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Correlation of serum prolactin level to Child-Pugh scoring system and its prognostic significance in cirrhosis of liver

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ABSTRACT

Background: With the growing incidence of liver cirrhosis among Asians, the use of a biomarker such as prolactin indicates the severity of the disease, its complications, and serves as a tool for the early intervention. **Aims and Objectives:** The aims of this study were to assess the correlation of serum prolactin level to the Child-Pugh Scoring System in liver cirrhosis patients and to find out its prognostic importance in liver cirrhosis. **Materials and Methods:** This is a cross-sectional study including 60 patients of liver cirrhosis. Complete history taking, physical examination, and relevant investigations were done. Frequency and percentage were calculated and Chi-square test was applied for significance. Correlation was assessed using Spearman's correlation coefficient. **Results:** Mean age was 44 ± 12.8 years. Cirrhosis was alcohol induced in 55%, hepatitis B related in 18.3%, and other causes related in 7.8%. Mean prolactin levels were 18.1 ± 11.3 µg/l. Strong positive correlation was found between prolactin level and bilirubin level (rs = 0.372, P = 0.003) and prolactin level and prothrombin time (rs = 0.490, P = 0.003). Statistically significant association was found between Child-Pugh score and prolactin level ($x^2 = 12.2$, P = 0.003). We found no significant association of prolactin level with age, albumin, creatinine, ascites, esophageal varices, etiology of cirrhosis, and hepatic encephalopathy. **Conclusion:** We observed that there was a strong correlation between Child-Pugh score and serum prolactin level. Although, Child-Pugh scoring system is a predictor of morbidity in liver cirrhosis patients, serum prolactin level can also be used as an indicator for predicting patients at high risk of developing complications and mortality due to liver cirrhosis.

Key words: Liver cirrhosis; Serum prolactin; Child-Pugh scoring; Ascites; Esophageal varices; Jaundice; Hepatic encephalopathy

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INTRODUCTION

Cirrhosis is a leading cause of liver related deaths at the present. It is the final stage of progressive liver fibrosis, in which the liver architecture is distorted and leads to death if liver transplantation is not done. The cause remains idiopathic in around 50% of the patients.[1] Mortality and morbidity associated with cirrhosis increases sharply once decompensation occurs, and depending on the etiology of compensated cirrhosis, the 1-year case fatality rate can be around 80%.[2] Serum prolactin and Child-Pugh scoring system are the two methods to estimate the severity of liver disease. Two pathways lead to hyperprolactinemia in liver cirrhosis. One is due to elevated circulating estrogens, which stimulate prolactin release by interfering with the dopamine secretion from the hypothalamus, and through a direct effect on the anterior pituitary.[3] Another pathway is by increase in the synthesis of false neurotransmitter such as octopamine and phenyl ethanolamine, which inhibit the dopamine release.[4] The Child-Pugh score system rates the long-term severity of liver disease and predicts mortality in patients with liver cirrhosis.[5] Globally, cirrhosis caused more than 1.32 million deaths in 2017, compared with less than 89,000 deaths in 1990.[2] Southeast Asia ranked fifth in terms of age-standardized death rate from cirrhosis across regions in 2017 (29.5 per

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100,000).[2] With the growing incidence of liver cirrhosis, especially among South East Asian Countries, prognostic criteria like the Child-Pugh scoring system alone does not give us a proper idea of the probability of complications in a patient presenting with liver cirrhosis, while prolactin levels does give an idea about the severity of disease and the possible complications. Thus, it is a very vital tool in the early intervention in such cases.[6] The aim of the present study was to assess the correlation of serum prolactin level to the Child-Pugh scoring system in liver cirrhosis patients and to find out its prognostic importance in liver cirrhosis.

Aims and objectives

The aims of this study were to assess the correlation of serum prolactin level to the Child-Pugh scoring System in liver cirrhosis patients and to find out its prognostic importance in liver cirrhosis.

MATERIALS AND METHODS

This cross-sectional study was conducted at the outpatient and inpatient of General Medicine department of Netaji Subhash Chandra Bose Medical College Jabalpur Madhya Pradesh, India from March 1, 2019, to August 31, 2020. The study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission. After obtaining the permission of IEC, the study was conducted. Sixty patients of liver cirrhosis diagnosed on ultrasonography were selected for the study using convenience sampling.

Sample size

The adequate required sample size was estimated using the following formula

$$n=z^2\ p\ q/d^2$$

where n=sample size, z=1.96 (considering 0.05 alpha, 95% confidence limits and 80% beta), p=assumed probability of occurrence or concordance of results, q=1–p, d=marginal error (precision), Sample size= 60

Exclusion criteria

The following criteria were excluded from the study:

1. Patients not willing to participate in the study
2. Patients having conditions, which significantly alter serum prolactin such as pregnant females, patients on anti-psychotic and anti-parkinsonian medications, and diagnosed case of pituitary macro- and microadenoma.

Consent

Written consent was obtained from the study participants after explaining them the nature and purpose of the study. The participants were assured that confidentiality would be strictly maintained. The option to withdraw from the study was always open.

Methodology

After taking the clearance from IEC, data were collected from the patients during outpatient department and inpatient department hours after the informed and voluntary consent with the help of pre-tested, pre-designed, and semi-structured questionnaire. Details regarding sociodemographic characteristics, addiction history, clinical signs, and symptoms were obtained from the study participants and the details regarding laboratory investigation were obtained from the records of the patient. The patients were selected based on clinical examinations, biochemical tests, and ultrasound abdomen. In all cirrhotic patient's, serum prolactin level was measured and it was correlated with Child-Pugh score in assessing the severity of the disease. Laboratory investigations done were complete blood count, blood sugar, liver function test, renal function test, serum prolactin level, serum ammonia (if required), ascitic fluid examination, serum electrolytes, ultrasound abdomen, hepatitis B antigen, human immunodeficiency virus, hepatitis C virus, prothrombin time (PT INR), and upper gastrointestinal endoscopy.

Statistical analysis

Data were entered into Microsoft Excel – 2007, analysis was done with the help of Epi-Info 7 software. Frequency and percentage were calculated and Chi-square test was applied for significance. Correlation was assessed using Spearman's correlation coefficient.

RESULTS

A total of 60 study participants were selected for 1½ year. The observations of the study are represented under following sections:

- Section A: Sociodemographic details of the study participants

Maximum participants (58.3%) were in 36–50 years of age group. The mean age of the study participants was 44.9±12.8 years (Table 1).

- Section B: Clinical profile of the study participants

Alcohol was the major cause of cirrhosis (55%) followed by hepatitis B (18.3%) (Table 2).

The complications of cirrhosis observed were esophageal varices, ascites, and hepatic encephalopathy (Table 3).

- Section C: Diagnostic test and association

In the present study, 34 (65.4%) patients had serum prolactin level in normal range, that is, between 2–18 ng/mL. Two

(3.8%) patients had serum prolactin <2 ng/ml, while 16 (30.8%) had hyperprolactinemia with serum prolactin level >18 ng/ml. The mean prolactin level of all the study participants was 18.1±11.3. The mean prolactin level of male was 17.0±10.8. The above table highlights that half of the patients, that is, 4 (50%) had serum prolactin level in normal range, that is, between 2 and 29 ng/ml, while the other 4 (50%) patients had hyperprolactinemia with serum prolactin level >29 ng/ml. The mean prolactin level of female was 24.7±13.1 (Table 4).

Out of 60 patients, 36 (60%) patients were classified as cirrhosis with Child-Pugh score between 7 and 9 followed by 19 (31.7%) patients had Child-Pugh score ≥10. Only 5 (8.3%) patients have Child-Pugh score between 5 and 6 (Table 5).

Majority of the patients, that is, 32 (61.5%) had Child-Pugh score between 7 and 9 (Class B), out of which 26 (81.3%) patients had normal serum prolactin level 2–18 ng/ml, while only 5 (15.6%) had hyperprolactinemia. Fifteen (28.9%) patients had Child Pugh Score ≥10 (Class C), out of which 9 (60%) had hyperprolactinemia, while 5 (33.3%) had serum prolactin level in the normal range. Five (9.6%) patients have Child-Pugh score between 5 and 6 (Class A), out of which 3 (60%) had serum prolactin level in the normal range, while 2 (40%) had hyperprolactinemia. Out of total eight females, equal number of females had Child-Pugh score between 7–9 and ≥10 (Class B and C). Out of 4 females with Child-Pugh score between 7 and 9 (Class B), out of which 3 (75%) had normal serum prolactin level 2–29 ng/ml, while 1 (25%) had hyperprolactinemia. Out of 4 females with Child-Pugh score ≥10 (Class C),

Table 1: Sex distribution across the age category

Age	Sex				Total	
	Female		Male			
	Count	Percentage	Count	Percentage	Count	Percentage
21–35	0	0.0	11	21.2	11	18.3
36–50	5	62.5	30	57.7	35	58.3
51–65	3	37.5	09	17.3	12	20.0
≥66	0	0.0	02	3.8	02	3.3
Total	8	100.0	52	100.0	60	100

Table 2: Distribution of the participants according to the cause of chronic liver cirrhosis

S. No.	Causes of chronic liver cirrhosis	Number of cases (n=60)	Percentage
1.	Alcohol	33	55.0
2.	Hepatitis B	11	18.3
3.	Hepatitis B and Hepatitis C	01	1.7
4.	Alcohol and Hepatitis B	06	10.0
5.	Others	09	15.0
Total		60	100

Table 3: Distribution of the participants based on the grading of esophageal varices and hepatic encephalopathy and severity of ascites

Esophageal varices grade	No. of cases	%	Severity of Ascites	No. of cases	%	Hepatic encephalopathy grade	No. of cases	%
Nil	34	56.7	No	6	10.0	Nil	49	81.7
Grade I	4	6.6	Mild	0	0.0	Grade I	0	0.0
Grade II	7	11.7	Moderate	07	11.7	Grade II	9	15.0
Grade III	8	13.3	Gross	47	78.3	Grade III	0	0.0
Grade IV	7	11.7				Grade IV	2	3.3
Total	60	100		60	100		60	100

Table 4: Distribution of the participants based on serum prolactin

Males			Females		
Serum prolactin level	Number of case (n=52)	Percentage	Serum prolactin level	Number of case (n=8)	Percentage
<2 ng/ml	02	3.8	<2 ng/ml	0	0.0
2–18 ng/ml	34	65.4	2-29 ng/ml	4	50.0
>18 ng/ml	16	30.8	>29 ng/ml	4	50.0
Total	52	100		8	100

out of which 3 (75%) of the study participants had hyperprolactinemia, while 1 (25%) had normal serum prolactin level (Table 6).

A Spearman's correlation was run to assess the relationship between prolactin level and age, albumin level, bilirubin level, prothrombin time, and creatinine. There was a strong positive correlation between prolactin level and bilirubin level, which was statistically significant (rs=0.372, P=0.003). Strong positive correlation was also found between prolactin level and prothrombin time, which was statistically significant, (rs=0.490, P=0.000). No significant association was found between prolactin level and age, albumin, and creatinine (Table 7).

There was statistically significant association between Child-Pugh score and prolactin level (x2=12.2, P=0.003). Strong statistically significant association was found between prolactin level and CPS Grade B and C with (P=0.001) each. However, no significant association was found between ascites and prolactin level (x2=1.231, P=0.570), esophageal varices and prolactin level (x2=2.805, P=0.605), cause of cirrhosis and prolactin level (x2=4.091, P=0.416), and hepatic encephalopathy and prolactin level (x2 =24.1, P=0.712). There was no statistical difference in the mean prolactin level between male and female (z=–1.300, P=0.114) (Table 8).

Table 5: Distribution of the participants based on Child-Pugh score

Child-Pugh score	Number of Case (n=60)	Percentage
5–6 – Class A	05	8.3
7–9 – Class B	36	60.0
≥10 – Class C	19	31.7
Total	60	100

DISCUSSION

Age

The mean age of the study participants was 44.9±12.8 years with maximum study participants were between 36 and 50 years of age group which is similar to the findings by Balakrishnan and and Rajeev[6] and by Arafa et al.,[7] and Velissaris et al.,[8] mean age of the study participants was 64.6± 9.5 years. The mean age was found to be 49.2±5.6 years according to the findings.

Sex

Majority of the patients encountered in the present study were male 52(86.7%) followed by 8 (13.3%) female. This is similar to the study findings by Balakrishnan and and Rajeev[6] and Khalil et al.,[9] in which 83% and 64% of the participants, respectively, were male.

Cause of liver cirrhosis

In the present study, in 33 (55%) patients, alcohol was identified as the major cause of cirrhosis followed by hepatitis B in 11 (18.3%) patients. The findings of our study were similar to the findings by Balakrishnan and and Rajeev[6] and Zacharias et al.[10] In a study by Hong et al.,[11] the most common cause of liver cirrhosis was found to be hepatitis B virus (56%).

Complications of cirrhosis

In the present study, out of 60 study participants, 26 (13.3%) patients had esophageal varices. Majority of the patients with cirrhosis, that is, 47 (78.3%) had gross ascites, 7 (11.7%) had moderate ascites, while 6 (10%) had no ascites. Hepatic encephalopathy Grade II and IV was observed in 9 (15%) and 2 (33%) cases, respectively. In study done by Velissaris et al.,[8] it was observed that out of

Table 6: Correlation of serum prolactin level in participants with Child-Pugh score

Males				Females			
Serum prolactin level n=52	Child-Pugh Score			Serum prolactin level N=8	Child-Pugh Score		
	Class-A (5–6)	Class-B (7–9)	Class-C (≥10)		Class-A (5–6)	Class-B (7–9)	Class-C (≥10)
<2 ng/ml	0	1 (3.1)	1 (6.7)	<2 ng/ml	0 (0)	0 (0)	0 (0)
2–18 ng/ml	3 (60)	26 (81.3)	5 (33.3)	2–29 ng/ml	0 (0)	3 (75)	1 (25)
>18 ng/ml	2 (40)	5 (15.6)	9 (60)	>29 ng/ml	0 (0)	1 (25)	3 (75)
Total	5 (9.6)	32 (61.5)	15 (28.9)	Total	0 (0)	4 (50)	4 (50)

Table 7: Correlation between serum prolactin level (ng/ml) and estimated parameters

Variable (n=60)	Spearman correlation coefficient (rhp;p)	P value
Age (years)	0.088	0.505
Albumin (mg/dl)	0.128	0.329
Bilirubin (mg/dl)	0.372	0.003
Prothrombin time (s)	0.490	0.000
Creatinine (mg/dl)	0.195	0.136

Table 8: Variations in the serum prolactin levels by patient's characteristics

Variable	Prolactin level (ng/ml)			Test	P-value
	Number	Mean	SD		
Sex					
Male	52	17.0	10.8	z=1.300	0.114
Female	8	24.7	13.1		
Ascites					
No	6	25.1	18.9	x^2=1.231	0.570
Gross	47	16.8	10.0		
Moderate	7	20.7	10.9		
Esophageal Varices					
Grade-1	4	18.1	12.8	x^2=2.805	0.605
Grade-2	7	18.4	8.3		
Grade-3	8	18.5	6.4		
Grade-4	7	19.6	11.3		
Causes of Cirrhosis					
Alcohol	33	29.1	37.8	x^2=4.091	0.416
Alcohol and HBV	6	14.9	10.2		
HBV	11	19.1	9.9		
HBV and HCV	1	16.2	NA		
Others	9	33.9	39.9		
Hepatic Encephalopathy					
Grade-2	9	33.9	13.5	x^2=24.1	0.712
Grade-4	2	25.0	7.0		
Child Pugh score					
A 5–6	5	13.7	5.7	x^2=12.2	0.003
B 7–9	36	14.8	7.6		
C ≥10	19	25.3	14.8		

26 study participants, two, 14, and 8 patients had ascites, splenomegaly, and esophageal varices, respectively.

Serum prolactin level

The mean prolactin level of male was 17.0±10.8. The mean prolactin level of female was 24.7±13.1. The mean prolactin level of all the study participants was 18.1±11.3. According to the findings by Balakrishnan and and Rajeev[6], out of the 60 participants, 73.3% had prolactin level above 19 ng/ml. Khalil et al.,[9] revealed that the serum prolactin level was 5.5–39 ng/ml with mean and SD (18.76±9.14 ng/dl).

Child-Pugh score system

Out of 60 patients, 36 (60%) patients were classified as cirrhosis with Child-Pugh score between 7 and 9 (Class B) followed by 19 (31.7%) patients had Child-Pugh score ≥10 (Class C). Only 05 (8.3%) patients have Child-Pugh score between 5 and 6 (Class A). In study of Velissaris et al.,[8] 22 patients were Class A, 4 patients with Class B. No patients were in Child-Pugh score Class C.

According to the findings by Balakrishnan and and Rajeev,[6] based on the Modified Turcotte Child-Pugh scoring system, 10%, 40%, and 50% of the patients belonged to Class A, B, and C, respectively. According to the findings by Khalil et al.,[9] the CPS level was from 5 to 14 with mean and SD of 9.16±3.16.

A strong positive correlation was found between prolactin level and bilirubin level, which was statistically significant strong positive correlation that was also found between prolactin level and prothrombin time, which was statistically significant. No significant association was found between prolactin level and age, albumin, and creatinine.

There was statistically significant association found between Child-Pugh score B and prolactin level. This finding is similar to the findings by Khalil et al.,[9] where statistically higher significant relation was found between serum prolactin level and Child-Pugh grading.

However, no significant association of prolactin level was found with ascites, varices, cause of cirrhosis, and hepatic encephalopathy. There was no statistical difference in the mean prolactin level between male and female. According to a study conducted by Arafa et al.,[7] the serum prolactin level was significantly increased with progression of liver diseases from Child-Pugh score A to C (P=0.023, P=0.000, and P=0.007, respectively). In a study conducted by Balakrishnan and and Rajeev[6], highest level of serum prolactin was seen in patients of Class C.

Limitations of the study

The main limitation of our study is the presence of confounding factors which could lead to raised prolactin levels, including undiagnosed comorbid conditions. We

have tried to exclude as many of these factors as possible. Another limitation is small sample size.

FUTURE SCOPE

In our study, higher prolactin level in patients with cirrhosis was significantly associated with worsening liver function as indicated by higher Child-Pugh scores. These results suggest that prolactin levels may be used for evaluation of liver functions in cirrhosis. Prolactin may also help to predict patients likely to develop complications. Studies having large sample size with follow-up are required to study prolactin levels into prognostic scoring systems of liver disease. Future studies are also required to compare the prolactin levels with the other complications of liver disease such as hepatopulmonary syndrome and hepatorenal syndrome. Cohort studies can be done to analyze the relation of elevated prolactin levels and mortality rates.

CONCLUSION

We observed that there was a strong correlation between Child-Pugh score and serum prolactin level. Although, Child-Pugh scoring system is a predictor of morbidity in liver cirrhosis patients, serum prolactin level can also be used as an indicator for predicting patients at high risk of developing complications and mortality due to liver cirrhosis.

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PP- Concept and design of the study, prepared first draft of manuscript; **AB**- Interpreted the results; reviewed the literature and manuscript preparation; **SR**- Concept, coordination, statistical analysis and interpretation; **SC**- Preparation of manuscript and revision of the manuscript.

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