P value of <0.001.

In Balakrishnan, C et al. [73] study, 73.33% of the patients had elevated blood prolactin levels, and patients in higher Child Pugh classes had higher prolactin levels as well (B and C). This was consistent with research by Arafa M. et al[84], which found that prolactin levels rose as the Child Pugh class rose from A to C. Further, Animesh, D et al.[80] study showed that class C (78.5%) had mean prolactin 43.638 ng/ml and usual serum prolactin levels was found in all class A subjects. Hence they found a significant (p value < 0.001) higher score with child pugh class C. Similarly in the present study a significantly higher prolactin was found in Class C compared to Class A and Class B.

Serum prolactin levels in patients with aetiology and complications of cirrhosis:

The present study found a significant (P value <0.001) higher prolactin levels in severe ascites cases compared to mild and moderate cases and compared to cases without ascites ((median/ range: severe- 58.00(44.0 to 68.5), moderate-52.00(40.0 to 58.0), mild-43.50(40.0 to 48.75), and no ascites -27.00(25.0 to 30.0)).In contrast to our study findings, Khalil, F et

al.[83] s found no significant higher prolactin levels with severity of ascites (severe - 21.06±5.32ng/dl, moderate-20.05±9.06, mild-13.67±6.48, no ascites-18.13±11.38ng/dl). Punekar, P et al[81] also found no significant association between prolactin level and ascites.

The present study found a significant (P <0.001) higher median prolactin levels in grade 4 hepatic encephalopathy compared to grade 3, 2 and grade 1 (grade 4- 66.00(61.5 to 71.5), grade 3- 47.00(42.0 to 54.0), grade 2-43.00(39.25 to 50.5) and grade 1-40.50(31.25 to 48.25), whereas in cirrhosis cases without hepatic encephalopathy we found significantly lesser prolactin levels (median- 27.00(range 25.0 to 33.0) compared to cases present with hepatic encephalopathy.

Khalil, F et al.[83] found a significant (p <0.001) association of higher levels of prolactin to higher grades if hepatic encephalopathy (grade 4-32.66±2.76, grade 3-30.37±1.8, grade2-23.87±1.96, grade 1-17.54±4.3, no hepatic encephalopathy-13.22±6.32). In contrast to our findings Punekar, P et al[81] found no significant association between prolactin level and hepatic encephalopathy.

In the current study we found that significant higher prolactin levels were associated with varices compared no varices. In contrast, Punekar, P et al[81] found no significant association. Similarly, median prolactin was significantly higher in spontaneous bacterial peritonitis compared to no spontaneous bacterial peritonitis. According to our study, individuals with liver cirrhosis sequelae such hepatic encephalopathy, varices, and spontaneous bacterial peritonitis had higher blood prolactin levels. This was in line with research byBalakrishnan, C et al. [73] Koller T et al [85], who discovered that patients with greater ascites and encephalopathy stages had higher prolactin levels.

Predictive value of prolactin in predicting severity of liver cirrhosis

The serum prolactin had sensitivity of 82.61% specificity was 73.91%, false positive rate was 26.09%, false negative rate was 17.39%, positive predictive value was 61.29%, negative predictive value was 89.47%, and the total diagnostic accuracy was 76.81% in predicting severe child pugh score.

Jha, S et al.[76] evaluated the predictive value of prolactin in mortality of the liver cirrhosis subjects. They found sensitivity of 40%, specificity of 73.3%, positive predictive value of 66.7%, negative predictive value of 47.8%.

CONCLUSIONS

Since blood prolactin levels and the Child Pugh scoring system have a strong correlation, the study demonstrates that serum prolactin levels in individuals with liver cirrhosis can be used as a marker for the severity of the condition. Additionally, it shows that individuals with problems such hepatic encephalopathy, ascites have considerably higher serum prolactin levels, and that the severity increases with prolactin level. As a result, we draw the conclusion that serum prolactin levels can be employed as a helpful prognostic marker and a precursor for cirrhosis related complications.

LIMITATIONS AND RECOMMENDATIONS

- Our study's primary limitation is the existence of confounding variables, such as undetected comorbid diseases, which may result in elevated prolactin levels.
- A further drawback is the smaller sample size and study design.
- Future research is also necessary to compare prolactin levels to other complications like hepatopulmonary syndrome and hepatorenal syndrome. It is possible to conduct cohort studies to examine the connection between high levels of prolactin and death rates.

SUMMARY

The present study was a cross-sectional study with 69 subjects. The mean age of the study population was 50.93±8.84 in the study population, with majority of them were males (85.51%) and female were 14.49%. Severe child pugh score, 82.61% participants had high serum prolactin and 17.39% showed low serum prolactin. In mild to moderate child pugh score, 26.09% participants had high serum prolactin and 73.91% had low serum prolactin. The difference in the proportion of serum prolactin between child pugh score was statistically significant with P value <0.001 Ascites: Mild ascites in 26.9%, moderate ascites in 18.84% and severe inn 18.84%; hepatic encephalopathy: grade 1 in 14.49%, grade 2 in 8.7%, grade3 in 18.84% and grade 4 in 10.14%. Majority (66.67%) of the study population found alcohol as the main aetiology for cirrhosis followed by viral in 23.19% and NASH in 10.14%. Complications: Varices was found in 10.14% and spontaneous bacterial peritonitis was observed in 10.14% of the study population. The present study found a significant (P <0.001) higher median prolactin levels in grade 4 hepatic encephalopathy compared to grade 3, 2 and grade 1 (grade 4- 66.00(61.5 to 71.5), grade 3- 47.00(42.0 to 54.0), grade 2-43.00(39.25 to 50.5) and grade 1-40.50(31.25 to 48.25), whereas in cirrhosis cases without hepatic encephalopathy we found significantly lesser prolactin levels (median- 27.00(range 25.0 to 33.0) compared to cases present with hepatic encephalopathy. The serum prolactin had sensitivity of 82.61% specificity was 73.91%, false positive rate was 26.09%, false negative rate was 17.39%, positive predictive value was 61.29%, negative predictive value was 89.47%, and the total diagnostic accuracy was 76.81% in predicting severe child pugh score.

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ANNEXURES

PROFORMA FOR DATA COLLECTION

NAME: **AGE:**
SEX: **UHID NO:**
ADDRESS: **OCCUPATION :**

HISTORY:

GENERAL PHYSICAL EXAMINATION:

HEIGHT: WEIGHT:

PULSE: BLOOD PRESSURE:

SPO2 : RESPIRATORY RATE:

SYSTEMIC EXAMINATION:

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

PER ABDOMEN:

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

Complete Blood Count

Renal Function Tests

Serum Electrolytes

Serum Prolactin Levels

Liver Function Tests

Urine Routine

Hepatitis C Virus Antibody Test

Hepatitis B Surface Antigen Test

Prothrombin Time (PT) / Activated Partial Thromboplastin time (aPTT) / International Normalized Ratio (INR)

Ultrasound Abdomen with Elastography

Upper Gastrointestinal Endoscopy (If history is suggestive of varices)

Thyroid Stimulating Hormone (TSH) levels

Computed Tomography of Brain (If history and clinical examination suggestive of Pituitary / Hypothalamic disease.)

Chest X Ray

Urinary Pregnancy Test (For Females in Reproductive Age Group)

PATIENT INFORMATION SHEET

Study: "CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORE IN CIRRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE.

Investigators: Dr V Sujitha / Dr Srinivas S.V.

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details- All patients with liver cirrhosis will be included in the study. Patients who underwent cranial surgery or patients with Pituitary or hypothalamic disease , chronic renal failure,seizure disorders and chest wall trauma will be excluded.

The study aims to evaluate the diagnostic and prognostic significance of serum prolactin concentration in ddetermining the severity of liver cirrhosis as identified through Child Pugh Score.

Please read the information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

Dr. V Sujitha

Post graduate

Dept of General medicine, SDUMC Kolar

Mobile no: 8328307493

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ:

ಪ್ರಕರಣ ವರದಿ: ಡಯೋಜ್ - ಪಾಟರ್ ಸಿಂಡ್ರೋಮ್: ಸಾಲಿಟರಿ ಪ್ಲೀರಲ್ ಫೈಬ್ರಸ್ ಟ್ಯೂಮರ್‌ನೊಂದಿಗೆ ಹೈಪೊಗ್ಲಿಸಿಮಿಯಾ

ಸ್ಥಳ: ಆರ್‌ಎಲ್ ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ, ಟಮಕ, ಕೋಲಾರ.

ಡೊಗೆ ಪಾಟರ್ ಸಿಂಡ್ರೋಮ್ ಒಂದು ಅಪರೂಪದ ಪ್ಯಾರಾನೋಪ್ಲಾಸ್ಟಿಕ್ ಸಿಂಡ್ರೋಮ್ ಆಗಿದ್ದು, 4% ಸಾಲಿಟರಿ ಪ್ಲೆರಲ್ ಫೈಬ್ರಸ್ ಟ್ಯೂಮರ್ ನಲ್ಲಿ ನಾವು ಮರುಕಳಿಸುವ ಹೈಪೊಇನ್ಸುಲಿನೆಮಿಕ್ ಹೈಪೊಗ್ಲಿಸಿಮಿಯಾವನ್ನು ಎದುರಿಸುತ್ತಿದ್ದೆವು. ರೋಗಿಯ ಪರಿಣಾಮ.

ಸಂಬಂಧಿತ ಇತಿಹಾಸವನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು. ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿಯನ್ನು ಪ್ರಕಟಣೆಗಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ.

ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತು ಬಹಿರಂಗವಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ಪರಿಶೀಲಿಸಿದೆ ಮತ್ತು ನೀವು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯ ಸದಸ್ಯರನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಈ ಪ್ರಕರಣ ವರದಿಯನ್ನು ಒಪ್ಪಿಕೊಳ್ಳಬೇಕೆಂಬ ಒತ್ತಾಯವಿಲ್ಲ. ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುವ ಕಾಳಜಿಯು ಬದಲಾಗುವುದಿಲ್ಲ. ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಂಡರೆ ಮಾತ್ರ ನೀವು ಹೆಬ್ಬೆರಳಿನ ಗುರುತು ಸಹಿ/ ಒದಗಿಸಬೇಕಾಗುತ್ತದೆ.

INFORMED CONSENT FORM

CORRELATION OF SERUM PROLACTIN LEVEL TO CHILD PUGH SCORE IN CIRRHOSIS OF LIVER IN ASSESSING THE SEVERITY OF THE DISEASE.

Date:

I, _____ aged _____ ,after being explained in my own vernacular language about the purpose of the study and the risks and complications of the procedure, hereby give my valid written informed consent without any force or prejudice for testing proclatin levels.The nature and risks involved have been explained to me to my satisfaction. I have been explained in detail about the study being conducted. *I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.* I hereby give consent to provide my history, undergo physical examination, undergo the procedure, undergo investigations and provide its results and documents etc to the doctor / institute etc. For academic and scientific purpose the operation / procedure, etc may be video graphed or photographed. All the data may be published or used for any academic purpose. I will not hold the doctors / institute etc responsible for any untoward consequences during the procedure / study.

A copy of this Informed Consent Form and Patient Information Sheet has been provided to the participant.

_____ _____

(Signature & Name of Pt. Attendant) (Signature/Thumb impression & Name of Patient/Guardian)

(Relation with patient)

Witness 1:

Witness 2:

_____

(Signature & Name of Research person /doctor)

ಮಾಹಿತಿ ಕಾನ್ಸೆಂಟ್ ಫಾರ್ಮ್

ಪಿತ್ತಜನಕಾಂಗದ ಕಾಯಿಲೆಯ ತೀವ್ರತೆಯನ್ನು ನಿರ್ಣಯಿಸುವಲ್ಲಿ ಸಿರೊಹೋಸಿಸ್ ಆಫ್ ಲಿವರ್‌ನಲ್ಲಿ ಸೀರಮ್ ಪ್ರೋಲ್ಯಾಕ್ಟಿನ್ ಲೆವೆಲ್ ಅನ್ನು ಮಕ್ಕಳ ಪುಗ್ ಸ್ಕೋರ್‌ಗೆ ಪರಸ್ಪರ ಸಂಬಂಧ.

ದಿನಾಂಕ:

ನಾನು, _____ ವಯಸ್ಸಿನ _____,
ಅಧ್ಯಯನದ ಉದ್ದೇಶ ಮತ್ತು ಕಾರ್ಯವಿಧಾನದ ಅಪಾಯಗಳು ಮತ್ತು ತೊಡಕುಗಳ ಬಗ್ಗೆ ನನ್ನ ಸ್ವಂತ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಿದ ನಂತರ, ಪ್ರೊಕ್ಲಾಟಿನ್ ಮಟ್ಟವನ್ನು ಪರೀಕ್ಷಿಸಲು ಯಾವುದೇ ಬಲ ಅಥವಾ ಪೂರ್ವಾಗ್ರಹವಿಲ್ಲದೆ ನನ್ನ ಮಾನ್ಯ ಲಿಖಿತ ತಿಳುವಳಿಕೆಯ ಒಪ್ಪಿಗೆಯನ್ನು ಈ ಮೂಲಕ ನೀಡುತ್ತೇನೆ. ಸ್ವಭಾವ ಮತ್ತು ಅಪಾಯಗಳು ಒಳಗೊಂಡಿರುವ ನನ್ನ ತೃಪ್ತಿಗೆ ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ. ನಡೆಸುತ್ತಿರುವ ಅಧ್ಯಯನದ ಬಗ್ಗೆ ನನಗೆ ವಿವರವಾಗಿ ವಿವರಿಸಲಾಗಿದೆ. ನಾನು ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆಯನ್ನು ಓದಿದ್ದೇನೆ ಮತ್ತು ಯಾವುದೇ ಪ್ರಶ್ನೆ ಕೇಳುವ ಅವಕಾಶ ನನಗೆ ಸಿಕ್ಕಿದೆ. ನಾನು ಕೇಳಿದ ಯಾವುದೇ ಪ್ರಶ್ನೆಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ. ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಾನು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪುತ್ತೇನೆ. ನನ್ನ ಇತಿಹಾಸವನ್ನು ಒದಗಿಸಲು, ದೈಹಿಕ ಪರೀಕ್ಷೆಗೆ ಒಳಗಾಗಲು, ಕಾರ್ಯವಿಧಾನಕ್ಕೆ ಒಳಗಾಗಲು, ತನಿಖೆಗೆ ಒಳಗಾಗಲು ಮತ್ತು ಅದರ ಫಲಿತಾಂಶಗಳು ಮತ್ತು ದಾಖಲೆಗಳನ್ನು ವೈದ್ಯರಿಗೆ / ಸಂಸ್ಥೆಗೆ ಒದಗಿಸಲು ನಾನು ಈ ಮೂಲಕ ಒಪ್ಪಿಗೆ ನೀಡುತ್ತೇನೆ. ಶೈಕ್ಷಣಿಕ ಮತ್ತು ವೈಜ್ಞಾನಿಕ ಉದ್ದೇಶಕ್ಕಾಗಿ ಕಾರ್ಯಾಚರಣೆ / ಕಾರ್ಯವಿಧಾನ ಇತ್ಯಾದಿಗಳನ್ನು ವೀಡಿಯೊ ಗ್ರಾಫ್ ಮಾಡಬಹುದು ಅಥವಾ hed ಾಯಾಚಿತ್ರ ತೆಗೆಯಬಹುದು . ಎಲ್ಲಾ ಡೇಟಾವನ್ನು ಯಾವುದೇ ಶೈಕ್ಷಣಿಕ ಉದ್ದೇಶಕ್ಕಾಗಿ ಪ್ರಕಟಿಸಬಹುದು ಅಥವಾ ಬಳಸಬಹುದು. ಕಾರ್ಯವಿಧಾನ / ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ಅಹಿತಕರ ಪರಿಣಾಮಗಳಿಗೆ ನಾನು ವೈದ್ಯರು / ಸಂಸ್ಥೆ ಇತ್ಯಾದಿಗಳನ್ನು ಹೊಣೆಗಾರರನ್ನಾಗಿ ಮಾಡುವುದಿಲ್ಲ.
ಭಾಗವಹಿಸುವವರಿಗೆ ಈ ತಿಳುವಳಿಕೆಯುಳ್ಳ ಒಪ್ಪಿಗೆ ನಮೂನೆ ಮತ್ತು ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆಯ ನಕಲನ್ನು ಒದಗಿಸಲಾಗಿದೆ.

_____ _____

(ಸಹಿ ಮತ್ತು ಪಂ. ಅಟೆಂಡೆಂಟ್ ಹೆಸರು) (ಸಹಿ / ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ ಮತ್ತು ರೋಗಿಯ / ರಕ್ಷಕರ ಹೆಸರು)

(ರೋಗಿಯೊಂದಿಗಿನ ಸಂಬಂಧ)

ಸಾಕ್ಷಿ 1:

ಸಾಕ್ಷಿ 2:

(ಸಹಿ ಮತ್ತತ□ ಸಂಶ□ಧನಾ ವಿಯಕ್ತಿ / ವ□ದಿಯರ ಹೆಸರ□)

MASTERSHEET

Sr.No	Child Pugh Score (Original)	Child Pugh Score	Age	Gender	Prolactin	TB (mg/dl)	Albumin (g/dl)	PT (sec)	INR	Ascites	Hepatic Encephalopathy Grade	Score	Etiology	Varices	Spontaneous bacterial peritonitis
1	Class A	Mild to Moderate	45	Male	22	3.7	4	16	1.2	Absent	None	6	Alcohol	No	No
2	Class A	Mild to Moderate	36	Male	23	3.2	3.9	14	1.5	Absent	None	5	Alcohol	No	No
3	Class A	Mild to Moderate	62	Male	23	4	3.4	17	1.4	Absent	None	5	Alcohol	No	No
4	Class A	Mild to Moderate	46	Male	25	3.4	3.4	14	1.3	Absent	None	5	Viral	No	No
5	Class A	Mild to Moderate	50	Female	26	3.6	3.3	15	1.1	Absent	None	5	Viral	No	No
6	Class A	Mild to Moderate	38	Male	27	3.4	2.7	16	1.6	Absent	None	6	Alcohol	No	No
7	Class A	Mild to Moderate	43	Male	25	3.5	2.9	15	1.8	Absent	None	6	Alcohol	No	No
8	Class A	Mild to Moderate	55	Male	25	5.1	5	16	1	Absent	None	5	Alcohol	No	No
9	Class A	Mild to Moderate	47	Male	26	4.2	2.4	17	1.1	Absent	None	6	Nash	No	No
10	Class A	Mild to Moderate	37	Male	27	3.7	3.1	15	1.4	Absent	None	5	Alcohol	No	No
11	Class A	Mild to Moderate	45	Male	30	3.9	4.8	14	1.6	Absent	Grade 1	6	Alcohol	No	No
12	Class A	Mild to Moderate	63	Female	28	3	3.2	16	1.8	Absent	None	5	Alcohol	No	No
13	Class A	Mild to Moderate	47	Male	22	3.5	3.1	15	1.3	Absent	None	5	Viral	No	No
14	Class A	Mild to Moderate	66	Female	26	3.9	2.9	15	1.5	Absent	None	5	Alcohol	No	No
15	Class A	Mild to Moderate	54	Male	27	4	2.6	16	1.6	Absent	None	6	Alcohol	No	No
16	Class A	Mild to Moderate	58	Male	28	3.2	3	12	1.1	Absent	Grade 1	6	Viral	No	No
17	Class A	Mild to Moderate	51	Male	27	3.8	2.9	13	1.4	Absent	None	5	Nash	No	No
18	Class A	Mild to Moderate	49	Male	25	3.6	3.1	11	1.3	Absent	None	5	Alcohol	No	No
19	Class A	Mild to Moderate	37	Male	22	5	2.9	17	1.6	Absent	None	5	Alcohol	No	No
20	Class A	Mild to Moderate	39	Male	30	3.7	4.7	15	1.6	Absent	Grade 1	6	Alcohol	No	No
21	Class A	Mild to Moderate	48	Male	31	4	4.1	13	1.2	Mild	None	6	Nash	No	No
22	Class A	Mild to Moderate	44	Male	28	3.6	3.1	13	1.5	Absent	None	5	Alcohol	No	No
23	Class A	Mild to Moderate	38	Male	25	2.9	4	16	1.6	Absent	None	5	Viral	No	No
24	Class B	Mild to Moderate	45	Male	52	4	3.9	18	1.3	Moderate	Grade 2	9	Nash	No	No
25	Class B	Mild to Moderate	56	Male	40	3.5	2.9	16	1.72	Mild	None	9	Alcohol	No	No
26	Class B	Mild to Moderate	49	Male	46	3	3.1	17	2.3	Absent	None	7	Alcohol	Yes	No
27	Class B	Mild to Moderate	39	Male	55	3.3	4	20	2.2	Mild	Grade 3	9	Alcohol	No	No
28	Class B	Mild to Moderate	42	Male	30	4	3	17	1.8	Mild	None	8	Viral	No	No
29	Class B	Mild to Moderate	55	Male	39	4.6	3.8	15	1.6	Moderate	Grade 2	9	Alcohol	No	No
30	Class B	Mild to Moderate	59	Male	35	3.2	4.3	18	1.83	Moderate	None	8	Alcohol	No	Yes
31	Class B	Mild to Moderate	60	Male	29	4.2	3.4	15	1.6	Absent	None	7	Viral	No	No
32	Class B	Mild to Moderate	62	Male	30	4.6	2.9	19	1.9	Absent	None	8	Alcohol	No	No

33	Class B	Mild to Moderate	59	Female	32	5	2	30	2.2	Absent	None	9	Alcohol	No	No
34	Class B	Mild to Moderate	60	Male	66	3.3	4.2	16	1.4	Severe	Grade 4	9	Viral	No	No
35	Class B	Mild to Moderate	57	Male	56	3.2	3.9	15	1.6	Mild	Grade 1	7	Viral	No	No
36	Class B	Mild to Moderate	59	Male	38	4.6	3.4	18	1.8	Mild	None	9	Alcohol	No	No
37	Class B	Mild to Moderate	54	Male	35	4.4	3.8	18	1.9	Absent	None	7	Alcohol	No	No
38	Class B	Mild to Moderate	36	Male	33	5.4	4.1	22	2.2	Absent	None	8	Alcohol	No	No
39	Class B	Mild to Moderate	33	Female	37	3.8	5.2	20	1.9	Absent	None	7	Viral	No	No
40	Class B	Mild to Moderate	38	Female	49	4.8	3.9	24	2.2	Mild	Grade 1	9	Viral	No	No
41	Class B	Mild to Moderate	49	Male	58	3.9	4.7	17	1.6	Severe	Grade 4	9	Alcohol	No	Yes
42	Class B	Mild to Moderate	55	Male	40	3.3	3.9	25	2.4	Moderate	None	9	Viral	Yes	Yes
43	Class B	Mild to Moderate	63	Male	54	3.1	4.1	15	1.6	Moderate	Grade 2	8	Alcohol	No	No
44	Class B	Mild to Moderate	59	Male	52	3	3.6	18	2.2	Moderate	Grade 1	9	Alcohol	Yes	No
45	Class B	Mild to Moderate	57	Male	41	4.9	5	19	2.2	Mild	Grade 1	9	Nash	No	No
46	Class B	Mild to Moderate	48	Male	35	8	2.9	25	2.2	Absent	None	9	Alcohol	No	No
47	Class C	Severe	55	Male	71	5.6	2.2	19	1.6	Moderate	Grade 4	13	Alcohol	No	No
48	Class C	Severe	62	Male	46	4.9	3.3	20	1.9	Mild	Grade 2	10	Viral	No	No
49	Class C	Severe	45	Female	54	5.9	2.2	26	2.3	Mild	Grade 3	13	Viral	No	No
50	Class C	Severe	49	Male	72	8.9	2.1	28	2.2	Moderate	Grade 4	14	Nash	No	No
51	Class C	Severe	59	Male	77	6.1	3.4	26	2.5	Severe	Grade 4	14	Alcohol	Yes	Yes
52	Class C	Severe	63	Male	65	3.4	4.6	20	1.9	Moderate	Grade 4	10	Alcohol	No	No
53	Class C	Severe	61	Male	47	4.9	2.9	25	2.4	Mild	Grade 3	12	Alcohol	No	No
54	Class C	Severe	48	Male	40	6.6	2.2	23	1.9	Mild	Grade 1	10	Alcohol	No	No
55	Class C	Severe	55	Male	55	7.9	3.4	17	1.7	Mild	Grade 3	11	Alcohol	No	No
56	Class C	Severe	59	Male	48	9.3	2.1	26	2.4	Mild	Grade 3	13	Alcohol	Yes	No
57	Class C	Severe	39	Male	40	10	1.9	24	1.9	Mild	Grade 2	12	Viral	No	No
58	Class C	Severe	38	Male	39	7	3.2	19	1.9	Moderate	Grade 2	12	Alcohol	No	Yes
59	Class C	Severe	49	Male	38	8.2	3.3	26	3.2	Mild	Grade 3	13	Alcohol	No	No
60	Class C	Severe	51	Female	35	7.2	2.1	30	3.3	Absent	Grade 1	12	Nash	No	No
61	Class C	Severe	39	Female	42	8	1.8	28	3.4	Moderate	Grade 3	15	Viral	Yes	No
62	Class C	Severe	66	Male	45	5.9	2.1	19	1.9	Mild	Grade 3	12	Alcohol	No	No
63	Class C	Severe	63	Male	47	4.5	2.9	18	1.6	Moderate	Grade 3	11	Alcohol	No	No
64	Class C	Severe	58	Male	58	6.6	2.4	20	1.8	Moderate	Grade 4	14	Alcohol	No	No
65	Class C	Severe	47	Male	39	5.9	1.7	30	3	Severe	Grade 3	15	Alcohol	No	No
66	Class C	Severe	49	Male	42	12	2.9	24	1.7	Severe	Grade 3	13	Alcohol	No	No
67	Class C	Severe	51	Male	46	6.2	3.5	19	1.8	Severe	Grade 1	12	Alcohol	Yes	Yes
68	Class C	Severe	57	Male	42	4.5	3.8	22	1.7	Mild	Grade 3	11	Alcohol	No	No
69	Class C	Severe	59	Female	71	11.7	2.1	30	2.4	Severe	Grade 3	15	Alcohol	No	Yes