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Serum Prolactin: A Possible New Marker for Severity of Liver Cirrhosis

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Abstract

Background: Liver cirrhosis (LC) is an irreversible condition which results from necrosis of hepatocytes with loss of reticular network and nodular regeneration of residual liver tissue. This study was undertaken to assess the relation between serum prolactin levels and the severity of the liver cirrhosis.Materials & methods: This cross-sectional observational study was conducted during one calendar year at a tertiary care center in Western India among 50 cases of established liver cirrhosis. Serum Prolactin was estimated using ADVIA Centaur® CP Immunoassay System (Siemens®) by Chemiluminescent technique. The modified Child Pugh score was calculated for each study participant. The patients were categorized into Classes A, B or C based on the score obtained. Hepatic encephalopathy was diagnosed and graded as per West Haven classification system. The grade I-II were taken as mild and grade III-IV as advanced hepatic encephalopathy for calculation of the modified Child-Pugh score. Ascites was graded as mild, moderate and severe. All the data were stored in excel sheet using Microsoft® Office 2007. Results: The mean serum prolactin, serum albumin, serum Bilirubin and INR were 48.1±26.8 ng/ml, 2.8±0.6 g/dl, 4.8±4.9 mg/dl and 2.2±1.0 respectively. (Table No. 1) The mean serum prolactin level in alcoholic cirrhosis (49.2±25.1 ng/ml) does not statistically differ from non-alcoholic cirrhosis (46.6±29.4 ng/ml) cases (p > 0.05). The mean serum prolactin level was statistically significantly higher among cases in Modified Child Pugh Class-C (68.91 ± 17.80 ng/ml) compared to Class B (33.26 ± 7.41 ng/ml) and Class A (10.03 ± 4.01ng/ml) cases. The mean serum prolactin level was 81.36 ± 19.85 ng/ml in cases with severe ascites, 60.09 ± 18.05 ng/ml in moderate ascites cases, 36.1583 ± 15..06 ng/ml in mild ascites cases and 19.79 ± 12.29 ng/ml in cirrhosis cases without ascites. The difference in mean serum prolactin level was significant among different severity of ascites. The serum prolactin level was 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. Conclusion: Serum Prolactin levels showed positive correlation with Modified Child Pugh Score and Fibroscan in predicting the severity of disease.

Key words: Prolactin, Liver cirrhosis

INTRODUCTION

Liver cirrhosis (LC)is an irreversible condition which results from necrosis of hepatocytes with loss of reticular network and nodular regeneration of residual liver tissue.[1- 4]There are various methods described in literature to assess severity of cirrhosis. The liver biopsy is the gold standard method to assess liver fibrosis but has major disadvantages of invasive, painful procedure and it may have rare but potential life threatening complications.

Recently, with advancement in diagnostic techniques, Fibroscan (Transient elastography) has emerged as a promising non-invasive technique to assess liver fibrosis.[5]Fibroscan is operated dependent and had variability in results measured by different assessors.

The modified Child-Pugh scoring system was designed to predict mortality in patients with cirrhosis but it may result in inconsistency in scoring and require various component parameters for its calculation.[5- 7]Therefore a simple, easily accessible test is needed to ascertain the severity of liver disease and forecast its complications timely.The liver cirrhosis is known to affect pituitary gonadal axis.[8-10]Human prolactin (PRL)is a hormone of pituitary origin whose production is controlled by dopamine (negative regulator) via hypothalamo-pituitary axis. In liver cirrhosis, a drop in dopamine levels in hypothalamo-pituitary axis has been noted resulting in augmented serum prolactin levels. [8- 10]Keeping this fact, in the search of a biomarker for liver cirrhosis; prolactin might be a promising approach. The data regarding prolactin and liver cirrhosis is scanty. So, this study was undertaken to assess the relation between serum prolactin levels and the severity of the liver cirrhosis.

MATERIALS & METHODS

Thiscross-sectional observational study was conducted during one calendar year at a tertiary care center in Western India among 50 cases of established liver cirrhosis (diagnosed as per clinical, laboratory and ultrasound criteria).[11]Patients of above 18 years of age with established diagnosis of liver cirrhosis were included in the study after written informed consent. Pregnant and lactating women, patients with history of cranial surgery/irradiation, endocrinal disorders, concomitant renal failure, drugs that influence prolactin level (e.g.anti-psychotics, anti depressants, D2 blockers, OCPs, H2 antagonist etc.) were excluded from the study. After history taking and through physical examination including search for evidence of cirrhosis and its complications including portal hypertension, ascites, and hepatic encephalopathy, venous blood sample was taken on empty stomach after overnight fasting at 8 A.M. Routine blood test (complete blood count, renal function tests, liver function tests, prothrombin time), thyroid function tests and prolactin assay was done. Serum Prolactin was estimated using ADVIA Centaur® CP Immunoassay System (Siemens®)by Chemiluminescenttechnique.

The modified Child Pugh score was calculated for each study participant. The patients were categorized into Classes A, B or C based on the score obtained.Hepatic encephalopathy was diagnosed and graded as per West Haven classification system. [12] The grade I-II were taken as mild and grade III-IV as advanced hepatic encephalopathy for calculation of the modified Child-Pugh score.

Ascites was graded as mild, moderate and severe.[13]

Grade 1 (mild): Ascites is only detectable by ultrasound examination.

Grade 2 (moderate): Ascites causing moderate symmetrical distension of abdomen.

Grade 3 (large): Ascites causing marked abdominal distension.

Fibroscan for Liver Stiffness Measurement (LSM) (Fibroscan®, M probe, Echosens®) was carried out by radiologist who was blinded to the study and clinical state of the patients. The median liver stiffness of the 10 successful measurements was noted (in kPa). Measurements were performed on the right lobe of the liver through intercostals spaces with the patient lying in dorsal decubitus with the right arm in maximal abduction.

Sample size calculation:

Sample size was calculated 50 cases as per previous study[3], showing correlation betweenserum prolactin and severity of liver cirrhosis (r=0.42) for 80% power and 0.05 error.

Statistical analysis:

All the data were stored in excel sheet using Microsoft® Office 2007. Chi-square test was used to analyze categorical data. For analysis of continuous variables, Student's t-test and One-Way ANOVA test were used. Karl–Pearson correlation coefficient was calculated to observe correlation between variables. P value < 0.05 was taken as significant.

RESULTS

Among 50 studied established liver cirrhosis cases, the mean age of study participants was 49.4±12.7 years (range 19-80 years) with male:female ratio of 2.6:1. Alcoholic cirrhosis was found in 28/50 (56%) of cases. The mean serum prolactin, serum albumin, serum Bilirubin and INR were 48.1±26.8 ng/ml, 2.8±0.6 g/dl, 4.8±4.9 mg/dl and 2.2±1.0 respectively. (Table No. 1)

The mean serum prolactin level in alcoholic cirrhosis (49.2±25.1 ng/ml) does not statistically differ from non-alcoholic cirrhosis (46.6±29.4 ng/ml) cases (p > 0.05). The mean serum prolactin level was statistically significantly higher among cases in Modified Child Pugh Class-C (68.91 ± 17.80 ng/ml) compared to Class B (33.26 ± 7.41 ng/ml) and Class A (10.03 ± 4.01ng/ml) cases (p <0.0001). The mean serum prolactin level was 81.36 ± 19.85 ng/ml in cases with severe ascites, 60.09 ± 18.05 ng/ml in moderate ascites cases, 36.1583 ± 15..06 ng/ml in mild ascites cases and 19.79 ± 12.29 ng/ml in cirrhosis cases without ascites. The difference in mean serum prolactin level was significant among different severity of ascites (P < 0.00001). The serum prolactin level was 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). (Table No. 2)

The mean serum prolactin had significant positive correlation with Modified Child Pugh Score (r + 0.9627, P< 0.0001), LSM (r + 0.9857, P< 0.0001), serum bilirubin (r + 0.4041, P 0.003) and INR (r + 0.7637, P< 0.0001). The mean serum prolactin had significant negative correlation with serum albumin (r - 0.7412, P < 0.0001) and platelet count (r - 0.8379, P < 0.00001). (Table No. 3, Fig No.1)).

Table No. 1: Characteristics of study participants

Age (years) (Mean±SD)	**49.4±12.7**
Sex (M/F)	36/14
Alcoholic cirrhosis	28 (56%)
S. Prolactin (ng/mL) (Mean±SD)	48.1±26.8

LSM (kPa)	11.97±3.66
S. Albumin (g/dL) (Mean±SD)	2.8±0.6
S. Bilirubin (mg/dL) (Mean±SD)	4.8±4.9
INR (Mean±SD)	2.2±1.0
Platelets (lakhs/uL)	1.09±0.57

Table No. 2: Association of mean serum prolactin with study variables

		S. Prolactin (ng/mL)	**P value**	
Cirrhosis	Alcoholic (N=28, 56%)	49.2±25.1	0.83	NS
	Non-alcoholic (N=22, 44%)	46.6±29.4		
Modified Child Pugh Class	Class-A (N=8, 16%)	10.03 ± 4.01	< 0.001	Sig
	Class-B (N=16, 32 %)	33.26 ± 7.41		
	Class-C (N=26, 52%)	68.91 ± 17.80		
Ascites	None (12, 24%)	19.79 ± 12.29	< 0.001	Sig
	Mild (12, 24%)	36.1583 ± 15..06		
	Moderate (18, 36%)	60.09 ± 18.05		
	Severe (8, 16%)	81.36 ± 19.85		
Hepatic Encephalopathy	None (23, 46%)	26.16 ± 13.99	< 0.001	Sig
	Mild (16, 32%)	56.89 ± 15.05		
	Advanced (11, 22%)	81.08 ± 18.04		

Table No. 3: Correlation of Serum Prolactin and other parameters

Variables	**Correlation coefficient (r)**	**P-value**	
Modified Child Pugh Score	+ 0.9627	< 0.001	Sig
LSM (kPa)	+ 0.9857	< 0.001	Sig
S. Albumin	- 0.7412	< 0.001	Sig
S. Bilirubin	+ 0.4041	0.003	Sig
INR	+ 0.7637	< 0.001	Sig
Platelets	-0.8379	< 0.001	Sig

Figure No. 1 A: Correlation between Modified Child Pugh Score and serum Prolactin level

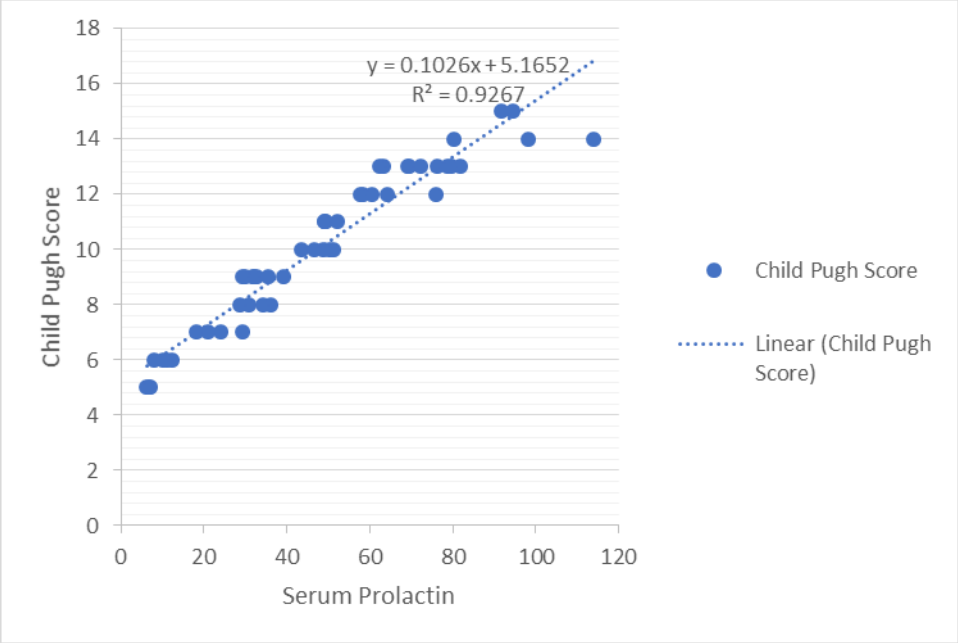
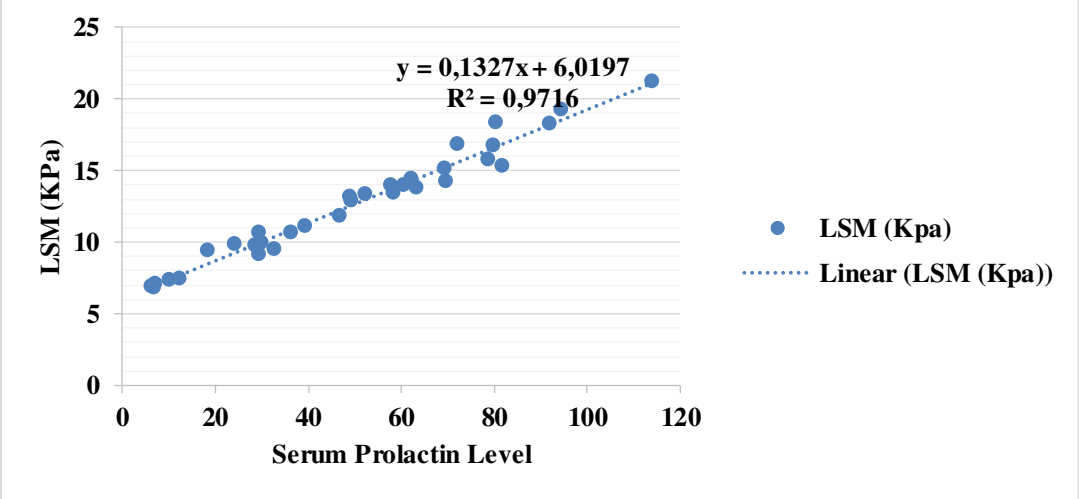


Figure No. 1 B: Correlation between Liver Stiffness Measurement (LSM) and serum Prolactin level



DISCUSSION

Liver cirrhosis is associated with significant morbidity and mortality. The fibroscan is non-invasive tool to assess cirrhosis but has the disadvantage of being operator dependent. The Modified Child-Pugh Score requires calculations of various parameters and is time consuming. This study was done to assess serum prolactin as a marker of liver cirrhosis compared to fibroscan (LMS) and Modified Child Pugh Score.

In our study, out of 50 subjects majority (26/50, 52%) were in Modified Child Pugh class-C followed by (16/50, 32%) were in class-B and least (8/50, 16%) were in class-A. Mean serum prolactin level in class-A was 10.03 ng/ml, in class-B was 33.26 ng/ml and in class-C was 68.91 ng/ml ($P < 0.0001$). Serum prolactin was significantly highest among patients with

severe liver disease (Modified Child Pugh Class -C). There was significant correlation or association of serum prolactin with the components of Modified Child Pugh score. A significant positive correlation between Modified Child Pugh score and Prolactin level was also found in current study (r + 0.962, P < 0.0001). This denotes that serum prolactin had significant association with severity of cirrhosis and increases with severity of liver cirrhosis. These results are consistent with previous reports.[14-18]Rajasekarapandianand Kanimozhi[14]also observed the correlation of serum prolactin with Modified Child Pugh scoring in the assessment of severity of liver cirrhosis and they suggested that it can be used as a negative prognostic marker.

Serum prolactin was significantly correlated with LMS (indicator of liver cirrhosis/fibrosis) on fibroscan (P < 0.0001). This finding was also similar to previous reports among liver cirrhosis patients.[4-5]

The possible explanation of the rise in serum prolactin with severity of liver cirrhosis is linked mainly to the fall in dopamine levels in the tuberofundibular tract of hypothalamo-pitutary axis. [8-10] In liver cirrhosis; decompensated liver function results in alteration in the type of amino acids entering the central nervous system. There is increase in concentration of circulating aromatic amino acids leads to increase synthesis of false neurotransmitters e.g.phenylethanolamine and octopamine which may inhibit dopamine release.[19]The resulting fall in dopamine leads to hyperprolactinemia.

The single center study, limited duration (one calendar year) and limited sample size were limitations of the current study. Based on the finding of this study, larger population based studies may be conducted in future to validate our results.

CONCLUSION

Serum Prolactin levels showed positive correlation with Modified Child Pugh Score and Fibroscanin predicting the severity of disease. Hence, Serum Prolactin level is an inexpensive, non-invasive marker which may be used to estimate the severity of liver cirrhosis.

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