

# Serum prolactin in patients with liver disease in comparison with healthy adults: A preliminary cross-sectional study

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## ABSTRACT

**Introduction:** Studies from the west have shown raised prolactin levels in patients with liver disease. Considering the lacunae on Indian context, we conducted the present study with an objective to assess the prolactin levels in patients with cirrhosis and viral hepatitis with or without features of encephalopathy. The data presented here are the results of the preliminary analysis. **Materials and Methods:** The present study was a prospective, cohort study among patients diagnosed as either viral hepatitis or cirrhosis liver. A cohort of normal healthy adults was selected based on history and laboratory investigations (complete blood count, liver and renal function tests). Serum prolactin was measured for all the study participants, and Kruskal–Wallis H-test with *post-hoc* Dunn's test was used to analyze the significance of the differences in the levels between various groups. Tests of diagnostic accuracy were used to assess the prediction capability of serum prolactin with a cut-off level of 50 ng/ml. **Results:** 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 ( $\rho = 0.67, P = 0.04$ ) and aspartate aminotransferase ( $\rho = 0.72, P = 0.05$ ). 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 (47.8%) died with values  $> 50$  ng/ml ( $P < 0.05$ ). Similarly, in patients with viral hepatitis with encephalopathy features, 1/4 (25%) with prolactin value of  $< 50$  ng/ml died while among those without any such features ( $n = 21$ ), 9 (42.9%) died ( $P < 0.05$ ). **Conclusion:** Serum prolactin has a significant association with patients with liver disease and predicts mortality.

**Key words:** Cirrhosis, hyperprolactinemia, viral hepatitis

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## INTRODUCTION

Hepatic encephalopathy is characterized by neuropsychiatric disturbances affecting consciousness, behavior and associated

with fluctuating neurological signs, asterixis or flapping tremors, and distinctive electroencephalogram changes.<sup>[1]</sup> Although precise pathophysiologic mechanism leading to the psychiatric disturbance has not been adequately established, alteration in the amino acid proportion and neurotransmitter levels in the brain have been found to be the potential reasons.<sup>[2]</sup> Among the neurotransmitter alteration, the principal one to be documented was dopamine. But

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dopamine is limited by the fact that it cannot be measured in any of the body fluids or brain. Since dopamine exerts negative control over prolactin, few studies from the west have shown prolactin to be a prognostic marker.<sup>[3,4]</sup> Considering the lacunae from Indian context, the present study was envisaged to assess and compare the prolactin levels in patients with liver disease with/without features of hepatic encephalopathy. The data presented here are the results of a preliminary analysis.

## MATERIALS AND METHODS

The present study was a prospective, cohort study conducted between January and April 2010 after obtaining permission from Institutional Ethics Committee and informed consent from the study participants. The patients of either sex aged between 15 and 70 years were enrolled in the study after being diagnosed as either viral hepatitis or cirrhosis liver. Further, diagnosis of hepatic encephalopathy was made based on West Haven criteria.<sup>[5]</sup> A cohort of normal healthy adults was selected based on history and laboratory investigations (complete blood count, liver and renal function tests). Patients who were pregnant, lactating women, concomitant chronic renal failure, altered thyroid state, on concomitant psychotropic agents, metoclopramide were excluded from the study.

All eligible participants were enrolled and the following laboratory investigations were performed for patients with liver disease: Complete blood count (hemoglobin, total and differential leukocyte count), erythrocyte sedimentation rate, random blood sugar, liver function tests (alanine and aspartate aminotransferases, serum bilirubin, prothrombin time, serum total protein, albumin and globulin), ascitic fluid examination for: Cytology, biochemical and microbiological staining, ELISA for HBsAg, serum prolactin assay, ultrasound abdomen and upper gastrointestinal endoscopy. Child–Pugh scoring system<sup>[6]</sup> was used to classify the severity of liver dysfunction in cirrhotic. For the cohort of normal healthy individuals, in addition to the investigations done pertaining to ensure their healthy status as mentioned above, serum prolactin was measured.

Demographic details were represented using descriptive statistics. Numerical variables were assessed for normality using Kolmogorov–Smirnov test, and correspondingly, Kruskal–Wallis H-test and *post-hoc* Dunn's test were used to analyze the difference of serum prolactin among various groups of individuals. Association between serum bilirubin and liver enzymes with serum prolactin was done using Spearman-rho test. Chi-square test for association was used to find out the significance of the cut-off value of prolactin.

Sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals were calculated. SPSS 17.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis, and a  $P < 0.05$  was considered significant.

## RESULTS

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. Among the 25 patients of acute viral hepatitis, 15 (60%) had symptoms and signs of encephalopathy, and among the 35 patients with liver cirrhosis, 20 (57.1%) had such features. Of the total 60 patients with liver disease, 19 were found to be positive for HBsAg (13 with viral hepatitis and 6 with cirrhosis liver). Also, 12/35 (34.3%) patients with liver cirrhosis belonged to category A of Child–Pugh classification, 8/35 (22.9%) were B and the remaining (15/35, 42.9%) were C type.

Serum prolactin levels in various groups of the study participants are represented in Table 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 ( $\rho = 0.67$ ,  $P = 0.04$ ) and aspartate aminotransferase ( $\rho = 0.72$ ,  $P = 0.05$ ). Of 35 study participants with cirrhosis, 15 died. 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 (47.8%) died with values  $> 50$  ng/ml ( $P < 0.05$ ). Similarly, in patients with viral hepatitis with encephalopathy features, 1/4 (25%) with prolactin value of  $< 50$  ng/ml died while among those without any such features ( $n = 21$ ), 9 (42.9%) died ( $P < 0.05$ ). Table 2 denotes the various parameters of diagnostic accuracy with serum prolactin in both the groups of study participants with encephalopathy features.

**Table 1: Serum prolactin levels among the study participants**

Group of study participants	Encephalopathy symptoms and signs	Serum prolactin (ng/ml) median (range)
Normal healthy adults (n=10)	NA	11.2 (6.2-18.6)
Viral hepatitis (n=25)	Present (n=15)	71.2 (30.6-119.7)*
	Absent (n=10)	9.7 (5.8-19.6)
Cirrhotics (n=35)	Present (n=20)	73.6 (37.6-210.7)**
	Absent (n=15)	21.5 (18.6-26.4)***

\* $P < 0.001$ : Viral hepatitis with clinical features of encephalopathy and healthy normal adults; \*\* $P < 0.001$ : Cirrhotics with clinical features of encephalopathy and healthy normal adults (also significantly different when cirrhotic patients without features suggestive of encephalopathy were compared to those with such features); \*\*\* $P < 0.05$ : Cirrhotics with clinical features of encephalopathy and healthy normal adults. NA: Not applicable

**Table 2: Diagnostic accuracy parameters with serum prolactin cut-off value of 50 ng/ml predicting mortality**

Parameter	Cirrhosis (%) (95% CI)	Viral hepatitis (%) (95% CI)
Sensitivity	40 (19.7-63.9)	20 (4.6-48.1)
Specificity	73.3 (44.9-92.1)	90 (55.5-98.3)
Positive predictive value	66.7 (34.9-89.9)	75 (20.3-95.9)
Negative predictive value	47.8 (26.9-69.4)	42.9 (21.9-66)

CI: Confidence interval

## DISCUSSION

Prolactin levels in patients with hepatic dysfunction have been controversial. Many authors have reported hyperprolactinemia although few have debated the same. Elevation of prolactin is attributed mainly to the fall in dopamine levels in the tuberoinfundibular tract. Hormonal disturbance in cirrhosis has been evaluated by few researchers, and the studies have established lower T3 and cortisol levels with raised prolactin in the serum.<sup>[7]</sup> Decompensated liver function leads to an alteration in the type of amino acids entering the central nervous system. Circulating concentrations of aromatic amino acids have been found to increase leading to an increase in the synthesis of false neurotransmitters such as octopamine and phenylethanolamine.<sup>[8]</sup> These false neurotransmitters may inhibit the dopamine release contributing to hyperprolactinemia. Cases of hypogonadism have also been reported in patients with cirrhosis attributing to hyperprolactinemia.<sup>[9]</sup> Prolactin release in human beings is normally associated with a pulsatile pattern, but a constant 24 h elevation has been found in patients with cirrhosis liver.<sup>[7]</sup> Although few researchers have associated the levels of prolactin with Child–Pugh's category of cirrhosis patients, the present study had few patient numbers in each of the categories limiting the interpretation. A similar correlation of mortality to serum prolactin levels was observed by McClain *et al.*<sup>[10]</sup> and Sharma *et al.*<sup>[11]</sup> with a higher risk of mortality with serum prolactin values of >50 ng/ml. Mukherjee *et al.*<sup>[12]</sup> analyzed the prolactin levels in patients with hepatic cirrhosis and found a higher levels in both patients with encephalopathy and mortality. Also, the authors found out a direct correlation between the clinico-biochemical severities of the condition and mortality. As against this, Velissaris *et al.*<sup>[7]</sup> evaluated levels of all the pituitary hormones and their circadian pattern of rhythm in patients with hepatic encephalopathy and found out that only melatonin was significantly associated with the degree of liver insufficiency. Although prolactin levels were not found to be elevated, clear-cut pattern of levels (lower levels in the afternoon and

higher in the evenings) was observed. Similarly, although we found out a cut-off level of 50 ng/ml of prolactin to predict the mortality, Koller *et al.*<sup>[4]</sup> did a cohort study in Russian population and estimated an amount of 10.5 µg/l of prolactin to predict mortality. However, patients in that study were exclusively chronic alcoholics, and the ethnic difference might be the attributing factors for observing this difference.

The findings of the present study have to be interpreted with the limitation of small sample size. Future studies have to be directed in a larger group of patients with different indications and their severity states.

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### Conflicts of interest

There are no conflicts of interest.

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