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Serum Prolactin Level as A Surrogate Marker of Severity in Liver Cirrhosis

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Abstract:

Introduction: Liver Cirrhosis is one of the reported pathological causes of endocrinological and hormonal disturbances like hyperprolactinemia. Elevated prolactin level has been suggested as an alternative marker of hepatic encephalopathy and death. The present study aimed to investigate the correlation of serum prolactin level with the severity of liver disease and its complications.

Materials And Methods: Patients aged >18 years, of either gender, diagnosed with liver cirrhosis were included in the study. Patients with major systemic diseases were excluded. The sample size was 60. The Child-Pugh score system was used to categorize the severity of liver cirrhosis. Ascites was diagnosed on the basis of clinical examination and ultrasonographic findings. The grading of Hepatic Encephalopathy was based on West Haven Criteria.

Results: The mean age of patients was 45.3years with male: female ratio of 6.5:1. The mean ± SD of serum prolactin level and Child-Pugh score were 29.75 ± 22.9 ng/dl and 9.31 ± 2.14, respectively. There was a statistically significant correlation between serum prolactin level and Child-Pugh criteria (p=0.00001), the severity of ascites (p=0.0013) and grades of Hepatic Encephalopathy (p=0.00001). The cut-off value of serum prolactin level for predicting the severity of liver cirrhosis was 24 ng/ml.

Conclusion: The present study found positive correlation of mean serum prolactin level with Child-Pugh score, severity of ascites and grade of hepatic encephalopathy, which was statistically significant. The serum prolactin level increased proportionally with increasing severity of liver cirrhosis. The study proposes, serum prolactin level as an alternate marker of severity in liver cirrhosis.

Keywords: Ascites, Child-Pugh score, Hepatic encephalopathy, Liver cirrhosis, Serum prolactin.

Introduction:

Liver cirrhosis is a global health problem linked with various complications and high mortality. Cirrhosis is a continuous process of destruction, inflammation, and regeneration of liver parenchyma, resulting in fibrosis and cirrhosis of liver [1]. As per National Health Interview Survey, 2018, The United States reported approximately 4.5 million individuals aged 18years and above suffering from chronic liver disease. There were 44,358 deaths (13.5 deaths per 100,000 population) from chronic liver disease and cirrhosis [2]. According to the latest data, India accounts for 18.3% of cirrhotic deaths globally [3].

Cirrhosis of the liver is one of the reported pathological causes associated with profound endocrinological and hormonal disturbances like

hyperprolactinemia (HPL), while mechanisms have not been identified yet [4]. The feminization process, which occurs in 40-50 percent of male patients with liver cirrhosis, is the most apparent hormonal abnormality correlated. Gynecomastia, palmar erythema, spider nevi, impotence, infertility, and altered gonadal function are characteristics of males' feminization process [5]. The hypothalamus-pituitary-gonadal axis is notably affected in liver cirrhosis. HPL and hyper-estrogenemia are associated causative factors for the clinical characteristics of feminization. Consequently, both can contribute to the genesis of hypogonadism [6].

Another research has elicited the Association of Pathological HPL with severe liver disease, especially cirrhosis [7]. In studies conducted by McClain et al.[8] and Sharma et al.[9], prolactin values of >50 ng/ml were reported with a higher mortality risk in liver cirrhosis. Koller et al. elicited prolactin concentration as an alternative marker of hepatic encephalopathy and death. Prolactin levels >11.91 microg/l had 80.8% sensitivity and 87.8% negative predictive value to predict death [10]. However, some studies donot support the correlation of

HPL with liver cirrhosis [4]. Therefore, the present study aimed to investigate the correlation of serum prolactin level with the severity of liver disease and its complications.

Materials And Methods:

The present study was a hospital-based cross-sectional, observational study conducted in the Department of Medicine, Pt. Jawaharlal Nehru Memorial Medical College and Hospital, Raipur, Chhattisgarh, India between November 2020 and October 2021. The calculated sample size was 60. Patients aged >18 years, of either gender, diagnosed with liver cirrhosis were included in the study. Patients with a major systemic disease like endocrinal disorders, non- cirrhotic hepatitis C or hepatitis B virus infection, Chronic renal failure, recent chest trauma or cranial surgery, receiving drugs that can influence serum prolactin level (Metoclopramide, Domperidone, Opioids, Estrogen, Verapamil, Haloperidol, Risperidone), Pregnant/lactating women were excluded from the study. The present study was approved by the Institutional Ethics Committee, and written informed consent was obtained from the participants.

Liver cirrhosis was diagnosed by biochemical evidence, clinical diagnosis and Ultrasonography. The following laboratory tests were done of patients diagnosed with liver cirrhosis Complete Blood Count (CBC), Renal function test, Liver function test, Serum electrolyte, Prothrombin time, International Normalised Ratio, Serum prolactin and viral markers. The Child-Pugh score system[11] was used to categorize the severity of cirrhotic liver dysfunction. The participants were classified into Child Class A (Mild liver cirrhosis), Child Class B (Moderate liver cirrhosis), Child Class C (Severe liver cirrhosis) according to total child-pugh score. The patients were also classified based on the severity of ascites and hepatic encephalopathy. Ascites was diagnosed on the basis of clinical examination and ultrasonographic findings. The grading of Hepatic Encephalopathy was based on West Haven Criteria (Grade 1 to 4) [12].

Demographic details were represented using descriptive statistics. The categorical variable was presented proportionally. Analysis of variance (ANOVA) was used to compare all quantitative

variables according to the severity of liver cirrhosis. Pearson's correlation analysis was used to find an association between serum prolactin and different variables. The student's T-test was used to find significance. In multivariate logistics, the ROC curve was used to find the cut off value of prolactin for severe liver cirrhosis and also for sensitivity and specificity. All statistical analysis was done in Microsoft Excel and SPSS 22.0. $P < 0.05$ was considered significant.

Results:

A total of 60 participants were enrolled in the study with a mean age of 45.3years in the range of 24-83 years. The male: female ratio was 6.5:1 in our region. The mean ± SD serum prolactin level and Child-Pugh score among all patients were 29.75 ± 22.9 ng/dl and 9.31 ± 2.14, respectively.

Based on child-pugh scoring system, the distribution of patients in Child A, B and C categories were 10% (n=6), 46.67% (n=28) and 43.33% (n=28), respectively. Patient's mean serum prolactin levels in Child A, B and C categories were 8.36, 19.83 and

Volume 5, Issue 2; March-April 2022; Page No 1328-1333

45.4 ng/ml, respectively. The serum prolactin level (ng/ml) was also compared with the severity of ascites and grades of Hepatic Encephalopathy. Patients with mild, moderate and severe ascites had mean serum prolactin levels of 15.26, 27.28, and 40.38 ng/ml, respectively. Similarly, the mean serum prolactin level in Grade 1, 2, 3, and 4 Hepatic Encephalopathy patients was 45.4, 42.27, 56.02 and 68.1 ng/ml, respectively. There was a statistically significant correlation between serum prolactin level and Child-Pugh criteria (p=0.00001), the severity of ascites (p=0.0013) and grades of Hepatic Encephalopathy (p=0.00001). The serum prolactin level increased proportionally with increasing severity of liver cirrhosis with respect to Child-Pugh score, ascites and hepatic encephalopathy. Detailed findings are illustrated in Table 1.

The ROC curve for serum prolactin level as a predictor for severe/moderate liver cirrhosis found a statistically significant (p=0.00001) cut-off value of 24 ng/ml with sensitivity 92.31%, specificity 78.57%, AUC is 0.8764 and 95% CI of 0.778 – 0.975 which is with (Table 2, Graph1).

Discussion:

Altered prolactin levels in patients with hepatic dysfunction have been a topic of debate among researchers. Several authors have supported the assertion of hyperprolactinemia in chronic liver disorders, while few have argued [4,8,9]. Dopamine is the main regulatory factor with its inhibiting activity on prolactin-release. Prolactin elevation is primarily due to a decrease in dopamine levels in the tuberoinfundibular tract [13]. Circulating oestrogens are elevated in liver cirrhosis due to increased peripheral aromatization of testosterone via androstenedione and to a lesser extent through a decreased elimination by the liver [14]. These oestrogens stimulate prolactin release by interfering with the dopamine secretion from the hypothalamus and directly affecting the anterior pituitary [15]. Chronic liver dysfunctions lead to an increase in the concentration of defective aromatic amino acids entering the brain, thereby causing a rise in neurotransmitters like octopamine and phenyl ethanolamine. These neurotransmitters inhibit dopamine release leading to hyperprolactinemia [16]. Although human prolactin release is generally associated with a pulsatile pattern, people with cirrhosis liver is found to have a consistent 24-hour rise [13].

The mean age of patients with liver cirrhosis enrolled in our study was 45.3years in the range of 24-83 years and male preponderance (6.5:1) was seen. This was supported by the findings of Metwally et al., in which maximum cases belonged to the 38-60 years age group with male preponderance of 62%[7]. Similarly, in another study by Balkrishnan et al., 75% of the patients with liver cirrhosis were in the age group of 40-50 years [17]. In another study, out of 76 patients with liver cirrhosis, 60 (78.95%) patients were male and 16 (21.05%) patients were female [18].

In the present study, the distribution of patients in Child A, B and C categories were 10% (n=6), 46.67% (n=28) and 43.33% (n=28), respectively. These findings were comparable with the

results of Kumar et al. having 19.74% (n=15) patients in Child-Pugh Scoring Class A, 30.26% (n=23) in Class B and 50%(n=38) in Class C [18].

In this study, mean serum prolactin levels in child A, B, and C were 8.36 ± 4.42, 19.83 ± 10.27,

45.4 ± 24.84, respectively. This was supported in the studies study by Arafa M et al.[6], Velissaris et al.[13], who found that prolactin levels increased as the CHILD PUGH class increased from A to C. Sakhnani et al. found serum prolactin was significantly highest among patients with severe liver disease (CHILD PUGH CLASS -C) (52%). A significant positive correlation between CHILD PUGH SCORE and Prolactin level was also found (r + 0.962, p- value < 0.0001) [19]. Hence, Serum prolactin levels were comparable with child Pugh score in predicting severity and complications of cirrhosis.

In the present study, the mean prolactin level increased with the severity of ascites. The mean serum prolactin level was 40.38 ± 21.1 ng/ml in cases with severe ascites, 27.28± 26.17 ng/ml in moderate, and 15.26± 10.88 ng/ml in mild cases. In a similar study by Khalil et al.[7] the mean prolactin levels were 13.67, 20.05, and 21.6 ng/ml in patients with first, second, and third degree of ascites, respectively. The study also demonstrated serum prolactin level as a biological marker of severity in liver cirrhosis.

Volume 5, Issue 2; March-April 2022; Page No 1328-1333

The mean serum prolactin level in Grade 1, 2, 3, and 4 Hepatic Encephalopathy patients was 45.4 ± 17.17, 42.27± 20.17, 56.02 ± 42.6 and 68.1 ± 21.36 ng/ml, respectively. Prolactin level was found highly significant in grade level of hepatic encephalopathy. (p-value= 0.000001). These findings were also in concordance with other studies in which increased prolactin levels were found in patients with hepatic encephalopathy [7,19,20].

The present study found a cut-off level of 50 ng/ml of prolactin to predict mortality in patients with liver cirrhosis. A similar correlation of mortality to serum prolactin levels was observed

by McClain et al.[8] and Sharma et al.[9] with a higher risk of mortality was associated with values >50 ng/ml in ascites and hepatic encephalopathy.

The results of this study must be viewed in light of the study's limited sample size. Future research should focus on a larger population and different regions of the country, revealing the hidden entities of chronic liver disorders.

Conclusion:

The present study found a positive correlation of mean serum prolactin level with Child-Pugh score, severity of ascites and grade of hepatic encephalopathy, which was statistically significant. The cut-off value of serum prolactin level for predicting the severity of liver cirrhosis was 24ng/ml. Thus, the study concludes serum prolactin level can be used as a surrogate marker of severity in liver cirrhosis.

References:

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. Lancet. 2021;398(10308):1359–76.
2. CDC. Centre for Disease Control and Prevention. 2018. Available at : https://www.cdc.gov/nchs/fastats/liver-disease.htm. CDC.
3. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. BMC Med. 2014;12:14–145.
4. Ress C, Maeser PA, Tschoner A, Loacker L, Salzmann K, Staudacher G, et al. Serum prolactin in advanced chronic liver disease. Horm Metab Res. 2014;46(11):800–3.
5. Maruyama Y, Adachi Y, Aoki N, Suzuki Y, Shinohara H, Yamamoto T. Mechanism of feminization in male patients with non-alcoholic liver cirrhosis: Role of sex hormone- binding globulin. Gastroenterol Jpn. 1991;26(4):435–9.
6. A Besheer T, Arafa M, Elkannishy G, A El-hussiny M, B Rakha E. Features of Hormonal Disturbances in Cirrhotic Patients with Hepatic Encephalopathy. Euroasian J Hepato-Gastroenterology. 2012;2(2):84–9.
7. Khalil F, Elassal M, Hussein A, Rizk M, Awadein M, Behiry E, et al. Serum prolactin level as a biological marker of severity in liver cirrhosis. Benha Med J. 2017;34(2):140– 5.
8. McClain CJ, Kromhout JP, Elson MK, Van Thiel DH. Hyperprolactinemia in portal systemic encephalopathy. Dig Dis Sci. 1981;26:353–7.
9. Sharma MP, Acharya SK, Karmarkar MG. Significance of prolactin levels in protosystemic encephalopathy. J Assoc Physicians India. 1988;36:207–9.
10. Koller T, Kollerová J, Huorka M, Hlavatý T, Payer J. Impact of basal prolactin levels on the prevalence of complications and the prognosis of patients with liver cirrhosis. Vnitr Lek. 2009;55(5):468–73.
11. Durand F, Valla D. Assessment of prognosis of cirrhosis. Semin Liver Dis.2008;28(1):110–22.
12. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–35.
13. Velissaris D, Karanikolas M, Kalogeropoulos A, Solomou E, Polychronopoulos P, Thomopoulos K, et al. Pituitary hormone circadian rhythm alterations in cirrhosis patients with subclinical hepatic encephalopathy. World J Gastroenterol. 2008;14:4190– 5.
14. Gordon GG, Olivo J, Rafii F, Southren AL. Conversion of androgens to estrogens in cirrhosis

Volume 5, Issue 2; March-April 2022; Page No 1328-1333

of the liver. J Clin Endocrinol Metab. 1975;40(6):1018–26.
15. Piercy M, Shin SH. Comparative studies of prolactin secretion in estradiol-primed and normal male rats induced by ether stress, pimozide and TRH. Neuroendocrinology. 1980;31(4):270–5.
16. Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017;5(5):CD001939.
17. Balakrishnan CH, Rajeev H. Correlation of serum prolactin level to child pugh scoring system in cirrhosis of liver. J Clin Diagnostic Res. 2017;11(7):OC30–3.
18. Kumar D, Kampani G. Study of correlation of serum prolactin levels with severity of liver disease and its association with Hepatic Encephalopathy in patients of cirrhosis liver. J Assoc Physicians India. 2020;68(1):91–8.
19. Sakhnani DR, Sharma CK, Mathur A. Serum Prolactin: A Possible New Marker for Severity of Liver Cirrhosis. Eur J Mol Clin Med. 2021;8(4):53–7.
20. Mukherjee S, Kar M, Dutta S. Observation on serum prolactin in hepatic cirrhosis. J Indian Med Assoc. 1991;89:307-8.

Tables And Graph:

Table 1: Correlation of serum prolactin level with Child–Pugh scoring system, the severity of ascites and grading of Hepatic Encephalopathy

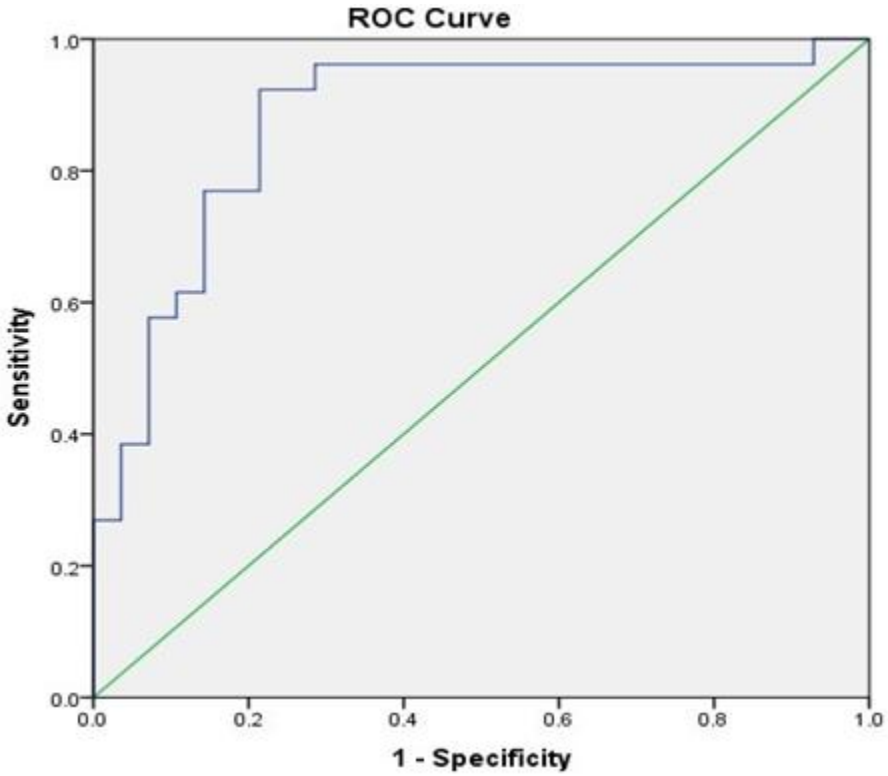
S.No	Parameters	Sub-category	Mean Prolactin level (ng/ml)	P value
1	Child-Pugh scoring system	Class A	8.36 ± 4.42	0.00001
		Class B	19.83 ± 10.27	
		Class C	45.4 ± 24.84	
2	Ascites	Mild	15.26± 10.88	0.00134
		Moderate	27.28± 26.17	
		Severe	40.38± 21.1	
3	Hepatic Encephalopathy	Absent	17.54± 8.84	0.000001
		Grade 1	45.4± 17.17	
		Grade 2	42.27± 20.17	
		Grade 3	56.02± 42.6	
		Grade 4	68.1± 21.36	

Table 2: Diagnostic accuracy of serum prolactin level in predicting severe / moderate liver cirrhosis

Cutoff Value (Serum Prolactin)	AUC	95% C I	Sensitivity	Specificity	P value
24 ng/ml	0.8764	0.778 – 0.975	92.31%	78.57%	0.000001

Volume 5, Issue 2; March-April 2022; Page No 1328-1333

Graph 1: ROC curve for serum prolactin level as a predictor for severe/moderate liver cirrhosis



Volume 5, Issue 2; March-April 2022; Page No 1328-1333