Study of Serum Prolactin as an Emerging Marker for Severity of Chronic Liver Disease and Its Correlation with Grading of Liver Fibrosis by Fibroscan

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Abstract:

Background: Chronic Liver Disease or Liver Cirrhosis is an irreversible disease that is predominantly caused by the necrosis of hepatocytes, the loss of the reticular network, and the regeneration of the remaining liver tissue by nodules. Transient elastography (FibroScan; Echosens, Paris, France) is a non-invasive, rapid, and innovative method for assessing liver stiffness. Cirrhosis of the liver is believed to be associated with ineffective elimination of hormones by the dysfunctional liver, which causes variety of endocrine system disturbances, including variation in Serum prolactin.

Aims & Objectives: The investigation of serum prolactin as an emerging marker for the severity of chronic liver disease and its correlation with the grading of liver fibrosis by FibroScan or Transient elastography.

Materials & Methods: An observational cross-sectional analytical Study with a total of 50 patients was conducted at SMS Medical College and attached group of hospitals, Jaipur for a time period of twelve months. Patients with more than 18 years of age and with an established diagnosis of liver cirrhosis were included. The study excluded pregnant and lactating women, patients with history of cranial surgery or irradiation, endocrine disorders, concomitant renal failure, and medications that affect prolactin levels (e.g., antipsychotics, antidepressants, D2 blockers, OCPs, H2 antagonists, etc.).

Results: In alcoholic cirrhosis patients, the mean serum prolactin level was 49.2 ng/ml, while in non-alcoholic cirrhosis patients, it was 46.6 ng/ml. In all patients, the mean Liver Stiffness Measurement (LSM) was highest (14.9 kPa) in cases with prolactin levels higher than 35 ng/ml, followed by 9.8 kPa in cases with prolactin levels between 20 and 35 ng/ml, and 7.5 kPa in cases with prolactin levels between 3 and 19 ng/ml. Serum prolactin was significantly raised in patients witn advanced fibrosis.

Conclusion: S. Prolactin levels have a substantial association with the severity of chronic liver disease, particularly in patients with decompensated liver functions. Additionally, there was a positive correlation between S.Prolactin and the grading of liver fibrosis carried out by FibroScan.

Keywords: FibroScan, Liver Cirrhosis, Transient elastography, Serum Prolactin

Introduction

Liver cirrhosis is the development of regenerative nodules and fibrosis in response to a prolonged hepatic insult. This process ultimately leads to liver failure and portal hypertension, which in turn leads to overt end-stage disease [1]. Cirrhosis is a significant cause of morbidity and mortality in individuals with chronic liver disease worldwide and was responsible for 2.4% of all global fatalities in 2019 [2]. Most prevalent cases of cirrhosis are caused by alcohol use disorder followed by hepatitis B, hepatitis C and nonalcoholic fatty liver disease (NAFLD) with many patients having overlapping causes [3].

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. Liver biopsy is currently considered the gold standard for assessing hepatic
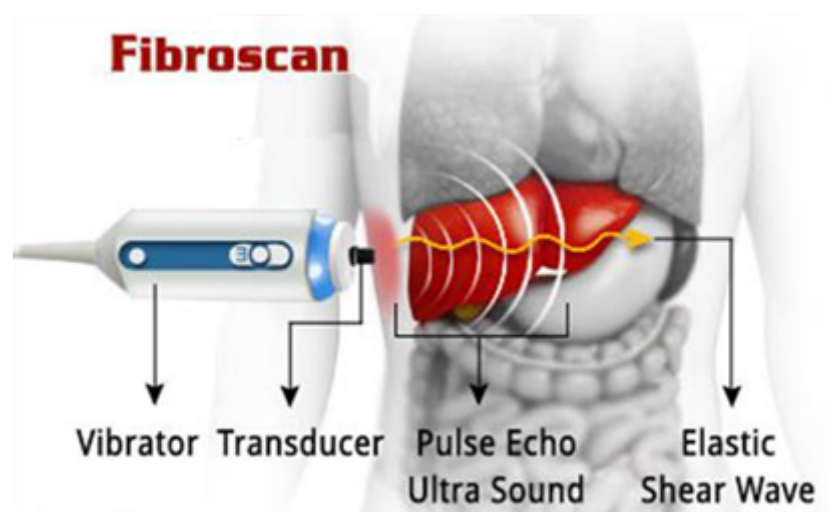
fibrosis but it's invasive and painful. Therefore, Transient elastography (FibroScan; Echosens, Paris, France) is considered as a novel, rapid, and non-invasive approach to measure liver stiffness [4]. The Child-Pugh scoring system, also referred to as the Child-Pugh-Turcotte score, was developed to predict mortality in patients with cirrhosis. Patients were classified according to five clinical and laboratory criteria in their initial scoring system: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status. Prothrombin time was substituted for clinical

nutrition status in the scoring system as a later modification. [5]

Cirrhosis of the liver is believed to be primarily caused by the ineffective elimination of hormones by the dysfunctional liver, which is associated with a variety of endocrine system disturbances. It is now recognized that the pathogenesis of perturbed hormonal function in liver cirrhosis is more intricate, involving altered secretion and feedback mechanisms. One such hormone in this respect is prolactin. Currently, human prolactin is considered a hormone of pituitary origin, and its secretion (i.e., serum levels) is regulated by dopamine [6]. There are numerous physiological factors that contribute to elevated levels of prolactin hormone, including puerperium, pregnancy, and breast stimulation. Pituitary tumors, head injury, brain surgery, chronic renal failure, hypothyroidism, cushing's syndrome, severe liver disease, particularly cirrhosis, celiac disease, and polycystic ovarian syndrome are among the pathological causes. [7]. This investigation was implemented to evaluate the correlation between serum prolactin concentrations and the severity of liver cirrhosis through FibroScan.

Transient elastography (FibroScan; Echosens, Paris, France) is a non-invasive, rapid, and innovative technique that quantifies liver stiffness. The probe of this system is an ultrasonic transducer that is affixed on the axis of a vibrator **[Figure 1]**.

Source: https://www.medindia.net/health/diagnosis/fibroscan-for-fatty-liver-cirrhosis-and-fibrosis.htm
Figure 1: Fibroscan Technique

The transducer transmits a low-frequency, mild-amplitude vibration from the vibrator to the tissue. This vibration generates an elastic shear wave that propagates throughout the tissue. In the interim, pulse-echo ultrasonic acquisitions are implemented to monitor the velocity of the shear wave and track its propagation, which is directly proportional to tissue stiffness. The shear wave propagates at a higher rate as the tissue becomes harder. FibroScan measurement of liver rigidity has been demonstrated to accurately predict hepatic fibrosis in patients with chronic HCV infection, according to recent reports. In patients with chronic hepatitis C, liver stiffness measurements ranged from 2.4 to 75 kPa, with a median value of 7.4 kPa. Based on the stiffness measurement distribution according to fibrosis stage and receiver operating characteristic (ROC) curves, the cut-off value for cirrhosis was 12.5 kPa [8].

 Materials & Methods

This cross-sectional observational study was conducted at SMS Medical College, and the attached group of institutions in Jaipur over twelve-month duration, with a total of 50 patients. The study included patients who were at least 18 years of age and had a confirmed diagnosis of liver cirrhosis. Pregnant and lactating women, patients with a history of cranial surgery/irradiation, endocrine disorders, concomitant renal failure, and medications that effect prolactin levels (e.g., antipsychotics, antidepressants, D2 blockers, OCPs, H2 antagonists,), were excluded from the study. The routine work-up for chronic liver disease was done on study subjects, which included: Complete blood counts, Urine routine, Renal function tests (RFT) , Coagulation Profile (PT-INR) and Liver Function Tests(LFT) , Serum Prolactin , Ultrasound abdomen for liver echotexture , size, splenic enlargement, and portal vein diameter ,Hepatitis B Antigen (HBsAg) , anti-Hepatitis C Virus (HCV) antibodies and Fibroscan.

The patients underwent a comprehensive clinical examination to detect the presence of cirrhosis of the liver and its complications, including portal hypertension, ascites, and hepatic encephalopathy,

as well as to obtain a detailed history, including their personal history and past treatment, in order to identify potential etiologies.

The Department of Radiology conducted Liver Stiffness Measurement (LSM) in Liver Cirrhosis patients using Fibroscan (Transient Elastography, M probe, Echosens). The median liver stiffness of the 10 successful measurements that met the criteria (success rate of greater than 60% and interquaartile range/median ratio of <30%) was recorded in kPa. During whole procedure , the patient were in dorsal decubitus with the right arm in maximal abduction, and measurements were taken on the right lobe of the liver through intercostal spaces and grading was done using Metavir Grading. [Figure 2]
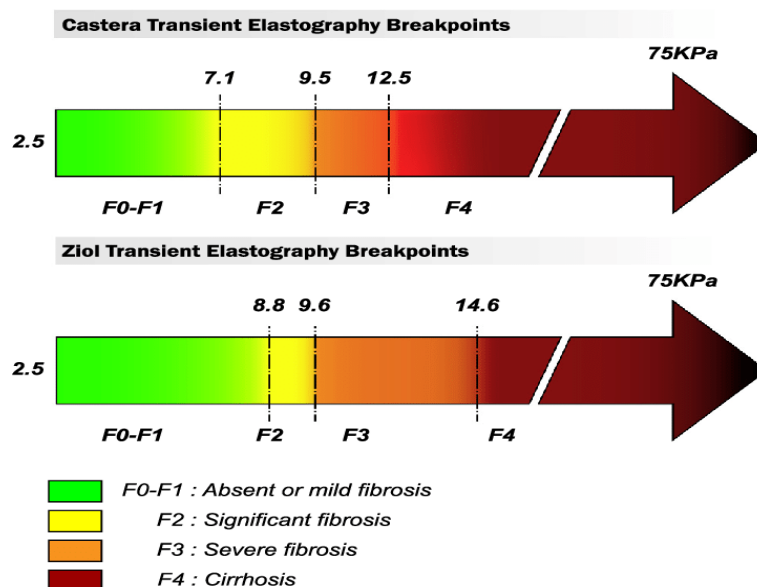

Figure 2: Grading of Liver Fibrosis by Fibroscan
Source: https://www.sciencedirect.com/science/article/abs/pii/S2352431618302396

Serum prolactin was quantified by using ng/mL (mass units) or μIU/mL (SI units). 1 ng/mL = 21.2 μIU/mL was the conversion formula. The data collected was analyzed using SPSS Version 19 software and e-computed on Microsoft Office version 2010.

Results & Observations

The mean age of patients was 49.4 years with majority 58% of cases belonged to 41-60 years age group and 18% cases were in age group of above 60 years. Majority 72% were males and

28% were females. Out of 50 cases 56% were having Alcoholic Cirrhosis and rest

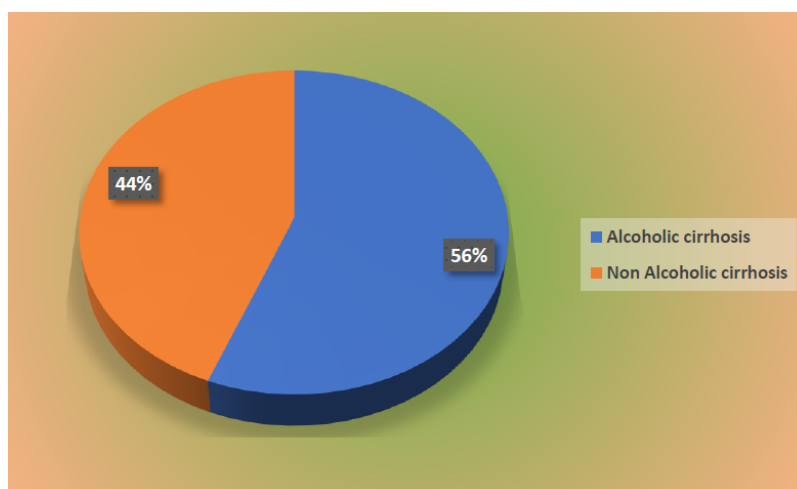44% were having Non-Alcoholic Cirrhosis. **[Figure 3]**

Figure 3: Distribution of cases according to etiology

In all cases mean albumin, bilirubin, INR and prolactin was 2.8 g/dl, 4.8 mg/dl, 2.2 and 48.1 ng/ml respectively. **Table No 1** shows 62% of cases had serum prolactin level >35 ng/ml followed by 22% had 20-35 ng/ml and 16% had 3-19 ng/ml. The mean serum prolactin level in cases was 48.10 ng/ml. In alcoholic cirrhosis, 71.4% cases had serum prolactin>35 ng/ml followed by 17.8% had serum prolactin level between 3-19 ng/ml and 10.7% had serum prolactin between 20-35ng/ml.

The mean serum prolactin was 49.2 ng/ml in alcoholic cirrhosis patients.

In non-alcoholic cirrhosis, 50% cases had serum prolactin>35 ng/ml followed by 36.3% had

serum prolactin level between 20-35 ng/ml and 13.6% had serum prolactin between 3-19 ng/ml. The mean serum prolactin was 46.6 ng/ml in non-alcoholic cirrhosis patients.

Table 1: Distribution of Serum Prolactin level in cases according to etiology

S. Prolactin (ng/mL)	All patients	Alcoholic cirrhosis (N=28)	Non Alcoholic cirrhosis (N=22)
	N(%)	N(%)	N(%)
3-19 ng/mL	8 (16%)	5 (17.8%)	3 (13.6%)
20-35 ng/mL	11 (22%)	3(10.7%)	8 (36.3%)
>35 ng/mL	31 (62%)	20(71.4%)	11 (50%)
Total	50	28	22
Mean±SD	48.1±26.8	49.2±25.1	46.6±29.4
P-value	0.8319		

As shown in **Table No 2**, Mean LSM was highest (14.9 kPa) in cases having prolactin >35 ng/ml followed by 9.8 kPa in cases having prolactin 20-35 ng/ml and 7.5 kPa in cases having prolactin 3-19 ng/ml. Serum prolactin was significantly raised in patients witn advanced fibrosis **[Figure 4]**.The result was highly significant with p-value less than 0.0001.

Table 2: Fibroscan results according to serum prolactin level

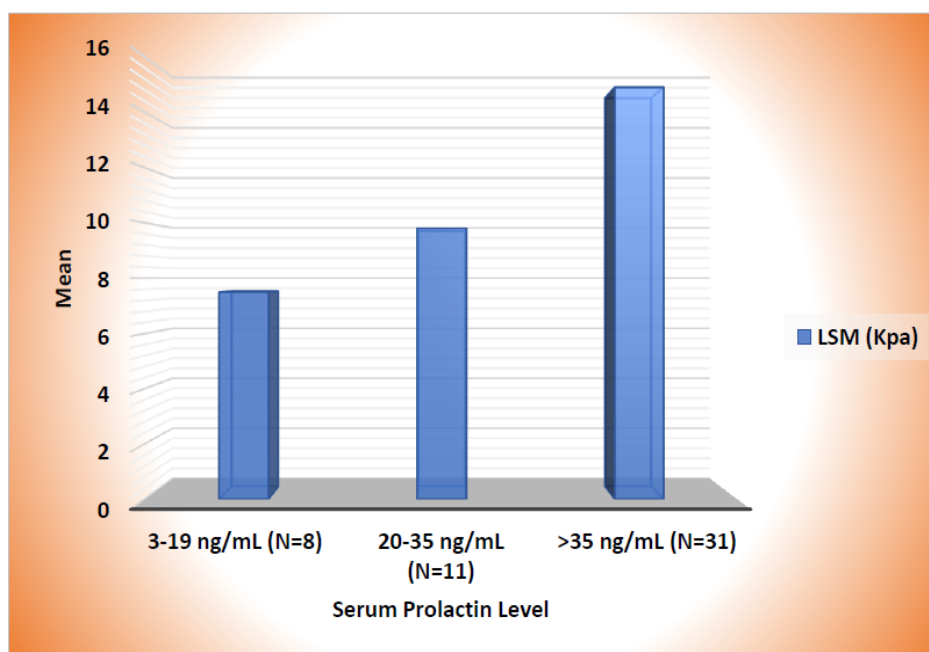| Prolactin	LSM (Kpa)	
	Mean	SD
3-19 ng/mL (N=8)	7.5	0.96
20-35 ng/mL (N=11)	9.8	0.49
>35 ng/mL (N=31)	14.9	2.7
P-value	<0.0001	

Figure 4: Correlation of Fibroscan with S. Prolactin

Discussion

Chronic Liver Disease or Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture. This distortion results in increased resistance to portal blood flow and leads to portal hypertension and in hepatic synthetic dysfunction. It results into progressive liver fibrosis which is a common consequence of chronic liver disease. The various etiologies are viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), autoimmune liver disease, and genetic disorders, amongst others [9].

A variety of scoring systems, such as the Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) score, MELD-Na, and MELD to serum sodium ratio (MESO), albumin-bilirubin (ALBI) score, and Fibrosis-4 (FIB-4) index, are beneficial in evaluating the severity of liver disease and predicting prognosis. [10] Traditionally, liver biopsy was considered to be the "gold standard" for evaluating liver pathology. It serves as a critical component for the diagnosis and treatment of the majority of liver diseases. However, it is an invasive procedure that necessitates the patient to be hospitalized for half a day, is costly, and is associated with certain risks, including bleeding and pain. Fibroscan is one such test that provides numerous benefits over liver biopsy. It is non-invasive, can be conducted at the point of care, does not induce discomfort, and does not require sedation. Also, the test is significantly less expensive than liver biopsy, requires only 5–7 minutes to perform, and has not been associated with any reported adverse effects. [11]

Cirrhosis may be compensated without overt complications or decompensated by the appearance of complications. Patients with compensated cirrhosis may exhibit nonspecific symptoms or may be asymptomatic. Their complaints may include fatigue, anorexia, or weight loss. Patients may exhibit jaundice, pruritus, symptoms of upper gastrointestinal bleeding, abdominal distension due to ascites, or confusion due to hepatic encephalopathy when decompensation occurs. In males, typical clinical examination findings include jaundice, stellate angiomas, palmar erythema, foetor hepaticus, asterixis, hypogonadism, and feminization. Other signs of portal hypertension include splenomegaly, cutaneous collateral venous circulation, and ascites. [12]

Prolatin is defined as a pituitary-secreted polypeptide hormone which was named for its stimulatory action on lactation [13]. After a report that the number of prolactin secreting cells in the anterior pituitary was increased in approximately a half of patients with Laennec-s cirrhosis, several studies reported elevated prolactin levels in this condition. In a study conducted by Malespin and Nassri, it was discovered that central hypogonadism also occurs in patients with cirrhosis, which leads to an increase in prolactin levels and a decrease in pituitary secretion of LH. The increased peripheral aromatization of testosterone to estrogen and impaired hepatic metabolism in men with cirrhosis frequently result in elevated estrogen levels. LH and FSH levels do not rise in response to a decrease in sex hormone production for reasons that remain unclear. The clinical consequences of antecedent hormonal alterations, such as hypogonadism and sexual dysfunction, may persist, despite the fact that this biochemical trend improves with liver transplantation. [14]

Generally prolactin levels seem to be higher in relation to the extent of the liver parenchymal damage, although this is not invariably so. Morgan et al. found hyperprolactinemia in 4% of patients with alcoholic steatosis and in 16% of patients with alcoholic hepatitis and cirrhosis. Wernze et al. found hyperprolactinemia in 27% of patients with cirrhosis with- out ascites but in 47% of patients with ascites, while Thiel et al. found a tendency towards a relationship between liver function parameters and basal plasma prolactin levels. Langer et al. found higher plasma prolactin concentrations in decompensated liver disease than in compensated liver disease, while the response to Thyrotropin-releasing hormone (TRH) was significantly increased. [15,16]

In our study, out of 50 cases 28 (56%) were having Alcoholic Cirrhosis and rest 22 (44%) were having Non-Alcoholic Cirrhosis. In alcoholic cirrhosis patients mean age was 48.5 years and in non-alcoholic cirrhosis patients was 50.5 years. The difference in both the groups was statistically non-significant as p-value was greater than 0.05. Maitra et al [17] found that alcohol was identified as the most common cause of cirrhosis (62.5%) followed by Hepatitis B (11%), cryptogenic (9.5%), NASH (9%) and Hepatitis C (3.5%). Chacko and Reinus studied that Men are more likely to develop ALD than women because men consume more alcohol. However, women are more susceptible to alcohol hepatotoxicity and have twice the relative risk of alcoholic liver disease (ALD) and cirrhosis compared with men. [18]

Our study shows 62% of cases had serum prolactin level >35 ng/ml followed by 22% had 20-35 ng/ml and 16% had 3-19 ng/ml. The mean serum prolactin level in cases was 48.10 ng/ml . Jha and Kannan (2016) conducted a study with an objective

to assess the prolactin levels in patients with cirrhosis and viral hepatitis with or without features of encephalopathy. A total of 70 patients (10-normal healthy; 25 - acute viral hepatitis; 35 - cirrhosis liver) were recruited in the present study with the median (range) age in years of 56 (34–68) and male: female ratio of 2:1. A statistically significant (P < 0.05) increase in the serum prolactin was observed in patients with cirrhosis with or without encephalopathy. But, among the patients with viral hepatitis, a significant elevation was observed only in patients with encephalopathy. Additionally, a statistically significant association was observed between serum prolactin levels with serum bilirubin (ρ =0.67, P = 0.04) and aspartate aminotransferase (ρ =0.72, P =0.05). A cut-off value of 50 ng/ml of serum prolactin was found to predict the mortality. A total of 4/12 (33.3%) with prolactin value of <50 ng/ml died while 11/23(47.82%) died with values >50ng/ml (P < 0.05). Similarly, in patients with viral hepatitis with encephalopathy features, 1/4 (25%) with prolactin value of <50ng/ml died while among those without any such features (n=21), 9 (42.9%) died (p<0.05). Serum prolactin has a significant association with patients with liver disease and predicts mortality [19].

In our study Mean LSM was highest (14.9 kPa) in cases having prolactin >35 ng/ml followed by 9.8 kPa in cases having prolactin 20-35 ng/ml and 7.5 kPa in cases having prolactin 3-19 ng/ml. Serum prolactin was significantly raised in patients witn advanced fibrosis. The result was highly significant with p-value less than 0.0001.Recently, FibroScan has been recommended as a useful tool to detect both hepatic steatosis and fibrosis in Non Alcoholic Fatty Liver Disease (NAFLD). [20] Consequently, FibroScan was employed to evaluate liver steatosis and significant fibrosis, and its correlation with serum Prolactin was also investigated in both genders. In females, the proportions of MAFLD, liver steatosis, and fibrosis were substantially reduced in the normal Prolactin (NP) group, while they increased in the high Prolactin (HP) group across the prolactin quartiles. This was not observed in males. [21,22]

Elzawawy et al (2017) evaluate the accuracy of fibroscan in the assessment of liver cirrhosis in chronic liver disease. Liver stiffness was significantly correlated with liver cirrhosis. The fibroscan technique has high sensitivity and high specificity of 100%, with the area under the receiver operating characteristic curve (95% confidence interval) of 1.00, at the cut-off level of 14.5 kPa. Transient elastography is a promising non-invasive method for detection of cirrhosis in patients with chronic liver disease. Therefore, fibroscan can be used regarding the decision of treatment and follow-up of patients with cirrhosis

for screening and detection of the complication [23]. Fosucher et al [24] evaluated the accuracy of liver stiffness measurement for the detection of cirrhosis in patients with chronic liver disease. Stiffness was significantly correlated with fibrosis stage (r = 0.73, p <0.0001). Thus it is quite evident from our study that Serum Prolactin is an appropriate marker for predicting Chronic liver disease or Liver cirrhosis as well as it exhibits a positive correlation with grading of liver fibrosis.

Conclusion

Therefore, our research clearly illustrates that serum prolactin is an ideal marker for the prediction of severity of chronic liver disease or liver cirrhosis, as well as shows a positive correlation with the grading of liver fibrosis through FibroScan.

Limitations

A limited sample size was taken as well as study was single-centered.

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