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General Medicine

CORRELATION OF SERUM PROLACTIN LEVELS WITH SEVERITY OF LIVER DISEASE AND ITS ASSOCIATION WITH HEPATIC ENCEPHALOPATHY IN PATIENTS OF CIRRHOSIS LIVER

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ABSTRACT
Introduction: Prolactin is a hormone of pituitary origin and its secretion follows a pulsatile pattern, with a characteristic nocturnal rise, but is associated with elevated 24-hour prolactin levels and loss of circadian prolactin rhythm in cases of cirrhosis liver. Previous studies have shown association of prolactin levels with severity of liver disease and complications in patients of cirrhosis liver. This study was conducted to study the association of prolactin with CTP score and severity of hepatic encephalopathy (HE) in cirrhosis liver. **Aim:** To study correlation of serum prolactin level with severity of liver disease as assessed by Child Pugh's score and its association with HE in cirrhosis liver. **Material & Methods:** An observational cross-sectional study was conducted on 76 patients of cirrhosis liver admitted in VMMC and Safdarjung Hospital, New Delhi. Serum prolactin level was measured and it was correlated with Child Pugh score in assessing the disease severity and the risk of HE. **Results:** The mean age of the patients was 41.83 ($\pm$10.07) yrs. Out of 76 patients of cirrhosis, 60 (78.95%) patients were male and 16 (21.05%) patients were female. Alcoholic cirrhosis accounted for 43(56.58%) patients, followed by hepatitis C virus related cirrhosis in 14(18.42%) patients, hepatitis B virus related cirrhosis in 10(13.16%) patients and cause was unknown in 9(11.84%) cases. Mean serum prolactin was 26.13 $\pm$ 11.58. Mean CTP score was 9.34 $\pm$ 2.6 and 15 (19.74%) patients were in CTP Score Class A, 23 (30.26%) patients were in CTP Class B while 38 (50%) patients were in CTP Class C. Serum prolactin levels correlated significantly with severity of liver disease assessed by CTP score with a p value < 0.0008. Patients with HE 39 (51.32%) had a significantly higher levels of prolactin with p value <0.0001 compared with patients without HE 37 (48.68%). Serum prolactin levels showed a significant correlation with severity of HE with a p value <0.0001. **Conclusion:** Serum prolactin levels correlate significantly with severity of liver disease as assessed by CTP score and also correlates with severity of HE. Thus serum prolactin can be used as biomarker of severity of cirrhosis and HE in cases of cirrhosis liver.

INTRODUCTION

Cirrhosis of liver is a diffuse process of liver fibrosis and replacement of normal hepatic architecture with structurally abnormal nodules[1] and is associated with several complications like coagulopathy, portal hypertension, HE, ascites, spontaneous bacterial peritonitis. Hepatic encephalopathy is a complication of cirrhosis characterized by neuropsychiatric disturbances affecting consciousness, behaviour and associated with fluctuating neurological signs, asterixis, flapping tremors and distinctive electroencephalogram changes[2]. Although precise pathophysiologic mechanism leading to the psychiatric disturbances has not been adequately established, alteration in amino acid proportion and neurotransmitter levels in the brain have been found to be the potential reason[3]. Cirrhosis of the liver is associated with various disturbances of the endocrine system, thought to be caused mainly by ineffective elimination of hormones by the diseased liver. It is now known that the pathogenesis of disturbed hormonal function in liver cirrhosis is rather more complex involving altered secretion and feedback mechanisms as well[4]. One such hormone in this respect is prolactin. Prolactin secretion is mainly regulated by tonic hypothalamic inhibition through dopamine and the stimulatory influences of hypothalamic releasing factors and circulating oestrogens. Prolactin secretion follows a pulsatile pattern, with a characteristic nocturnal rise, but cirrhosis is associated with elevated 24-hour prolactin levels and loss of circadian prolactin rhythm[5]. Severity of liver disease is assessed according to CTP Score. This scoring system includes 5 factors: serum bilirubin, serum albumin, ascites, HE and prothrombin time (PT). CTP score is a reasonably reliable predictor of survival and predicts the likelihood of major complications like variceal bleed, spontaneous bacterial peritonitis, HE[6]. Studies have shown the association of serum prolactin with severity of hepatic encephalopathy and other complications of cirrhosis as portal hypertension, upper GI bleed, spontaneous bacterial peritonitis. With the growing incidence of cirrhosis of the liver, use of prolactin whose levels can predict the severity of liver disease and the possibility of complications, can be an important biomarker. Association of prolactin with severity of cirrhosis is well known but few Indian studies have been done using prolactin and its association with the occurrence of hepatic encephalopathy. Due to paucity of Indian literature on use of prolactin and its association with hepatic encephalopathy in cirrhosis liver this study was undertaken.

Material and methods:

This was an observational study on 76 patients with cirrhosis liver admitted in the General Medicine wards of VMMC and SAFDARJUNG HOSPITAL, NEW DELHI from 2017-2020. Each patient was subjected to detailed history and examination of past records with special emphasis on development of upper GI bleed, SBP and alteration of sensorium. Each patients was subjected to detailed history and clinical examination: History included asking patients for: Jaundice, abdominal distension, altered sensorium, swelling of feet, fever, hematemesis, melena, any drug intake, blood transfusion in past and relevant family history.

Diagnosis of cirrhosis was based on:
1. Clinical findings
2. Biochemical findings (low serum albumin, AST: ALT ratio >1)
3. Imaging findings[7] (USG finding-heterogenous echotexture of liver with irregular outline, altered liver size and presence of portosystemic collaterals).

All routine investigations along with coagulation profile, and kidney function test were done. Serum Prolactin levels were performed on ADVIA Centaur fully automated biochemistry analysis. The test was based on two-site sandwich immunoassay using direct chemiluminometric technology. Severity of liver disease was assessed according to CTP

Score. This scoring system includes 5 factors : serum bilirubin, serum albumin, ascites, HE and prothrombin time (PT). Based on the classification, patients were divided into three Classes – A (score of 5-7), B (score of 7-9) and C (score 10-15).

Statistical analysis
The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-
1. Pearson correlation coefficient/Spearman rank correlation coefficient (for non normally distributed data) was used to assess correlation of serum prolactin level with severity of liver disease
2. Diagnostic test was used to find out sensitivity, specificity, NPV and PPV.
   A p value of <0.05 was considered statistically significant.

Observations and results:
The study was conducted on 76 patients of liver cirrhosis after fulfilling the inclusion and exclusion criteria. The mean age of the patients was 41.83 (±10.07) yrs. Out of 76 patients of cirrhosis, 60 (78.95%) patients were male and 16 (21.05%) patients were female.

Alcohol was the most common cause of liver cirrhosis in our study with 43(56.58%) patients. 14(18.42%) patients were hepatitis C related cirrhosis, while 10(13.16%) patients were hepatitis B related cirrhosis and cause was undetermined in 9(11.84%) patients.

Among the study population, mean serum prolactin was 26.13 ± 11.58. 18 patients (23.68%) had normal serum prolactin levels (3-19 ng/ml). 46 patients (60.53%) had prolactin levels in the range of (20-35ng/ml) and 12 patients (15.79%) had prolactin in the range of 36-60 ng/ml.

In our study, mean CTP score was 9.34 ± 2.6 and 15 (19.74%) patients were in CTP Score Class A, 23 (30.26%) patients were in CTP Class B while 38 (50%) patients were in CTP Class C.

In our study 37 (48.68%) patients were not in HE while 39 (51.32%) patients were in HE. Of the 39 patients in HE, 18 were in grade 1, 10 each in grade 2 and 3 while 1 patient was in grade 4 HE.

Table 1: Basic parameters of patients.

PARAMETER	RESULTS
Age	41.83 (±10.07) yrs
Sex	60 (78.95%) male
	16 (21.05%) female
Bilirubin	3.85 ± 3.57
Creatinine	1.56 ± 0.62
INR	1.76 ± 0.46
Albumin	2.72 ± 0.56
PT	15.52 ± 2.41
Ascites	Absent 19 (25%)
	Present 57(75%)
S. prolactin	26.13 ± 11.58
CTP Score	9.34 ± 2.6
HE	Absent 37 (48.68%)
	Present 39 (51.32%)

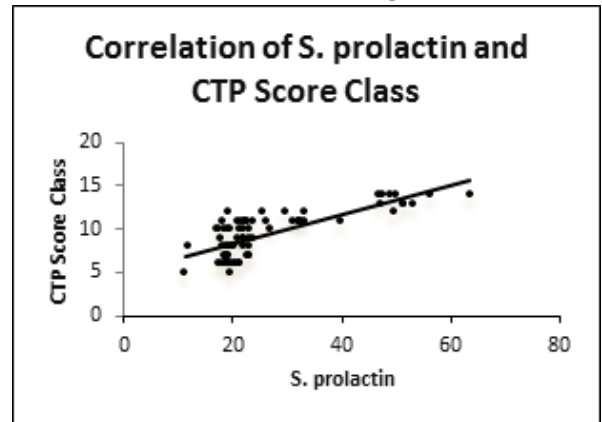### Correlation of Serum prolactin with CTP Score
In our study, of the 18 patients with normal serum prolactin

levels (3-19 ng/ml) 7 cases were in CTP Class A, 7 in Class B and 4 in Class C. Of the 46 cases with serum prolactin (20-35ng/ml) 8 were in CTP Class A, 16 in Class B and 22 in Class C. Of the 12 cases with serum prolactin 36-60 (ng/ml) all the cases were in CTP Class C while no cases were in Class A and Class B. All the cases with high serum prolactin levels had a higher severity of liver disease with a p value < 0.0008.
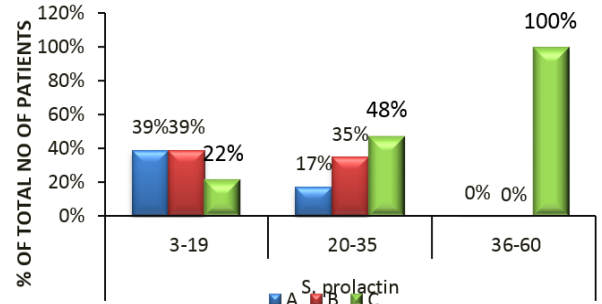
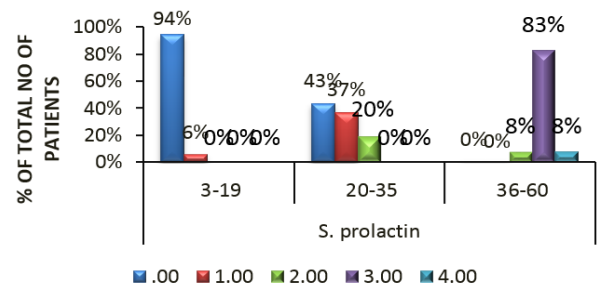Fig 1: Correlation of Serum prolactin with CTP Score Class

On statistical analysis significant positive correlation was observed between serum prolactin with Severity of liver disease assessed by CTP Score with spearman's rank correlation coefficient (rho) = 0.713 and p value <0.0001.

Fig 2: Correlation between serum prolactin and CTP Score

Correlation of serum prolactin with HE Grade:
In our study, of the 18 patients with normal serum prolactin levels (3-19 ng/ml) 17 cases had no HE while 1 was in HE grade 1 and no cases were in grade 2, grade 3 or grade 4 HE. 46 cases had serum prolactin 20-35 ng/ml, of these 20 had no HE, 17 were in grade 1 while 9 were in grade 2 and no patient had HE grade 3 or grade 4.12 patients had serum prolactin levels in 36-60ng/ml of these none had grade 0 and grade 1 HE, 1 patient had grade 2 HE while 10 were in grade 3 and 1 was in grade 4 HE. This indicates increased severity of HE in cases with higher serum prolactin levels and had a p value <0.0001.

Fig 3: Correlation of serum prolactin with HE Grade

On statistical analysis significant positive correlation was observed between serum prolactin with HE with spearman's

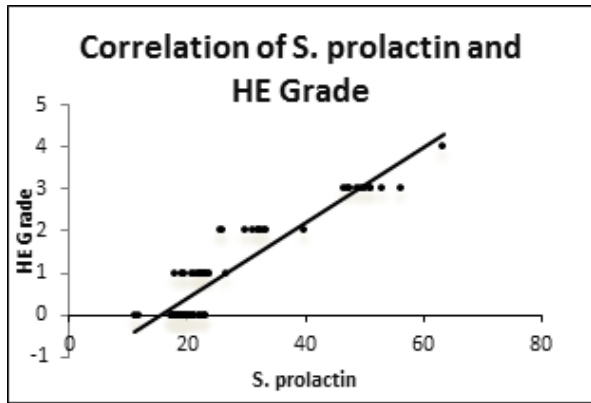rank correlation coefficient (rho) = 0.837 and p value <0.0001.

Fig 4: Correlation between serum prolactin and HE

Correlation between serum prolactin and mortality

12 patients in the present study expired. All these 12 cases had serum prolactin level in the range of 36-60 ng/ml. This indicated that higher prolactin levels were seen in cases with mortality with p value <0.0001.
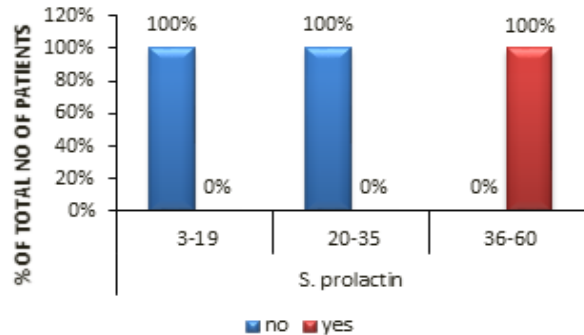

Fig 5: Correlation between serum prolactin and mortality

By using the ROC curve serum prolactin level of >33.3 ng/ml can be used to predict mortality in cases of cirrhosis liver with a sensitivity of 100%, specificity of 100%, PPV of 100% and NPV of 100%.
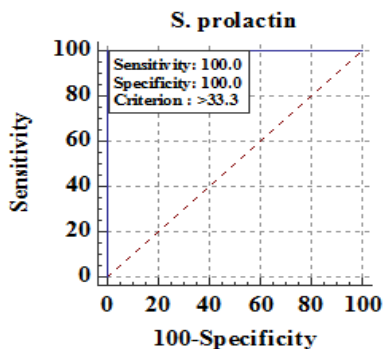

Fig 6: ROC analysis between serum prolactin and mortality

DISCUSSION:

Our study showed high serum prolactin levels were associated with increase severity of liver disease with p value <0.0008 and increased severity of HE was seen in cases with higher serum prolactin levels with a p value <0.0001. In a study by Chaitanya H. Balakrishnan et al., on 60 cases of cirrhosis liver, serum prolactin levels correlated with CTP score and all cases of HE had raised serum prolactin levels[6]. Arafa et al. noticed significant positive correlation of serum T3 and cortisol with serum albumin and prothrombin time (PT). There was a significant negative correlation between prolactin levels with and serum albumin and PT indicating direct correlation of severity of liver disease[8]. They also found significantly raised prolactin levels in cirrhotic patients with HE and a cutoff value of 18.85 ng/dl could predict HE in cirrhotic patients with sensitivity of 88% and a specificity of 90.3%. Similar results were seen by Koller T et al also[9]. Ramy a. Metwally et al. found negative correlation of serum prolactin with albumin and positive correlation with PT and serum bilirubin. They also found significant increase in prolactin with increasing grade of HE[10]. Juraj Payer et al. also noticed significant increase in prolactin levels with severity of liver disease especially in cases of ascites and HE. On regression analysis prolactin levels were significantly dependent on Child-Pugh and MELD score[11]. Sumit Kant Jha reported raised levels of prolactin ($P < 0.05$) in cases of cirrhosis irrespective of the presence of HE[12]. Our study showed patients who expired had serum prolactin level in the range of 36-60 ng/ml. This indicated that higher prolactin levels were seen in cases with mortality with p value <0.0001. Thus we concluded that serum prolactin levels correlate significantly with severity of liver disease as assessed by CTP score and also correlates with HE. Thus serum prolactin can be used as biomarker of severity of cirrhosis and HE and also as a predictor of mortality in cases of cirrhosis liver.

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