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"CORRELATION OF SERUM PROLACTIN LEVELS WITH CHILD PUGH SCORING IN CIRRHOSIS OF LIVER TO ASSESS THE SEVERITY OF THE DISEASE"

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Abstract:

Background:

Cirrhosis of the liver is associated with various disturbances of the endocrine system. Prolactin secretion follows a pulsatile pattern with characterisitic nocturnal rise. In patient with cirrhosis , associated with elevated 24 hours prolactin level and loss of circadian rhythm. Increased level of serum prolactin associated with increased risk of hepatic encephalopathy and progression of severity of hepatic disease,With the growing incidence of cirrhosis of the liver, prognostic criteria like the child pugh scoring system do not give us an idea of the probability of complications in a patient presenting with cirrhosis of the liver .Hence, the use of a biomarker such as prolactin, whose levels give us an idea about the severity of the disease and the possibility of complications, is a very vital tool in early intervention in such cases.

AIM: The study aims to investigate the prevalence of hyperprolactinemia in cirrhotic patients, examine the relationship between serum prolactin levels and the severity of the disease along with the prediction of complications, and compare serum prolactin levels with the Child Pugh scoring system in cirrhosis.

METHODS: A correlational prospective study was undertaken among patients fulfilling the inclusion criteria , admitted in medical wards. A total of 120 cases constituted study sample.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Patients having cirrhosis of liver are evaluated with proper clinical history, laboratical investigation like Liver function test, coagulation profile, serum prolactin levels.

RESULTS: In our study population of 120 cirrhotic patients of various etiologies,Alcohol tops the list in males with most of them are in the age group of 31 to40 years. , while in females viral etiologies play an important role.The mean prolactin value found to be 37.3ng/ml in patients with massiveascites ; and in patients with grade 3 or 4 varices it is found to be around 35.80 ng/ml and 37.3 ng/ml respectively.Mean prolactin value was found to be , 12.9, 23.6 and 28.7ng/ml in ChildPugh Class A ,B and C found to be increasing correlating with the severity ofthe disease.In patients with and without encephalopathy, mean prolactin value found to be 28.7ng/ml and 12.90ng/ml .

CONCLUSION: Prolactin levelsignificantly correlates with severity of the liver disease and predicting therisk of complications and helpful in preventing them. The rise in prolactinlevel also had a synonymous relationship with the Child Pugh Scoringsystem thus validating the use of Prolactin as a prognostic marker in hepaticcirrhosis

Keyboard: Cirrhosis of the Liver, Serum Prolactin Levels, Child Pugh Scoring, Hepatic Encephalopathy, Prognostic Biomarker

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

INTRODUCTION

The main goal of this study was to evaluate the diagnostic andprognostic significance of serum prolactin concentration in cirrhosis indetermining the severity of hepatic disease and its correlation with CHILDPUGH score.

Prolactin secretion followa pulsatile pattern with characterisiticnocturnal rise. In patient with cirrhosis , associated with elevated 24 hoursprolactin level and loss of circadian rhythm. Increased level of serum prolactinassociated with increased risk of hepatic encephalopathy and progression ofseverity of hepatic disease.

Patients with end-stage liver disease have several endocrinedysfunctions, which include alterations in the functioning of the hypothalamic-pituitary-gonadal axis and the serum levels of sex hormones.

Our prospective study showed that cirrhotic men have significantalterations in the pituitary regulatory functions, and that these disorders arecompletely reversed after liver transplantation. In cirrhosis, excess productionof SHBG in liver and increased prolactin levels were detected while exploringthe cause of gynecomastia and high level of liver estrogen receptors was addedto the direct suppressing effect of estrogen on Leydig cell functions [5].

Decompensated liver function leads to an alteration in the type of aminoacids entering the central nervous system. Circulating concentrations ofaromatic amino acids have been found to increase leading to an increase in the2synthesis of false neurotransmitters such as octopamine and phenylethanolamine[8]. These false neurotransmitters may inhibit thedopamine release contributing to hyperprolactinemia. Cases of hypogonadismhave also been reported in patients with cirrhosis attributing tohyperprolactinemia[9]. A similar correlation of mortality to serum

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

prolactin levels was observed by McClain *et al*[10] and Sharma *et al*[11]. with a higher Risk of mortality with serum prolactin values of >50 ng/ml. Mukherjee *etal*[12]. analyzed the prolactin levels in patients with hepatic cirrhosis and founda higher levels in both patients with encephalopathy and mortality.Patient withliver cirrhosis complicated by hepatic encephalopathy found to have low serumtotal T3, serum cortisol and high prolactin level. These are early indicators ofimpending hepatic encephalopathy and progression of liver disease.Serumprolactin was found to be elevated in 39 to 75 percent cirrhotic patients.

CHILD PUGH SCORING SYSTEM:

- Cirrhosis can be staged clinically. A reliable scoring system is the modified CHILD PUGH scoring system. It ranges from 5 to 15.
- Child Pugh CLASS A : Score of 5 and 6 , consistent with compensated cirrhosis.
- Child Pugh CLASS B : Score of 7 to 9 , consistent with decompensated cirrhosis.
- Child Pugh CLASS C : Score more than 10 , consistent with decompensated cirrhosis.

This scoring system includes 5 factors : serum bilirubin, serum albumin,ascites, hepatic encephalopathy and pro-thrombin time. It is reasonably areliable predictor of survival and predicts the likelihood of major complicationslike bleeding from the varices and spontaneous bacterial peritonitis.It was alsoused to assess the prognosis in cirrhosis and to provide a standard criteria inlisting the patient for liver transplantation.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Thus comparing the serum prolactin level with the Child pugh scoringsystem in assessing the severity of the liver disease and predicting the risk ofcomplications.

MATERIAL AND METHODS

1 Source of data:

The study will be conducted on 120 patients admitted to Department of general medicine in ESIC MC & PGIMSR MODEL HOSPITAL BENGALURU during the study period from January 2019 to June 2020.

2 Method of collection of data:

Informed consent will be obtained from all patients to be enrolled for the study. In all the patients relevant information will be collected in a predesigned proforma.The patients are selected based on clinical examinations, biochemical tests and ultrasound abdomen.

SAMPLE SIZE : 120 PATIENTS

STUDY DESIGN : PROSPECTIVE STUDY

STUDY DURATION : JANUARY 2019 TO JUNE 2020

SAMAPLE SIZE ESTIMATION:

$$\text{Sample size } (n) \text{ based on sensitivity} = \frac{Z^2_{1-\alpha/2} \times S_N \times (1-S_N)}{L^2 \times Prevalence},$$

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

S_N	Guestimated Sensitivity	0.6774*
L	Absolute precision (20-25% of S)	0.15
1-α/2	Set level of confidence (<1.0)	0.95
Z	Z value associated with alpha	1.959964
Prevalence	Prevalence of disease (0-1)	0.339#
n	Minimum sample size	111

INCLUSION CRITERIA

Patients above the age 18 years both males and females with diagnosis of cirrohosis of liver

EXCLUSION CRITERIA

a) History of cranial surgery/ irradiation

b) Polycystic ovarian syndrome patients

c) Herpes zoster

d) Cushing's syndrome

e) Pregnant women

f) Chest wall trauma

g) History of pituitary or hypothalamic disease

h) Chronic renal failure

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

i) Patient on medications known to elevate prolactin levels suchas neuroleptics, metoclopramide, methyl dopa, reserpine, cyproterone acetate, aldosterone antagonists, morphine,cimetidine, anti- androgens, H2-receptor antagonists, anti-convulants.

STATISTICAL ANALYSIS

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean±standard deviation (SD) were used. For categorical data, the number and percentage wereused in the data summaries and diagrammatic presentation.Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript “c” are the degrees of freedom. “O” is observed value and E is expected value. C= (number of rows-1)*(number of columns-1)

The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

ANOVA

Source	d.f.	SS	MS	F
Treatment	$a-1$	SS_{treat}	$\frac{SS_{treat}}{a-1}$	$\frac{MS_{treat}}{MS_{error(a)}}$
Error (a)	$N-a$	$SS_{error(a)}$	$\frac{SS_{error(a)}}{N-a}$	
Time	$t-1$	SS_{time}	$\frac{SS_{time}}{t-1}$	$\frac{MS_{time}}{MS_{error(b)}}$
Treat x Time	$(a-1)(t-1)$	$SS_{treat\ x\ time}$	$\frac{SS_{treat\ x\ time}}{(a-1)(t-1)}$	$\frac{MS_{treat\ x\ time}}{MS_{error(b)}}$
Error (b)	$(N-a)(t-1)$	$SS_{error(b)}$	$\frac{SS_{error(b)}}{(N-a)(t-1)}$	
Total	$Nt-1$	SS_{total}		

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

The sources of the variation include treatment; Error (a); the effect of Time; the interaction between time and treatment; and Error (b). Error (a) is the effect of subjects within treatments and Error (b) is the individual error in the model. All these add up to the total.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23(IBM Statistics, Chicago, USA)and Microsoft office 2007.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

OBSERVATION AND RESULTS

TABLE 1 AND 2: AGE DISTRIBUTION AMONG PATIENTSPRESENTING WITH CIRRHOSIS OF LIVER

Age(yrs)	N	%
21-30	10	8.3
31-40	41	34.2
41-50	31	25.8
51-60	22	18.3
61-70	16	13.3
Total	120	100.0

Descriptive Statistics	Min	Max	Mean	SD
Age(yrs)	26	72	46.1	2.9

Figure 7 : Distribution of Cases according to Age

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

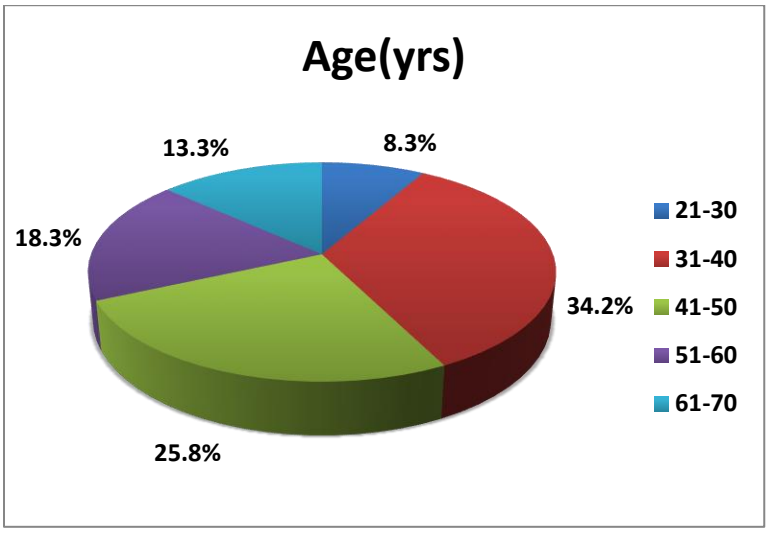


Table 3: Distribution of Cases according to Gender

Gender	N	%
Male	82	68.3
Female	38	31.7
Total	120	100.0

Figure 8: Distribution of Cases according to Gender

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

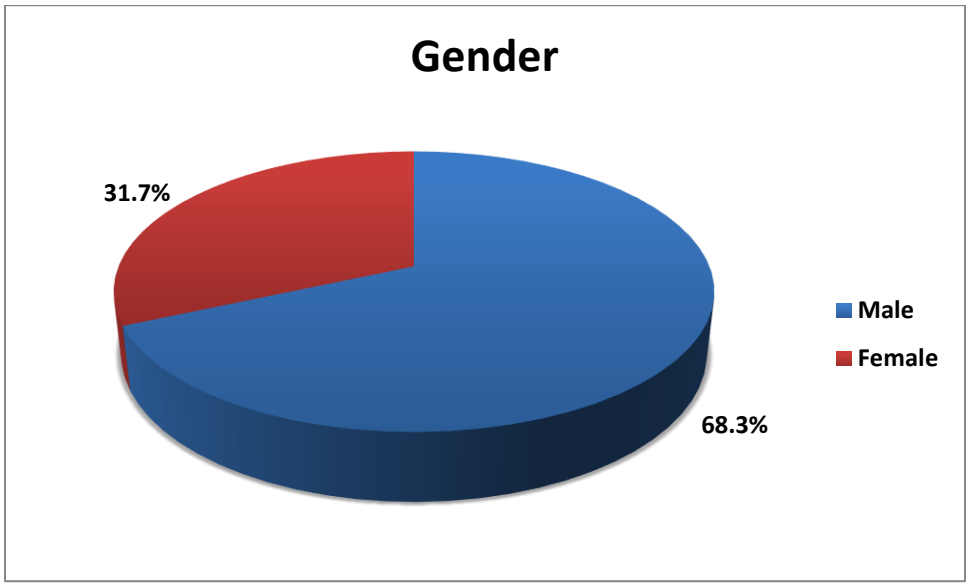


Table 4: Distribution of Cases according to Etiology

Etiology	**N**	**%**
Alcohol	52	43.3
Hepatitis B	25	20.8
Hepatitis C	11	9.2
Alcohol + Hepatitis B	6	5.0
Alcohol + Hepatitis C	8	6.7
Others	18	15.0

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Total	120	100.0

Figure 9: Distribution of Cases according to Etiology

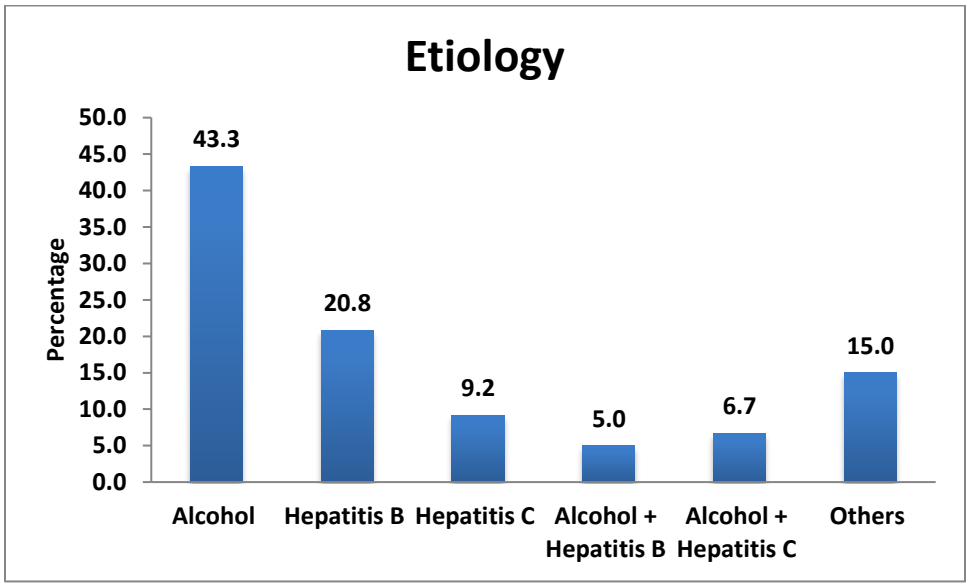


Table 5: Distribution of Cases according to Severity of cirrhosis

Severity of cirrhosis	**N**	**%**
Mild	45	37.5
Moderate	39	32.5
Severe	36	30.0
Total	120	100.0

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Figure 10: Distribution of Cases according to Severity of cirrhosis

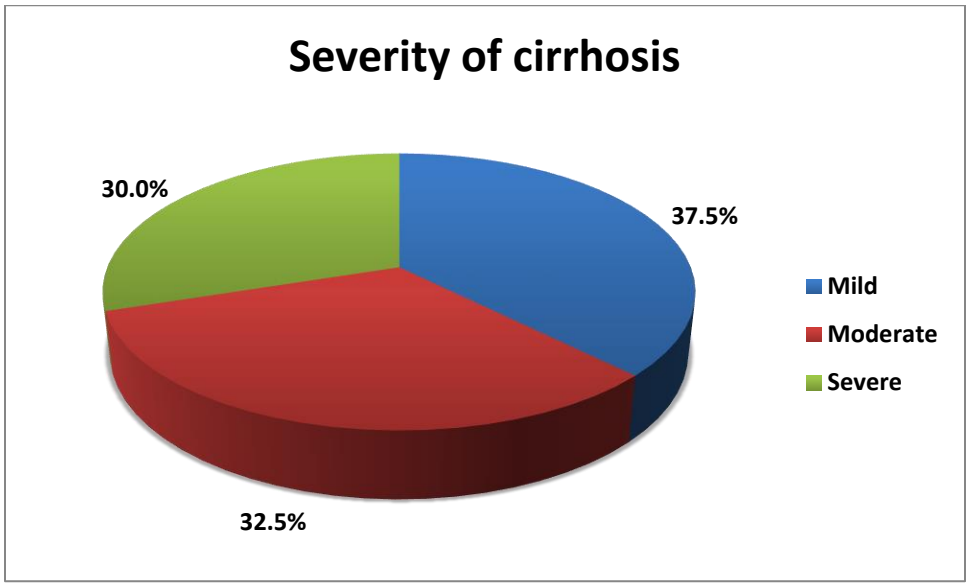


Table 6: Distribution of Cases according to Ascites

Ascites	**N**	**%**
No	10	8.3
Mild	46	38.3
Moderate	40	33.3
Severe	24	20.0
Total	120	100.0

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Figure 11: Distribution of Cases according to Ascites

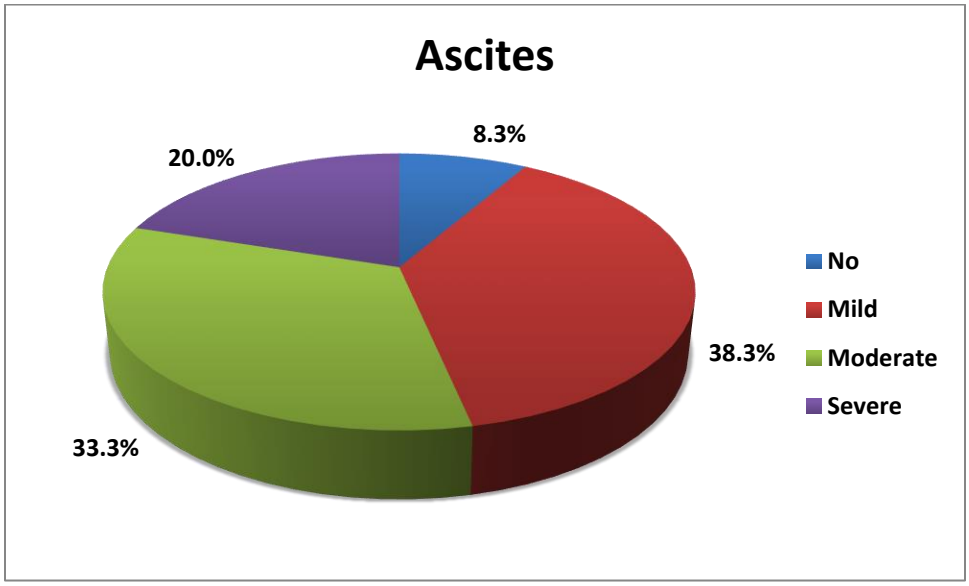


Table 7: Distribution of Cases according to Encephalopathy Grading

Encephalopathy Grading	N	%
Nil	20	16.7
Grade I	31	25.8
Grade II	44	36.7
Grade III	18	15.0

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Grade IV	7	5.8
Total	120	100.0

Figure 12: Distribution of Cases according to Encephalopathy Grading

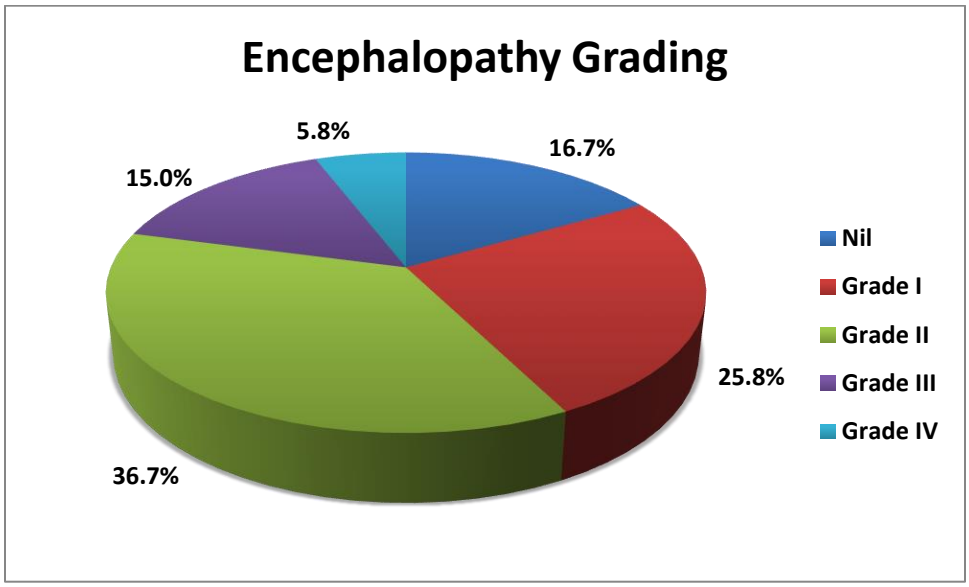


Table 8: Distribution of Cases according to Varices Grading

Varices Grading	**N**	**%**
Nil	21	17.5
Grade I	12	10.0
Grade II	31	25.8
Grade III	35	29.2

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Grade IV	21	17.5
Total	120	100.0

Figure 13: Distribution of Cases according to Varices Grading

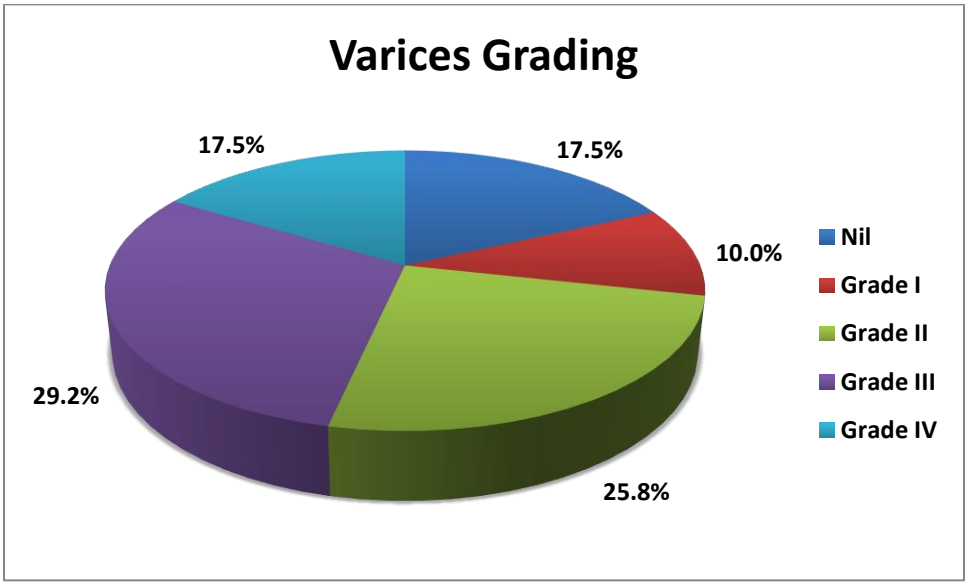


Table 9: Distribution of Cases according to Child–Pugh score

Child–Pugh score	**N**	**%**
A	47	39.2
B	36	30.0
C	37	30.8

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Total	120	100.0

Figure 14: Distribution of Cases according to Child–Pugh score

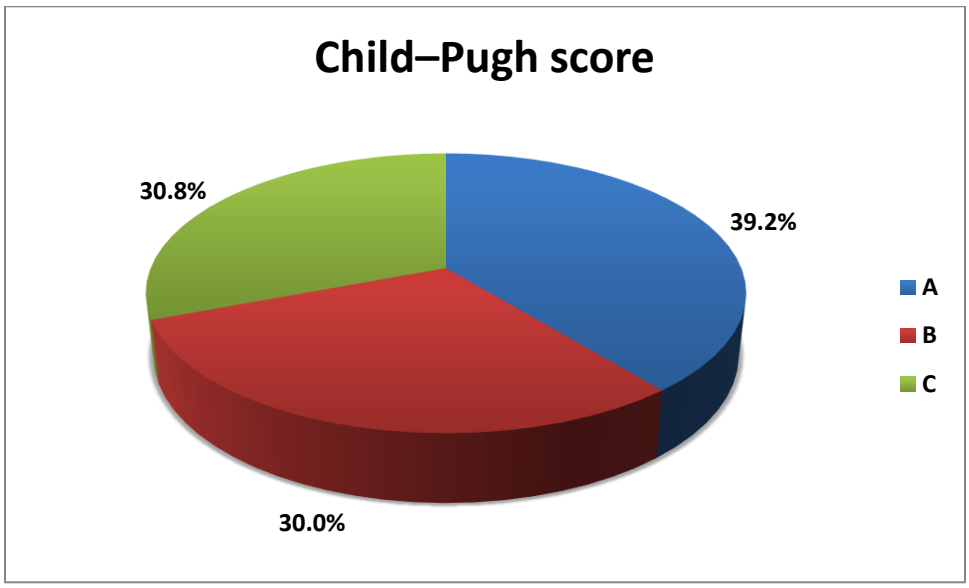


Table 10: Distribution of Age according to Severity of cirrhosis

Parameters	Severity of cirrhosis						p value
	Mild		Moderate		Severe		
	Mean	SD	Mean	SD	Mean	SD	

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Age(yrs)	48.2	6.9	45.3	2.3	44.9	1.9	0.784

Figure 15: Distribution of Age according to Severity of cirrhosis

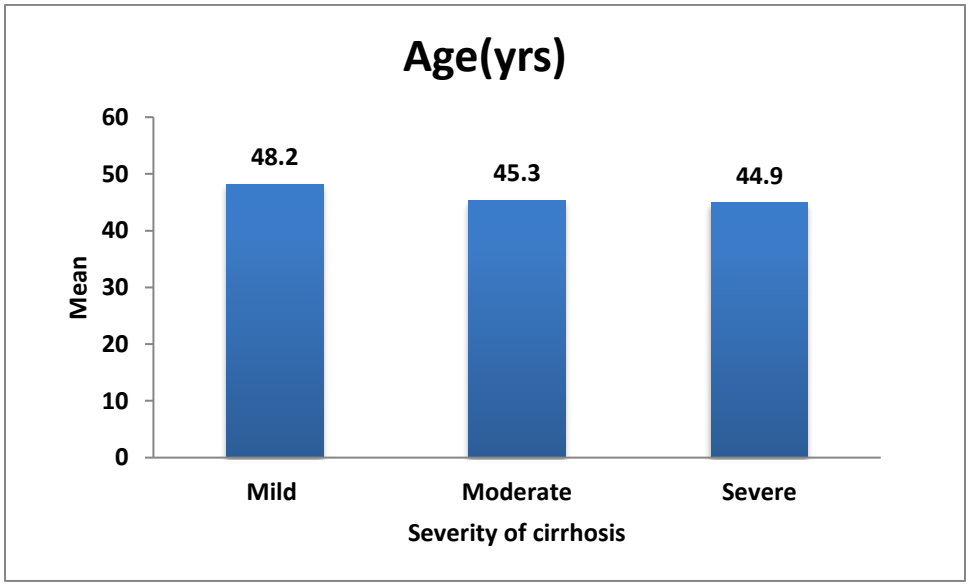


Table 11: Distribution of Sex according to Severity of cirrhosis

Sex	**Severity of cirrhosis**			**p value**
	Mild	**Moderate**	**Severe**	

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

	N	%	N	%	N	%	
Male	28	62.2%	26	66.7%	28	77.8%	0.192
Female	17	37.8%	13	33.3%	8	22.2%	
Total	45	100.0%	39	100.0%	36	100.0%	

Figure 16: Distribution of Sex according to Severity of cirrhosis

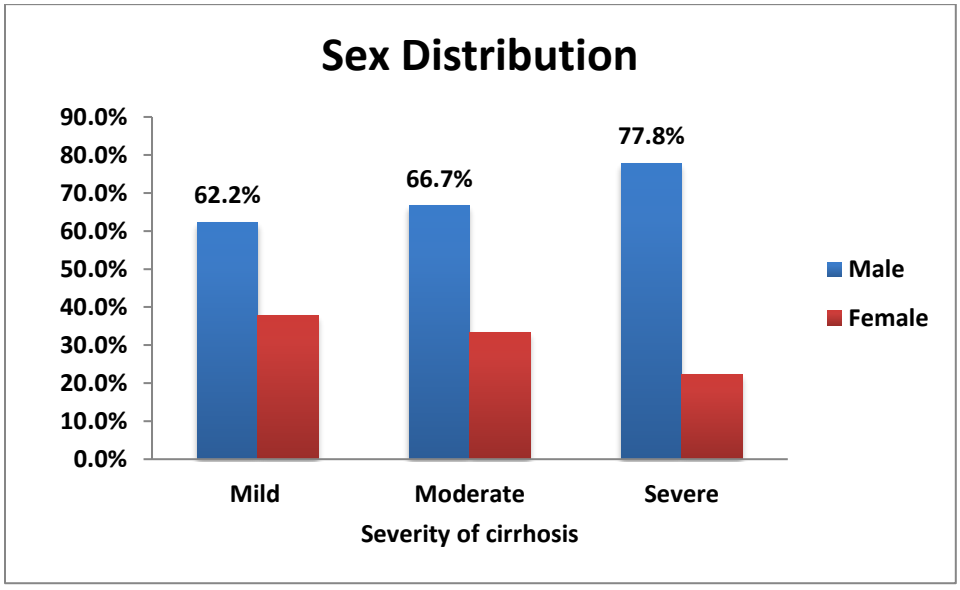


Table 12: Mean Sr Prolactin level according to Severity of cirrhosis

Parameters	Severity of cirrhosis	p value

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

	Mild		Moderate		Severe		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Sr Prolactin level	12.9	5.6	23.6	6.3	28.7	8.6	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 17: Mean Sr Prolactin level according to Severity of cirrhosis

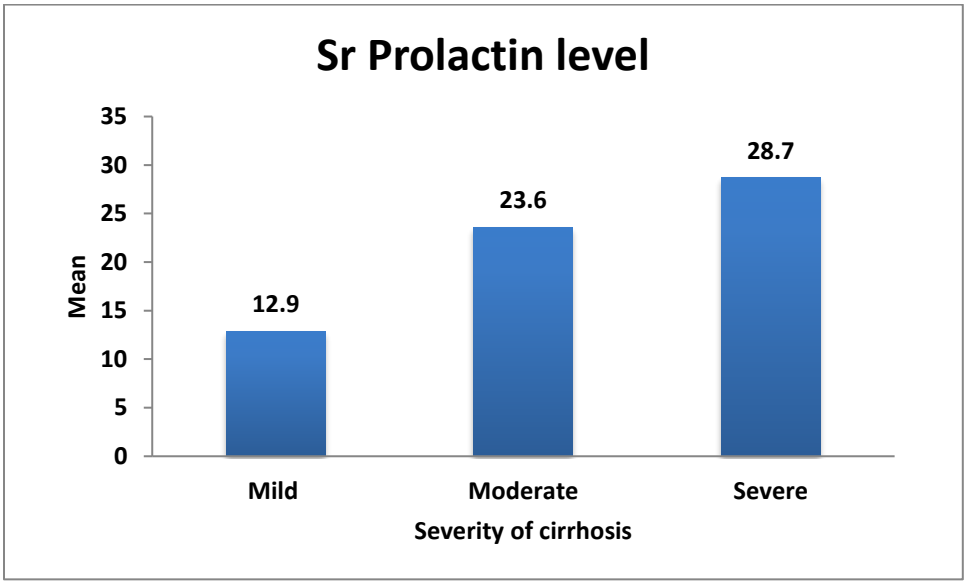


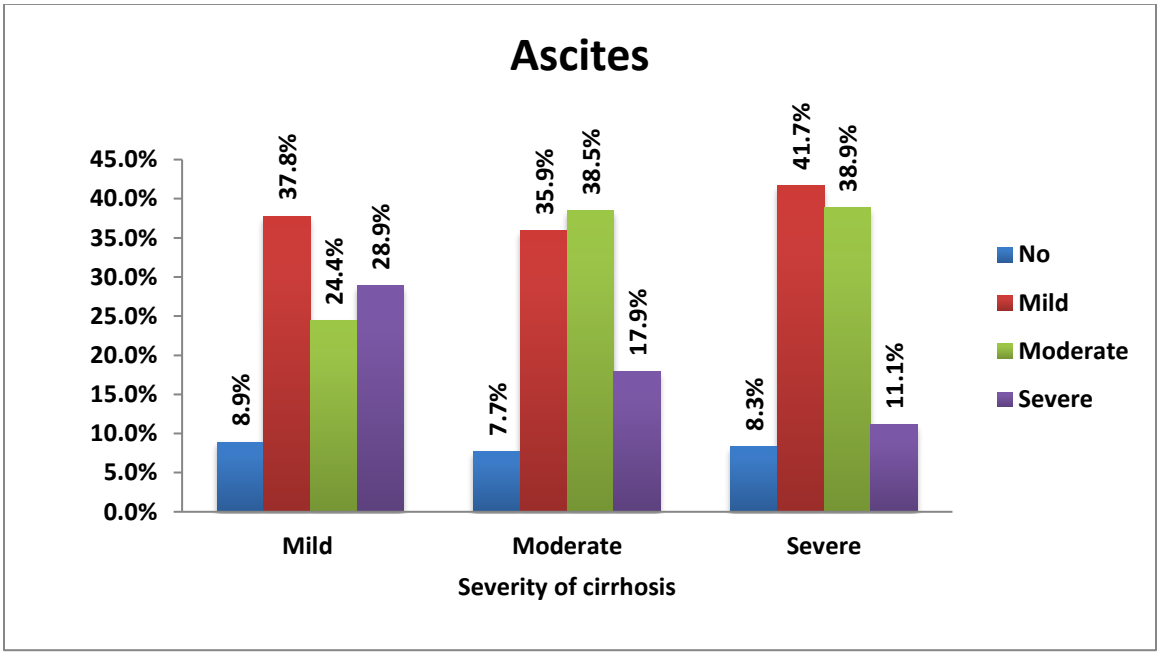
Table 13: Distribution of Ascites according to Severity of cirrhosis

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Ascites	Severity of cirrhosis						p value
	Mild		Moderate		Severe		
	N	%	N	%	N	%	
No	4	8.9%	3	7.7%	3	8.3%	0.412
Mild	17	37.8%	14	35.9%	15	41.7%	
Moderate	11	24.4%	15	38.5%	14	38.9%	
Severe	13	28.9%	7	17.9%	4	11.1%	
Total	45	100.0%	39	100.0%	36	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Figure 18: Distribution of Ascites according to Severity of cirrhosis



ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

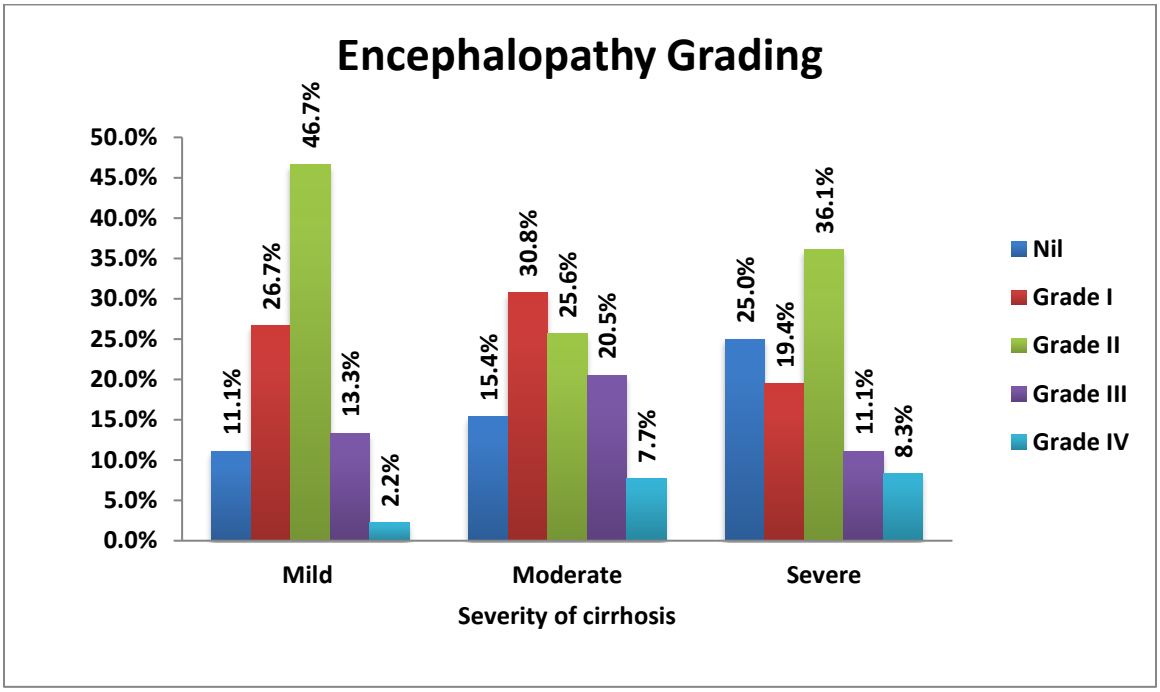
Table 14: Distribution of Encephalopathy Grading according to Severity of cirrhosis

Encephalopathy Grading	Severity of cirrhosis						p value
	Mild		Moderate		Severe		
	N	%	N	%	N	%	
Nil	5	11.1%	6	15.4%	9	25.0%	0.041*
Grade I	12	26.7%	12	30.8%	7	19.4%	
Grade II	21	46.7%	10	25.6%	13	36.1%	
Grade III	6	13.3%	8	20.5%	4	11.1%	
Grade IV	1	2.2%	3	7.7%	3	8.3%	
Total	45	100.0%	39	100.0%	36	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Figure 19:Distribution of Encephalopathy Grading according to Severity of cirrhosis



ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

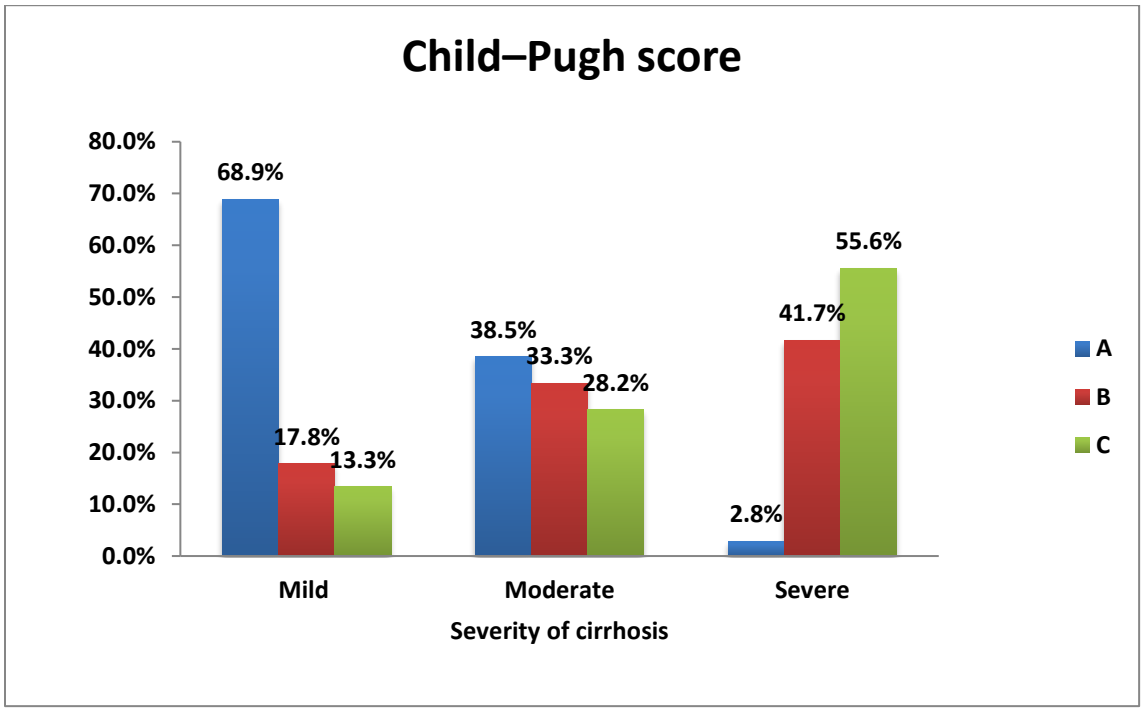
Table 15: Distribution of Child–Pugh score according to Severity of cirrhosis

Child–Pugh score	Severity of cirrhosis						p value
	Mild		Moderate		Severe		
	N	%	N	%	N	%	
A	31	68.9%	15	38.5%	1	2.8%	<0.001*
B	8	17.8%	13	33.3%	15	41.7%	
C	6	13.3%	11	28.2%	20	55.6%	
Total	45	100.0%	39	100.0%	36	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

Figure 20: Distribution of Child–Pugh score according to Severity of cirrhosis

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024



DISCUSSION

Prolactin level in hepatic dysfunction is always controversial.

Among the neurotransmitter alteration, the principal one to bedocumented was dopamine. Dopamine is limited by the fact that it cannot bemeasured in any of the body fluids or brain. Since dopamine exerts negativecontrol over prolactin, few studies from the west have shown prolactin to be aprognostic marker[1,2] .

Elevation of prolactin is attributed mainly to the fall in dopamine levelsin thetuberoinfundibular tract. Hormonal disturbance in cirrhosis has been evaluatedby few researchers, and the studies

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

have established lower T3 and cortisollevels with raised prolactin in the serum[3] . Decompensated liver functionleads to an alteration in the type of amino acids entering the central nervoussystem. Circulating concentrations of aromatic amino acids have been found toincrease leading to an increase in the synthesis of false neurotransmitters suchas octopamine and phenylethanolamine[8] .

In our study population of 120 cirrhotic patients of various etiologies,Alcohol tops the list in males with most of them are in the age group of 31 to40 years. , while in females viral etiologies play an important role.

On comparing the Prolactin level, with the various complications ofchronic liver disease like Ascites , oesophageal varices and hepaticencephalopathy we are able to find a significant correlation with the severity ofthe disease.

The mean prolactin value found to be 37.3ng/ml in patients with massive
ascites ; and in patients with grade 3 or 4 varices it is found to be around 35.80 ng/ml and 37.3 ng/ml respectively. Thus it has better correlation with severity ofdisease in our study population. A similar correlation of mortality to serumprolactin levels was observed by McClain *et* al[10]. and Sharma *et al*[11]. witha higher risk of mortality with serum prolactin values of >50 ng/ml.

Limitations:

1. Sample size was a small and single-centre study.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 02, 2024

Conclusion: Prolactin level rises in hepatic cirrhosis ,with the loss of normalcircadian rhythm. Since the dopamine level cannot be directly measured inthe body fluids , we used prolactin to measure the severity of the liverdisease, as it is normally kept under the check of dopamine .Prolactin levelsignificantly correlates with severity of the liver disease and predicting therisk of complications and helpful in preventing them. The rise in prolactinlevel also had a synonymous relationship with the Child Pugh Scoringsystem thus validating the use of Prolactin as a prognostic marker in hepaticcirrhosis.

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