Original Article

Serum Prolactin as a Marker of the Severity of Liver Cirrhosis in a Tertiary Hospital in India: A Cross-Sectional Study

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Abstract

Background: In India, cirrhosis is becoming a growing concern, leading to an unmet need for new non-invasive markers to assess the severity of liver disease. Serum prolactin is one such marker. **Aim:** To determine the association between serum prolactin, the severity of liver cirrhosis, and its complications such as ascites, hepatic encephalopathy, and esophageal varices. **Methods:** This cross-sectional study involved 117 patients with liver cirrhosis. They were evaluated for some complications such as ascites, esophageal varices, and hepatic encephalopathy, as well as for severity by using the Child-Turcotte-Pugh (CTP) score. Serum prolactin levels were measured, and their relationship with both the severity and complications of liver cirrhosis was determined. A *P* value of < 0.05 was considered significant. **Results:** The mean age of the patients was 48.3 ± 12.08 years, and the majority (80.3%) were males. Seventy-one percent of the patients had elevated serum prolactin levels (>19.40 ng/mL). Elevated serum prolactin was found in approximately 95.0% and 86.8% of patients with hepatic encephalopathy and ascites, respectively. The median serum prolactin levels were significantly associated with esophageal varices grades ($P = 0.043$) and hepatic encephalopathy ($P < 0.001$). The sensitivity and specificity of serum prolactin for predicting severe CTP scores were 81.6% and 91.2%, respectively, with a diagnostic accuracy of 87.2%. On multivariate regression analysis, ascites (AOR = 3.8, 95%CI = 1.29–10.98, $P = 0.015$), hepatic encephalopathy (AOR = 6.1, 95%CI = 0.68–53.78, $P = 0.012$), CTP class B (AOR = 5.9, 95%CI = 1.39–24.68, $P = 0.016$), and CTP class C (AOR = 13.4, 95%CI = 2.25–82.21, $P = 0.004$) were significantly associated with elevated serum prolactin levels. **Conclusion:** There was a significant association between serum prolactin levels and CTP classes, esophageal varices, ascites, and hepatic encephalopathy in patients with liver cirrhosis.

Keywords: *Cirrhosis, CTP, hepatic encephalopathy, NASH, prolactin*

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Introduction

Globally, cirrhosis is the eleventh leading cause of death.[1] The global burden of cirrhosis was estimated to be 20.7 per 100,000 in 2015, which marks a 13% increase since 2000.[2] In India, it contributed to 18.3% of the two million global liver disease deaths reported in 2015.[3] Cirrhosis of the liver represents a late stage of progressive hepatic fibrosis, characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stage and is associated with several complications such as ascites, gastrointestinal bleeding, hepatic encephalopathy, and death. In earlier stages, specific treatments aimed at the underlying cause of liver disease may improve or even reverse cirrhosis.

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Various manifestations of endocrine system disturbances in cirrhosis of the liver are mainly linked to the diseased liver due to altered hormone secretion and feedback mechanisms.[4] Prolactin is one such hormone in this regard. Dopamine regulates the production of prolactin in the human pituitary gland, which negatively regulates prolactin secretion. However, in humans, its main function is related to lactation and reproduction.[5] It is believed that the main reason behind the increased level of serum prolactin in chronic liver disease (CLD) is the decreased level of dopamine.[6] Circulating estrogen levels are increased due to increased peripheral aromatization of testosterone to estradiol by enzyme aromatase and reduced clearance in CLD.[7,8] Estrogen stimulates prolactin release due to interference with dopamine secretion from the hypothalamus and also directly causes lactotroph hyperplasia in the anterior pituitary gland.[6] Similar to other anterior pituitary hormones such as cortisol, which peaks in the morning and troughs at night, prolactin secretion has a diurnal variation with peak levels at night. However, in the case of liver cirrhosis, this rhythmicity is disrupted and patients have increased prolactin levels throughout the day.[9]

Over the last decade, there has been increasing interest in the rise of serum prolactin levels in CLD and its utility in predicting complications. Increased serum prolactin in CLD is associated with worsening encephalopathy.[8] Various studies have found a relationship between increased serum prolactin levels and mortality in cirrhosis of the liver.[10,11] Therefore, we aimed to determine if serum prolactin levels could be used as a serum biomarker to predict complications in cirrhosis of the liver by comparing it with Child-Turcotte-Pugh (CTP) scores.

Materials and Methods

This cross-sectional study was conducted at Hamdard Institute of Medical Sciences and HAHC Hospital, Delhi from February 2021 to September 2022. All liver cirrhosis patients aged >18 years were included in the study. Patients on medications known to elevate prolactin levels, those with sepsis, cardiac failure, nephrotic syndrome, history of chronic renal failure, chest wall trauma, cranial surgery/irradiation, pituitary or hypothalamic disease, herpes zoster, seizure disorder, pregnancy were excluded from the study.

Sample size calculation

The proportion of patients with hyperprolactinemia was taken as 16.7 from a previous study by Koller *et al*.[12] The sample size was calculated using a formula according to Pourhoseingholi *et al*.:[13]

$$\text{Sample size } (n) = \frac{z^2(1-P)P}{E^2}$$

Z = 1.96; P = Prevalence (16.7%); E = relative error (7%)

$n = 1.96 \times 1.96(1\text{-}0.167) \times 0.167/0.07 \times 0.07 = 109$

The minimum sample size required for this study was 109.

Ethical consideration

On the recommendation of members of the Protocol Evaluation meeting held on February 24, 2021 at the college council room, the Institutional Ethics Committee, the Hamdard Institute of Medical Sciences and Research and Associated HAH Centenary Hospital (IEC-HIMSR) approved the study with the protocol number HIMSR/IEC/48/2021. While entering the data in the Excel sheet, each patient was assigned a specific code number without mentioning their name or unique patient ID. In addition, written informed consent was obtained through signatures or thumb impressions, and each patient was provided a printed information sheet.

Data collection

All patients underwent a detailed evaluation, including history, treatment, and personal history, to identify possible etiologies and a thorough clinical examination to identify evidence of cirrhosis of the liver and the presence of its complications including ascites and hepatic encephalopathy.[14] Patients underwent the routine workup for CLD, including complete blood count, kidney function test, liver function test, coagulation profile, hepatitis B and C screening, autoimmune markers such as antineutrophil antibody, and other relevant markers. An ultrasound of the abdomen and upper gastrointestinal endoscopy were conducted on all patients. Serum prolactin was measured by chemiluminescent microparticle immunoassay technology with flexible assay protocols, referred to as Chemiflex.

The reference range for serum prolactin at our institution is 3.46–19.40 ng/mL. The severity of liver cirrhosis was assessed by CTP scores,[15] which has three classes based on the involvement of various variables, including ascites, bilirubin, encephalopathy, albumin, and international normalized ratio. Based on these variables, it is divided into the following classes:

- Child-Pugh A: 5–6 points
- Child-Pugh B: 7–9 points
- Child-Pugh C: 10–15 points

- Classes A and B were designated as mild to moderate, while Class C as severe.

Statistical analysis

The recorded data were compiled and entered into a spreadsheet (Microsoft Excel) and then exported to the data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as median (interquartile range), while categorical variables were expressed as percentages or frequencies. The Mann-Whitney U test and the Kruskal-Wallis test were used to compare the median values of prolactin in the various complications of liver cirrhosis. The Chi-square test was used to determine the association between elevated serum prolactin and the complications of liver cirrhosis. Multivariate regression analysis was done to identify the factors associated with elevated serum prolactin levels. Pearson's correlation coefficient was used to determine the correlation between serum prolactin levels and CTP classes. A *P* value of <0.05 was considered statistically significant. The utility of serum prolactin level in predicting the severity of CTP scores was assessed by receiver operating curve (ROC) analysis. To determine the optimal cutoff prolactin level in ROC, the Youdens J statistic method was used. The sensitivity and specificity of serum prolactin levels to predict severe CTP scores are also presented.

Results

The study involved 117 patients, comprising 94 (80.3%) males and 23 (19.7%) females, with a mean age of 48.3 ± 12.08 years [Table 1]. Elevated prolactin levels (>19.40 ng/mL) were observed in 83 (71%) patients. There was a significant association between elevated serum prolactin and ascites (*P* = <0.001); hepatic encephalopathy (*P* = 0.007); and CTP classes (*P* < 0.001) [Table 2]. There were more patients in CTP class A (47%) compared to those in CTP class C (41.9%) and CTP class (11.1%). The median serum prolactin levels in classes A, B, and C were 9.6 (7.89–11.75) ng/mL, 26.5 (18.90–30.86) ng/mL, and 50.1 (40.24–67.720 ng/mL), respectively. The median

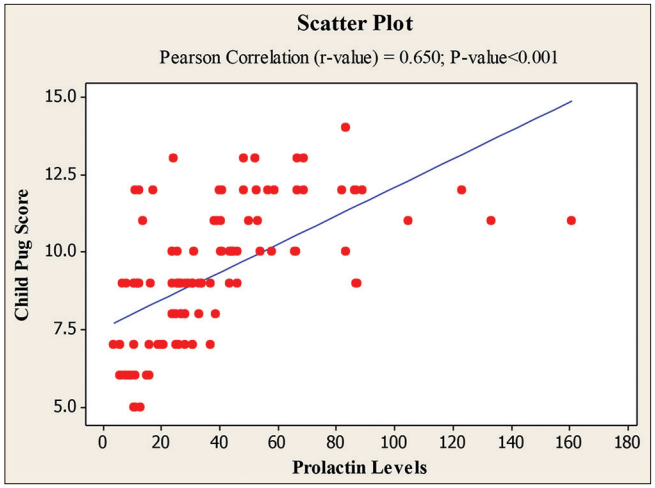

Figure 1: Shows a correlation between serum prolactin and CTP

Table 1: Demographic and clinical characteristics of the study population

Parameter	*n* (%)
Gender	
Male	94 (80.3)
Female	23 (19.7)
Age distribution (years)	
20–29	6 (5.10)
30–39	24 (20.5)
40–49	33 (28.2)
50–59	26 (22.2)
60–69	24 (20.5)
≥70	4 (3.4)
Urban	95 (81.1)
Rural	22 (18.9)
Comorbidities	
Hypertension	15 (12.82)
Diabetes Mellitus	21 (17.9)
Etiology of cirrhosis	
Alcoholism	70 (59.8)
Hepatitis B	18 (15.5)
Hepatitis C	12 (10.2)
Others	17 (14.5)
Complications of cirrhosis	
Ascites	68 (58.1)
Jaundice	59 (50.4)
Hepatic encephalopathy	21 (17.9)
Upper GI bleed	18 (15.4)

Table 2: Association between elevated serum prolactin levels and complications of liver cirrhosis

Parameter		Normal Prolactin (≤19.40 ng/mL) *n* (%)	Elevated Prolactin (>19.40 ng/mL) *n* (%)	*P*
Ascites	Present	9 (13.2)	59 (86.8)	<0.001*
	Absent	25 (51)	24 (49)	
Hepatic encephalopathy	Present	1 (4.8)	20 (95.2)	0.007*
	Absent	33 (34.4)	63 (65.6)	
CTP classes	A	13 (100)	0 (0.0)	<0.001*
	B	17 (31)	38 (69)	
	C	4 (8.2)	45 (91.8)	
Grades of esophageal varices[16]	I	6 (17.6)	28 (82.4)	0.814
	II	7 (21.9)	25 (78.1)	
	III	3 (25)	9 (75)	
	IV	0 (0.0)	3 (100)	

*P< 0.05 considered significant

Table 3: Association between CTP classes, hepatic encephalopathy, esophageal varices and median serum prolactin levels

Variables		*n* (%)	Median (prolactin level) ng/mL	IQR (Q1–Q3)	*P*
CTP Classes	Class A	13 (11.1)	9.6	7.89–11.75	<0.001*
	Class B	55 (47)	26.5	18.90–30.86	
	Class C	49 (41.9)	50.1	40.24–67.72	
Hepatic encephalopathy	Present	21 (17.9)	52.0	43.53–74.92	<0.001*
	Absent	96 (82.1)	26.4	13.93–43.53	
Esophageal Varices	Grade I	34 (42)	33.4	25.58–44.80	0.043*
	Grade II	32 (39.5)	40.3	23.94–55.78	
	Grade III	12 (14.8)	42.3	20.71–63.20	
	Grade IV	3 (3.7)	58.6	28.90–89.80	

*P< 0.05 considered significant. IQR: Interquartile range

Table 4: Multivariate logistic regression analysis depicting independent factors associated with elevated serum prolactin levels

Parameters	Adjusted odds ratio (AOR)	95% confidence interval (CI)	*P*
Ascites	3.8	1.29–10.98	0.015
Hepatic encephalopathy	6.1	0.68–53.78	0.012
CTP B	5.9	1.39–24.68	0.016
CTP C	13.4	2.25–82.21	0.004

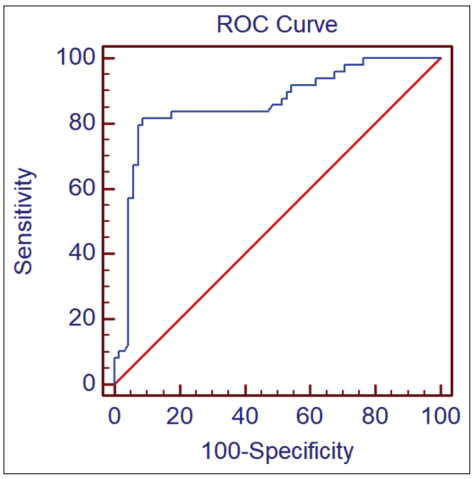

Figure 2: Shows the ROC between serum prolactin and severe CTP

serum prolactin levels significantly increased across classes A, B, and C (P < 0.001). Grade I, II, III, and IV esophageal varices were present in 34 (42%), 32 (39.5%), 12 (14.8%), and 3 (3.7%) of the study participants, respectively [Table 3].

There was a significant correlation between serum prolactin levels and CTP score, as shown in Figure 1. The sensitivity and specificity of serum prolactin in predicting severe CTP score were 81.6% and 91.2%, respectively, and the area under the receiver operating curve (ROC) was 0.861, as shown in Figure 2. The serum prolactin level that predicts a severe CTP score was 36.9 ng/mL. On multivariate regression analysis, ascites (AOR = 3.8, 95% CI = 1.29–10.98, P = 0.015), hepatic encephalopathy (AOR = 6.1, 95% CI = 0.68–53.78, P = 0.012), CTP B (AOR = 5.9, 95% CI = 1.39–24.68, P = 0.016), and CTP C (AOR = 13.4, 95% CI = 2.25–82.21, P = 0.004) were independent factors significantly associated with elevated prolactin levels [Table 4].

Discussion

In the current period, this study aimed to investigate whether serum prolactin, a simple biomarker, could be used to predict complications in CLD compared to the CTP scoring system, despite advancements in diagnostic medicine.

There were more males with liver cirrhosis in this study. This is similar to that reported in the studies by Paul *et al*.[17] and Balakrishnan and Rajeev[18] The predominant male involvement may be due to the high incidence of alcohol intake among males leading to CLD. Alcohol and chronic hepatitis B infection were common causes of liver cirrhosis in this study, which is similar to the report of a previous study by Punekar *et al*.[19]

Approximately 71% of patients with cirrhosis had elevated serum levels of prolactin using a cutoff value of above 19 ng/mL. This is similar to the report by Balakrishnan and Rajeev,[18] which showed that 73.3% of the patients with liver cirrhosis had serum prolactin levels elevated above 19 ng/mL.

According to the CTP classification, CTP B was the most common class. This is similar to the report by Punekar *et al*.[19] The median values of serum prolactin significantly increased across patients in CTP classes A, B, and C. This is similar to the report by Arafa M *et al*.[20] Similarly, there was a significant correlation between the CTP score and prolactin levels, which is consistent with the report by Khalil *et al*.[21] The sensitivity and specificity of serum prolactin in predicting severe

CTP scores were 81.6% and 91.2%, respectively. The finding of this study showed that serum prolactin can predict severity in patients with liver cirrhosis. This is supported by the study by Vemanamanda *et al*.,[22] which reported the sensitivity and specificity of serum prolactin in predicting severe CTP to be 82.6% and 73.9%, respectively.

Approximately 95% of patients with hepatic encephalopathy had elevated serum prolactin levels. This is closely related to the finding of the study by Balakrishnan and Rajeev,[18] where 100% of patients with hepatic encephalopathy had elevated serum prolactin levels. There was a significant association between elevated serum prolactin levels and hepatic encephalopathy. This is consistent with the findings of studies done by Giri *et al*.[23] and Koller *et al*.[12] In addition, Mukherjee *et al*.[24] analyzed the prolactin levels in patients with hepatic cirrhosis and found higher levels in those with hepatic encephalopathy.

Approximately 80% of patients with esophageal varices had elevated prolactin levels. This is higher than that reported by Balakrishnan and Rajeev (60.7%).[18] There was a significant association between serum prolactin levels and esophageal varices. This finding is similar to reports by Balakrishnan and Rajeev[18] and Sujitha Vemanamanda *et al*.[22] However, the study conducted by Punekar *et al*.[19] found no significant association between esophageal varices and serum prolactin levels.

There was also a significant association between ascites and elevated serum prolactin levels in this study. This is at variance with the report of the study done by Punekar *et al*.,[17] where there was no significant association. However, Payer *et al*.[25] found a significant increase in prolactin levels in patients with liver cirrhosis who had complications such as ascites and hepatic encephalopathy.

The limitation of the study was the relatively small sample size. In addition, the relationships between serum prolactin levels and hepatorenal, hepatopulmonary syndromes, and mortality rate were not studied.

Conclusion

Serum prolactin, an easy biomarker, could be used to predict various complications of liver cirrhosis, such as ascites, esophageal varices, and hepatic encephalopathy, despite advancements in modern medicine.

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Conflicts of interest

There are no conflicts of interest.

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