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Study Of Serum Prolactin Levels in Cirrhosis Of Liver and its Correlation With Child-Pugh Score in Assessment of Severity of the Disease

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ABSTRACT

BACKGROUND

In this study, we wanted to evaluate the correlation of serum prolactin in assessing the severity of cirrhosis in patients, estimate the level of serum prolactin in cirrhotic patients, and study the correlation of serum prolactin with Child Pugh score in assessing the severity of cirrhosis.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study conducted among 102 patients who presented with cirrhosis to the Department of General Medicine, OPD and IPD, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, Assam, over one year from 1st September 2020 to 31st August 2021 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

RESULTS

The correlation of serum prolactin with the severity of ascites was found to be significant (p=0.0085). The mean level of serum prolactin was 22.27±7.22 ng/ml, 37.89±9.1 ng/ml and 57.97±6.14 ng/ml in patients with none, minimal (grade I-II) and advanced (grade III-IV) encephalopathy respectively. We found the mean serum prolactin as 15.35±3.22 ng/ml, 28.5±7.72 ng/ml and 50.9±8.9 ng/ml in patients with Child Pugh scores class A, class B and class C respectively (p<0.0001).

CONCLUSION

Serum prolactin can be utilized as a single marker to identify the severity of cirrhosis.

KEYWORDS: Serum Prolactin Levels, Cirrhosis of Liver, Child-Pugh Score

INTRODUCTION

In the year 1826, Laennec first coined the word cirrhosis. The word cirrhosis takes its origin from the Greek term '**scirrhus'** and refers to the orange-brown or tawny surface of the liver that was seen at autopsy. Cirrhosis of the liver is defined as the terminal stage of chronic liver disease which is a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into the structurally abnormal nodule.[1]

The aetiology of cirrhosis can usually be identified by the history of the patient combined with serological and histological evaluation. In the Western world, alcohol followed by hepatitis C are the most common causes, while hepatitis B prevails in most parts of Asia and Sub-Saharan Africa. In 1989, following the discovery of the hepatitis C virus and nonalcoholicsteatohepatitis (NASH), the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is now rarely made.[2]

The epidemiology of cirrhosis is still under study in developing countries, but in developed countries, it is one of the leading causes of death among productive age groups.[3] According to a surveillance study in the United States, cirrhosis was the 10th leading cause of death in men and 12th in women.[4]

Patients with compensated liver cirrhosis are usually asymptomatic. Once the patient is in decompensated stage, they commonly present with complications such as gastroesophagealvariceal haemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatopulmonary syndrome and even hepatocellular carcinoma.[5]The 5-year survival rate is 14% to 35% in patients with decompensated cirrhosis while it is 84% in patients with compensated cirrhosis.[6]

Patients with cirrhosis undergo several endocrine dysfunctions, including the altered functions of the hypothalamic-pituitary-gonadal axis and the serum levels of hormones. One such hormone is prolactin. It is a polypeptide hormone composed of 199 amino acids and is regulated by prolactin-releasing factors (PRFs) and prolactin inhibitory factors (PIFs).[7,8]

Hyperprolactinemia was found to be associated with people with chronic liver disease. Physiologically, prolactin levels are elevated in pregnancy and lactation and disorders like pituitary tumours, renal failure, failure of hypophysis and medications like anti-psychotics, anti-depressants, metoclopramide, etc.

It is hypothesised that a decrease in dopamine levels in the tuberoinfundibular tract causes an increase of serum prolactin in cirrhotics.[9]The tuberoinfundibular tract is a collection of dopamine neurons that project into the medial eminence from the arcuate nucleus of the mediobasal hypothalamus. Regulation of prolactin secretion is mainly mediated by pulsatile hypothalamic inhibition by dopamine and the stimulatory influences of hypothalamic releasing factors and circulating oestrogens. Increased peripheral aromatization of testosterone via androstenedione and, to a lesser extent, reduced oestrogen clearance by the liver cause elevated circulating oestrogens in liver cirrhosis.[10] These oestrogens subsequently stimulate prolactin release by blocking hypothalamic dopamine secretion and acting directly on the anterior pituitary.[11]

The relationship between chronic liver disease and serum prolactin was suggested by Morgan way back in 1978. In his study, he found that serum prolactin was unexpectedly high in patients with chronic liver disease.[12] Also, it was found that prolactin levels were elevated in cirrhotic patients with a Child-Pugh score of C suggesting the correlation with the severity of the disease in a study by Zietz et al.[13]

Serum prolactin is a straight forward and affordable marker that can help determine the severity of the condition and forecast the likelihood of complications. As a result, determining the relationship between serum prolactin and the severity of cirrhosis would aid in improving the clinical treatment and patient outcomes, and will serve as an independent measure of severity in cirrhotic patients.

AIMS AND OBJECTIVES

1. To estimate the level of serum prolactin in cirrhotic patients.
2. To study the correlation of serum prolactin with a Child-Pugh score in assessing the severity of cirrhosis.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study conducted among 102 patients who presented with cirrhosis to the Department of General Medicine, OPD and IPD, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, Assam, for one year from 1st September 2020 to 31st August 2021 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

1. Patients above 18 years.
2. Patients with diagnosed cirrhosis of the liver.

Exclusion Criteria

1. Patients below 18 years.
2. Pregnancy and Lactation.
3. Diagnosed case of any gynaecological pathology.
4. History of cranial surgery/Irradiation.
5. History of chest trauma
6. Diagnosed case of pituitary or hypothalamic disease.
7. Diagnosed case of chronic renal failure.
8. Patients on medications known to elevate prolactin levels.

Study Procedure

All patients included in the study were evaluated in detail. A detailed history, thorough clinical examination and relevant investigations were done in these patients to confirm the diagnosis of liver cirrhosis and then study the serum prolactin levels. Written informed consent was obtained for clinical examination, lab investigations and procedures such as paracentesis and upper gastrointestinal endoscopy. All investigations were done at the clinical pathology, microbiology and biochemistry laboratories in Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, Assam.

Sample Size Estimation [14]

The sample size is estimated using the formula, $S=Z2\times P\times (1-P)/C2$ S= Sample size
Z=1.96 is constant for a 95% confidence interval P= prevalence of the disease
C= Allowable error
A total of 102 patients were included using this formula.

Statistical Methods

Data were collected, revised, coded and entered into the statistical package for social science (IBM SPSS) version 20. Qualitative data were presented as numbers and percentages while quantitative data were presented as mean, standard deviations and ranges when parametric. The comparison between two groups with qualitative data was done by using the chi-square test and/or the Fisher exact test was used instead of the chi-square test when the expected count in any cell was found less than 5. The comparison between more than two independent groups regarding quantitative data with parametric distribution was done by using a one-way analysis of variance (ANOVA) followed by post hoc analysis using the LSD test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non- significant < 0.05: significant and P < 0.01: Highly significant.

RESULTS

Age bar	**Frequency**	**Percentage %**
18-27	4	3.92
28-37	52	50.98
38-47	37	36.27
48-57	9	8.82
Grand Total	102	100
Age Distribution		
Sex	**No of patients (n=102)**	**Percentage (%)**
MALE	73	71.57%
FEMALE	29	28.43%
Sex Distribution		
Table 1 Demographic Distribution		

Of a total of 102 patients, 73 cases were males and 29 cases were females accounting for 71.57% and 28.43% of the total population respectively. The most common cause of cirrhosis was alcohol (85.3%) followed by NASH and cryptogenic which were 5% respectively. 2% of the patients had alcohol plus hepatitis B as the aetiology while in the remaining patients they were hepatitis C (1%), Wilson disease (1%) and hepatitis B (1%).

Aetiology of CLD	**Frequency**	**Percentage (%)**
Alcohol	86.00	84.31
Autoimmune	1.00	0.98
Nash	5.00	4.90
Cryptogenic	5.00	4.90
Alcohol hepatitis B	2.00	1.96
Hepatitis C	1.00	0.98
Wilson disease	1.00	0.98
Hepatitis B	1.00	0.98
Total	102	100
Aetiology of cirrhotic patients		
Symptoms	**No of cases**	**Percentage (%)**
Weakness/fatigue	91	89.22%
Anorexia	11	10.78%
Nausea/vomiting	2	1.96%
Abdominal distension	46	45.10%
Leg swelling	33	32.35%
Hematemesis/melena	31	30.39%
Presenting symptoms of the cirrhotic patients		
Examination findings	**no of patients**	**Percentage (%)**
Pallor	25	24.51%
Icterus	29	28.43%
Pedal oedema	32	31.37%
Ascites	56	54.90%
Splenomegaly	34	33.33%
Asterisks	30	29.41%
Petechial/purpura	20	19.61%
Dilated veins over the abdomen	41	40.20%

Examination findings in the study population

Table 2

The most common cause of cirrhosis was alcohol (85.3%) followed by NASH and cryptogenic which were 5% respectively. 2% of the patients had alcohol plus hepatitis B as the aetiology while in the remaining patient's, it was hepatitis C (1%), Wilson disease (1%) and hepatitis B (1%).

91% had weakness/fatigue. About 46% of the patients had abdominal distension followed by 30% bilateral leg swelling and the other 30% of the patients were suffering from hematemesis/melena. About 11% of the patients had anorexia and the remaining 2% of the patients had nausea.

Ascites was the most common examination finding present in 54.90% of patients, followed by dilated veins over the abdomen (40.20%), splenomegaly (33.33%), pedal oedema (31.37%), asterisks (29.41%), icterus (28.43%), pallor (24.51%) and petechiae/ purpura (19.61%).

Complications	**No**		**Yes**		**Total**	
	No of cases	**%**	**No of cases**	**%**	**No of cases**	**%**
Hepatic encephalopathy	74	73%	28	27%	102	100%
Hepatorenal syndrome	101	99%	1	1%	102	100%
SBP	97	95%	5	5%	102	100%
Portal hypertension	68	67%	34	33%	102	100%
Upper GI bleed	71	70%	31	30%	102	100%

Complications of cirrhosis in the patients

Table 3

The most common complication found was portal hypertension (33%) followed by upper GI bleeding (30%) and hepatic encephalopathy (27%). 5% of the patients suffered from spontaneous bacterial peritonitis and 1% from the hepatic-renal syndrome.

The mean value of serum prolactin for a patient with mild ascites (easily controlled) was 31.5± 8.3 ng/ml while in moderate to severe ascites (poorly controlled) it was 31.5 ± 8.3 ng/ml. The mean value of serum prolactin for patients with no ascites was 19.8 ±6.1 ng/ml. The correlation of serum prolactin with the severity of ascites was found to be significant (p=0.0085).

The mean level of serum prolactin was 22.27±7.22 ng/ml, 37.89±9.1 ng/ml and 57.97±6.14 ng/ml in patients with none, minimal (grade I-11) and advanced (grade III-IV) encephalopathy respectively. The correlation of serum prolactin with the severity of hepatic encephalopathy was found significant (p<0.0001).

The mean serum prolactin level was 15.4±3.2 ng/ml, 15.3 ± 4.1 ng/ml, 30.4 ±10 ng/ml, 42.7±14 ng/ml in patients with none, grade I, grade II, and grade III varices respectively (p=0.03).

Values	**Easily controlled (ng/ml)**	**Poorly controlled d (ng/ml)**	**None (ng/ml)**	**p-value**
Average of serum prolactin	31.5 ± 8.3	49.6 ±10.0	19.8±6.1	0.0085

Serum prolactin in various grades of ascites

Grades of hepatic encephalopathy	**None(ng/ml)**	**Minimal(m)(ng/ml)**	**Advanced(a)(ng/ml)**
	Mean±SD	Mean±SD	Mean±SD
S. Prolactin	22.27±7.22	37.89±9.1	57.97±6.14
p-value	<0.0001		

Serum prolactin according to grades of hepatic encephalopathy

Varices	**Average of serum prolactin**	**Stddev of serum prolactin**	**p-value**
grade 1	15.3	4.1	0.0352
grade 2	30.4	10.0	
grade 3	42.7	14.0	
None	15.4	3.2	
Total	28.1	12.8	

Serum prolactin in different grades of varices

Table 4

	A (N=27)	**B (N=61)**	**C (N=14)**
Prolactin median(IQR)	15.2(12.8,18.2)	27.9(24.3,31.1)	49.15(43.775,59.3)

Prolactin mean ± SD	15.35±3.22	28.5±7.72	50.9±8.9
P-value	<0.0001		
Serum prolactin according to Child-Pugh score			
Table 5			

We found the mean serum prolactin as 15.35±3.22 ng/ml, 28.5±7.72 ng/ml and 50.9±8.9 ng/ml in patients with Child-Pugh scores Class A, Class B and Class C respectively ($p<0.0001$).

DISCUSSION

The study was primarily aimed to estimate the serum prolactin levels in cirrhotic patients and their correlation with Child Pugh scores in the assessment of the severity of the disease. In this study, the majority of the patients i.e. 52% of them were in the age group of 28-37 yrs. About 37 % of the patients were in the age group of 38-47 yrs., followed by 4% in the age group of 18-27 yrs. The mean age of the population was 37.7± 6.7(Mean± SD). In similar studies carried out by Juraj Payer et al,[15] Deepak Raj Sakhnani et al,[16] and F.Khalil et al,[17] mean ages were 57 (95% CI 54.98–59.08), 49.4±12.7 years (range 19-80 years), and 51.94±5.99 (Mean ± SD) years respectively.

In a study by Balakrishnan CH et al,[18] 45 (75%) patients belonged to the age group of 40-50 years, 8 (13%) patients in the age group of 30-40 years and 7 (12%) patients belonged to the age group of 50-60 years.

In this study of a total of 102 patients, 73 cases were males accounting for 71.57%, whereas 29 cases were females comprising 28.43%.

In a similar study carried out by Juraj Payer et al,[15] out of 114 patients, 74 (51.38%) were men and 40(35.08%) were women.

In another study carried out by Balakrishnan CH et al,[18] 60 patients were studied, in which 50 were males comprising 83% and 10 (17%) were females consisting of the remaining 17%. In studies done by Deepak Raj Sakhnani et al,[16] and F. Khalil et al.[17] 50 patients were studied of which 72% were males and 28% females, 62% were males and 38% were females respectively.

In our study, out of 102 patients, the most common cause of cirrhosis was alcohol (85.3%) followed by NASH and cryptogenic which were 5% respectively. 2% of the patients had alcohol plus hepatitis B as the aetiology while in the remaining patients it was hepatitis C (1%), Wilson disease (1%) and hepatitis B(1%). In similar studies reported by Juraj Payer et al,[15] Deepak Raj Sakhnani et al[16] and F.Khalil et al,[17] and Balakrishnan CH et al[18] alcohol was reported as the most common aetiology contributing 77.2%, 56%, 44%, 73% and 73% respectively.

In our study, the majority of the patients i.e., 91% had weakness/fatigue. About 46% of the patients had abdominal distension followed by 30% with bilateral leg swelling and the other 30% of the patients were suffering from hematemesis/melena. About 11% of the patients had anorexia. The remaining 2% of the patients had nausea. In similar studies carried out by Deepak Raj Sakhnani et al,[16]Balakrishnan CH et al[18] and F. Khalil et al,[17] abdominal distension was the most common symptom reported in 76%, 83.3% and 76% of the patients respectively. Ascites was the most common finding present in 54.90% of patients, followed by dilated veins over the abdomen (40.20%), splenomegaly (33.33%), pedal oedema (31.37%), asterisks (29.41%), icterus (28.43%), pallor (24.51%) and petechial purpura (19.61%). Many patients had more than one clinical finding. In other similar studies done by Deepak Raj Sakhnani et al,[16]Balakrishnan CH et al[18] and F. Khalil et al,[17] ascites was reported as the most common finding in 60%, 88.3% and 60% of the patients respectively.

In our study, the most common complication found was portal hypertension (33%) followed by upper GI bleeding (30%) and hepatic encephalopathy (27%). 5% of the patients suffered from spontaneous bacterial peritonitis and 1% from the hepatic- renal syndrome. Balakrishnan CH et al [18] in their study, found the most common complication of cirrhosis to be portal hypertension in 50 (83.3%), followed by esophagealvarices 39 (65%). 22 patients (36.7%) had upper GI bleeding and 15 (25%) had hepatic encephalopathy.

In our study, the Child-Pugh Score was applied to assess the severity of the disease and accordingly patients were distributed into different Child-Pugh Score classes. 27(26.47%) of the patients were grouped under class A, while 61(59.80%) patients were in class B and the remaining 42 (32.3%) patients were present in class C. In similar studies by Balakrishnan CH et al[18] and Deepak Raj Sakhnani et al,[16] it was found that 6 (10%) patients were reported in Class A, 24 (40%) patients in Class B and 30 (50%) in Class C and 8(16%) in Class A, 16(32%) in class B and the remaining 26(52%) in class C respectively. The normal value of prolactin in the laboratory was 3-25 ng/ml. In our study, 58(56.86%) of the patients had prolactin levels above 25 ng/ml and the highest value of serum prolactin was 65.4 ng/ml. The mean value of serum prolactin for males and females was found to be 29.2 ± 13.8 and 25.4 ± 9.4 respectively.

In a study by Balakrishnan CH et al[18] of 60 patients, 44 (73.33%) of them had serum prolactin levels elevated above 19 ng/ml. The highest value of prolactin noted was 60 ng/ml.

In studies carried out by Deepak Raj Sakhnani et al,[16] and Ramy a. Metwally et al,[19] the mean prolactin values were 48.1±26.8 ng/ml and 18.76±9.14 ng/dl.

In our study, the mean value of serum prolactin for a patient with mild ascites (Grad I) was 31.5± 8.3 ng/ml while in moderate to severe ascites (Grade II and III) it was 31.5 ± 8.3 ng/ml. The mean value of serum prolactin for patients with no ascites was 19.8±6.1ng/ml. The correlation of serum prolactin with the severity of ascites was found to be significant (p=0.0085).

In studies done by Deepak Raj Sakhnani et al, prolactin levels were found to be significantly related to ascites degree. Mean prolactin levels were 19.79 ± 12.29 ng/ml, 36.1583 ± 15.06 ng/ml, 60.09 ± 18.05 ng/ml in patients with 1st, 2nd and 3rd degrees of ascites respectively (p-value <0.00001). In another similar study by, Ramy a. Metwally et al,[19] the mean prolactin level reported was 13.67±6.48 ng/ml, 20.05±9.06 ng/ml and 21.06±5.32 ng/ml in patients with 1st, 2nd and 3rd-degree ascites respectively (p=0.19).

In our study, the mean level of serum prolactin was 22.27±7.22 ng/ml, 37.89±9.1 ng/ml and 57.97±6.14 ng/ml in patients with none, minimal (grade I-11) and advanced (grade III-IV) encephalopathy respectively. The correlation of serum prolactin with the severity of hepatic encephalopathy was found significant (p<0.0001). Deepak Raj Sakhnani et al in a study reported the mean level of serum prolactin as 81.08 ± 18.04 ng/ml in cases with advanced hepatic encephalopathy, 56.89 ± 15.05 ng/ml in cases with mild hepatic encephalopathy and 26.16 ± 13.99 ng/ml in cirrhosis cases without encephalopathy (P < 0.00001). In another similar study by RamyaMetwally et al., the mean prolactin levels were 13.22± 6.32 ng/ml, 17.54±4.3 ng/ml, 23.87±1.96 ng/ml, 30.37±1.8 ng/ml and 32.66±2.76 ng/ml for patients with none, grade I, grade II, grade III and grade IV encephalopathy respectively (p <0.001). In our study, the mean serum prolactin level was 15.4±3.2 ng/ml, 15.3 ± 4.1 ng/ml, 30.4 ±10 ng/ml, 42.7±14 ng/ml in patients with none, grade I, grade II, and grade III varices respectively. There was a significant correlation between serum prolactin and the severity of varices. (p=0.03). In a similar study by Balakrishnan CH et al among 39 patients with esophagealvarices, 26 (66.7%) had elevated serum prolactin.

In our study, we found the mean serum prolactin as 15.35±3.22 ng/ml, 28.5±7.72 ng/ml and 50.9±8.9 ng/ml in patients with Child-Pugh scores Class A, Class B and Class C respectively (p<0.0001). In a study by Deepak Raj Sakhnani et al, the mean serum prolactin level in Child-Pugh score, class-A was 10.03ng/ml, class-B was 33.26 ng/ml and class-C was 68.91 ng/ml (p < 0.0001). In a similar study by RamyaMetwally et al, mean serum prolactin levels were 13.84± 8.99 ng/ml, 19.35 ± 10.6 and 20.09 ± 7.41 ng/ml in Child-Pugh score class A, class B and class C respectively (p=0.04).

CONCLUSION

Alcohol was shown to be the most prevalent etiological agent of cirrhosis in our study, and it was found to be more common in males than in females. The patients presented with complaints of weakness and fatigue, and ascites and dilated abdominal veins were the most common signs on inspection. Patients with decompensated cirrhosis were more likely to have portal hypertension, which was followed by an upper GI bleed. Serum prolactin levels were higher in patients with decompensated cirrhosis than in those with compensated cirrhosis, and they were related to the severity of complications. Child-Pugh score, which was divided into three grades A, B, and C, was used to determine the severity of cirrhosis. In our research, we discovered a strong association between the Child Pugh score and serum prolactin in cirrhosis assessment (p<0.001). As a result, serum prolactin can be utilized as a single marker to identify the severity of cirrhosis, as demonstrated in our study. Limitations of the study: The sample size was relatively small. In addition, the research was conducted in a cross-sectional design. Therefore, further studies are required to determine serum prolactin as a single prognostic marker in assessing the severity of cirrhosis.

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