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Serum Prolactin levels as a marker of severity of Cirrhosis of Liver

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1. INTRODUCTION

Liver cirrhosis is defined as the distortion of the hepatic parenchyma due to diffuse fibrosis and replacement its architecture by regenerative nodules.[1] The prevalence of chronic liver disease is estimated to be 1.28% among the Indian population and alcohol was the most common etiology for cirrhosis (33.3%).[2] Chronic insult to the hepatic parenchyma causes hepatocyte necrosis and fibrosis, activation of hepatic stellate cells and increase in the hepatic vascular resistance leading to portal hypertension.[3] Various methods have been described in literature to assess the severity of cirrhosis. The liver biopsy is the gold standard for assessment of liver fibrosis but has disadvantages of being invasive and painful procedure. Recently, with advancement in diagnostic techniques, Fibroscan (Transient elastography) has emerged as a non-invasive technique to assess liver fibrosis.[4] Over time many prognostic scores have been developed which can be used for the prediction of clinical prognosis in liver disease.
The modified Child-Pugh scoring system is a composite ordinal score, which incorporates three laboratory based parameters (serum albumin, serum bilirubin and prothrombin time) and two clinical variables (ascites and hepatic encephalopathy) designed to predict mortality in patients with liver cirrhosis but it may result in inconsistency in scoring and requires various component parameters for its calculation.[4-6] The MELD (Model for End Stage Liver Disease) score is used commonly in practice to predict the survival in cirrhosis and for the prioritisation of patients who are candidates for liver transplant and comprises of three laboratory parameters: Serum bilirubin, International Normalized Ratio (INR) and Serum creatinine.[7]
Some novel biochemical parameters are evolving and are the current field of research. Serum Therefore a simple and easily accessible test is required to ascertain the severity of liver disease and forecast its complications timely. The liver cirrhosis is known to affect hypothalamic-

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pituitary gonadal axis.[8] Human prolactin is a hormone of pituitary origin which is regulated by is dopamine in the hypothalamo- pituitary axis. Decompensated liver function leads to alteration in the type of amino acids entering the brain leading to an increase in the false neuro-transmitters which inhibit dopamine release thus leading to hyperprolactinemia. Also, increase in the estrogen levels found in patients of liver cirrhosis, stimulates prolactin release by interference with the secretion of dopamine from the hypothalamus via its direct effect on the anterior pituitary secretion.[9] Prolatcin has a promising approach in the search of a biomarker for liver cirrhosis. This study was conducted to assess the role of serum prolactin levels in the estimation of severity of the liver cirrhosis.

2. MATERIALS & METHODS

This cross-sectional study was conducted on the patients admitted to a tertiary care centre in North-West India over a time period of 1 April 2021 to 31 July 2022, on 150 cases of established liver cirrhosis (diagnosed as per clinical, laboratory and ultrasound criteria), who consented to participate in the study. Pregnant and lactating women, patients with concomitant renal failure, history of cranial surgery/ irradiation, pituitary or hypothalamic disease, seizure disorder, polycystic ovarian syndrome, hypothyroidism, Celiac disease and intake of 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), prolactin assay was done. Serum Prolactin was estimated using ADVIA Centaur® CP Immunoassay System (Siemens®) by chemiluminiscence 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.

Sample size calculation

Sample size was calculated 150 cases as per previous studies, showing correlation between serum 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.

3. RESULTS

Table No. 1: Characteristics of study participants

Age (years) (Mean±SD)	(53.19±12.56)
Sex (M/F)	128/22
Etiology	Alcohol n=90 (60%)
S. Prolactin (ng/mL) (Mean±SD)	25.26±14.88

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S. Bilirubin (mg/dL) (Mean±SD)	4.88± 3.15
S. Albumin (g/dL) (Mean±SD)	2.42± 0.67
Prothrombin time(sec) (Mean±SD)	20.94± 8.34
Platelets (lakhs/uL)	1.64± 0.98

Among 150 patients of established liver cirrhosis cases, the mean age was (53.19±12.56 years) with maximum patients in age group (51-60years) among which 85.3% (n= 128) were male and 14.67% (n= 22) were female with a male:female ratio of 5.8:1. Abdominal distension was the most common presenting complaint in 46.66% patients (n=70). Alcohol was the most common etiology of cirrhosis was found in 60% (n=90) of patients, 4 (2.6%) and 8 (5.3%) patients who were Hepatitis B and C positive respectively, were also alcoholic.

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

Study variable		Number of patients	S. Prolactin (ng/mL)	P value(S/NS)
Modified Child Pugh Score	A	16	8.38 ± 1.50	<0.001 (S)
	B	57	16.06 ± 3.62	
	C	77	35.76 ± 14.30	
MELD-Na Score	<9	13	12.58± 5.18	<0.001 (S)
	10-19	79	20.93± 11.52	
	20-29	48	31.49± 15.18	
	30-39	10	47.44± 16.08	
	>40	0	0	
Cirrhosis	Alcoholic	102	38.12± 14.26	0.42(NS)
	Non alcoholic	48	32.6±19.4	
Complications of cirrhosis	Ascitis	92	29.33 ± 16.02	0.424(NS)
	Splenomegaly	62	26.65 ± 14.68	
	SBP	11	26.87 ± 19.84	
	Varices	18	25.08 ± 13.64	
	Encephalopathy	95	30.64±14.98	
Grade of Hepatic	None	55	16.24 ± 10.46	0.019(S)

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encephalopathy (West Haven criteria)	Grade I	25	19.18 ± 5.52	
	Grade II	31	28.40 ± 11.66	
	Grade III	37	38.34 ± 14.98	
	Grade IV	2	66.30 ± 18.40	
Grade of ascites	None	58	17.18 ±10.02	0.001(S)
	Mild	26	24.54 ±10.40	
	Moderate	39	31.50 ± 16.80	
	Gross	27	34.34 ±15.62	

Among a total of 150 patients 10.67% were in Child Class A (n=16), 38% were in Child Class B (n=57) and 51.33 % patients (n=77) were in Child class C (n=77). MELD-Na Score was calculated in 150 patients. Out of total 150 patients, 79% patients(n=79) were in MELD-Na category 10-19 (n=79), 32% patients (n=48) were in MELD-Na category 20-29 (n=48), 8.67% were in MELD-Na category <9 (n=13) and 6.67% patients were in MELD-Na category 30-39(n=10) and no patient was found in MELD-Na category >40. A total of 63.33% patients (n=25) had evidence of encephalopathy in them, 61.3% patients(n=92) had ascites, 41.3% (n=62) had splenomegaly, 12%(n=18) had variceal bleed,7.33% (n=11) were having SBP.
The mean serum prolactin levels were (38.12± 14.26 ng/mL) in patients with Alcoholic cirrhosis, which did not statistically differ from non-alcoholic cirrhosis (32.6±19.4 ng/ml) cases ($p > 0.05$). Mean serum prolactin were 29.33 ± 16.02 ng/mL in patients with ascites, 26.65 ± 14.68 ng/ mL in patients with splenomegaly, 26.87 ± 19.84 ng/mL in patients with SBP, 25.08 ± 13.64 ng/mL in patients in which variceal bleed was found and 30.64±14.98 ng/mL in patients with encephalopathy. No significant association was found in serum prolactin levels with complications of cirrhosis (with $p>0.05$). Mean serum Prolactin level is 16.24 ± 10.46 ng/mL in patients without encephalopathy, 19.18 ± 5.52 ng/mL in grade I encephalopathy, 28.40 ± 11.66 ng/mL in grade II encephalopathy, 38.34 ± 14.98 ng/mL in grade III encephalopathy and 66.30 ± 18.40 in grade IV encephalopathy. The values were significant with a p-value of 0.019. Mean serum Prolactin level is 17.18 ± 10.02 ng/mL in patients with no ascites 24.54 ± 10.40 ng/mL in mild ascites, 31.50 ± 16.80 ng/mL in moderate ascites, 34.34 ± 15.62 ng/mL in gross(tense) ascites. The values were significant with a p-value of 0.001.

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

Variables	Correlation coefficient(r-	Level of significance (p-
Modified Child Pugh score	0.672	0.001
MELD-Na score	0.485	0.001
S. Bilirubin	0.191	0.019
Prothrombin time	0.644	0.001
Albumin	-0.348	0.001

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Sodium	-0.166	0.043

The mean serum prolactin had significant positive correlation with Modified Child Pugh Score (r + 0.672, P 0.001), MELD-Na Score (r + 0.485, P 0.001), serum bilirubin (r + 0.191, P 0.019) and Prothrombin time (r + 0.644, P< 0.001). The mean serum prolactin had significant negative correlation with serum albumin (r - 0.348, P 0.001) and serum sodium (r - 0.166, P 0.043).

4. DISCUSSION

Cirrhosis of liver is one of the top 10 leading causes of death. Globally, mortality of cirrhosis has increased by 47.15% from 1990 to 2017. India had observed the maximum number of deaths in 2017 from cirrhosis across the globe. The age standardised rate of mortality caused by chronic hepatitis C (HCV), alcohol consumption and non-alcoholic steatohepatitis (NASH) has increased with an estimated annual percentage change of 0.17, 0.20 , 1.00 respectively.[10] Calculation of Modified Child Pugh score and MELD-Na score are the methodsbeing used in practice to estimate the severity of cirrhosis of liver. This study was done to assess serum prolactin as a marker of severity of liver cirrhosis as compared to Modified Child Pugh Score and MELD-Na score.

In our study, out of 150 patient's majority mean Serum Prolactin levels were 8.38 ± 1.50 ng/mL in Child Class A (n=16), 16.06 ± 3.62 ng/mL in Child Class B(n=57) and 35.76 ± 14.30 ng/mL in Child Class C(n=77) with (p<0.001). The levels of serum prolactin increased with increase in severity of liver cirrhosis assessed by Modified Child Pugh sore with a significant positive correlation (r +0.672). These results are consistent with previous reports by Ramy et al[11], Zietz et al[12], Arafa et al[13], Sakhnani et al[14], Patel et al[15], Paternostro et al[16]. Balakrishnan et al[9], Punekar et al[17], T.K Rajasekarpandian et al[18] and Animesh et al[19].

In our study, the mean serum prolactin levels were 12.58 ± 5.18 ng/mL in (MELD score<9) , 20.93± 11.52ng/mL in (MELD score 10-19) , 31.49 ± 15.18 ng/mL in (MELD score 20-29) and 47.44 ± 16.08 ng/mL in (MELD score 30-39). The levels of serum prolactin increased with increase in MELD-Na score with a significant positive correlation (r +0.485). Similar findings were obtained in study by Vikash et al[20] in their study.

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 as the 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 leading to increase in synthesis of false neurotransmitters e.g. phenylethanolamine and octopamine which may inhibit dopamine release thus leading to hyperprolactinemia. Increase in estrogen levels in liver cirrhoisis also contribute to hyperprolactinemia.

Significant rise in serum prolactin levels were found with increase in grade of hepatic encephalopathy which was in consistence with previous studies conducted by Ramy et al[11], Arafa et al[13], Ramani et al[21], Sakhnani et al[22] and Giri R et al[23].Also, increase in the severity of ascites leads to statistically significant rise in serum prolactin which was also reported in previous studies by Ramy et al[11], Punekar et al[17] and Sakhnani et al[22]. Serum prolactin also showed significant positive correlation with total serum bilirubin, prothrombin time and negative correlation with serum albumin levels and serum sodium. However, no significant association of serum prolactin was found with the etiology of cirrhosis and complications of cirrhosis.

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The single center study and limited duration (one calendar year) 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.

5. CONCLUSION

Serum Prolactin levels showed positive correlation with Modified Child Pugh Score and MELD-Na score, 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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