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Assessment Of Adrenal Insufficiency In Chronic Liver Disease Patients Via Measurment Of Serum Cortisol And Serum Acth Level: An Observational Cross Sectional Study

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Abstract:
Background: *Activation of HPA axis represent one of several important response to severe stress or critical illness. Cortisol, the main glucocorticoid hormone of adrenal cortex in response to activation of HPA Axis has important role in many of the physiological functions necessary during critical illness. But in cirrhosis there is suppression of HPA axis due to low level of serum cholesterol, HDL & LDL which in turn worsen the outcome due to relative deficiency of cortisol. Measurement of serum cortisol and ACTH to assess AI in CLD is widely acceptable, noninvasive methodology and might be helpful to make opinion about further appropriate management in decompensated patients of CLD with AI.*
Aims and objectives:
The aim is to observe serum cortisol and ACTH level and to see prevalence of AI in chronic liver disease patients along with to understand pathophysiology of AI in CLD if feasible.
Materials and methods:
It is a hospital based observational cross-sectional study involving 50 patients carried out in the department of General Medicine of Medical College and Hospital, Kolkata from August 2020 to October 2021. The study population was all patient of CLD with variable etiologies attending inpatient and outpatient department of General Medicine and Gastromedicine, Medical College, Kolkata. Patients were selected on the basis of certain inclusion and exclusion criteria. They were evaluated based on clinical history, physical examination findings and certain investigation parameters such as complete hemogram, liver function test, coagulation parameters and serum cortisol and ACTH level and also USG whole abdomen with SPD. The data collected were analysed with a suitable statistical analysis software package.
Results:
In our study we have observed that majority of the patient were males. Overall the disease is more common in males at the age group of 36-50 years. In our study high percentage of patients were decompensated according to Child Pugh Score and among decompensated which includes class B and class C, Adrenal Insufficiency is present in 40% and 80% respectively, suggesting that most decompensated cirrhosis patients are having more chance of Adrenal Insufficiency.
Conclusion: *Chronic liver Disease with cirrhosis is a major cause of mortality World Wide, since cirrhosis and severe illness including sepsis has many hemodynamic abnormalities such as hyper dynamic circulatory failure, decrease peripheral vascular resistance, increase cardiac output, decrease responsiveness to vasopressor, increased level of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha) and it has been consequently reported that AI is common in critically ill cirrhotic patients.*

In patients having chronic liver disease due to any etiology who comes under decompensated disease according to child pugh score i.e. class B and class C adrenal insufficiency is present in about 40% to 80% respectively. So, in such patients with decompensated chronic liver disease we should looked for signs of adrenal insufficiency and management should be done accordingly.
Although management for such condition is not completely estabilized yet, hence there is a need for further longitudinal, multicentric studies in these subcontinent to support our findings.

Key words:
Chronic Liver Disease, Adrenal Insufficiency, Decompensated disease, HPA axis, serum cortisol, serum ACTH

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I. Introduction:

Chronic liver disease (CLD) is a term used to describe a disease process of theliverthat involves a process of progressive destruction and regeneration of the liverparenchymaleading tofibrosisand cirrhosis. The most common causes of chronic liver disease in general order of frequency world-wide are chronic hepatitis

C, alcoholic liver disease, Nonalcoholic steatohepatitis (NASH), chronic hepatitis B, autoimmune hepatitis, Sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease [1]. The exact prevalence of cirrhosis worldwide is unknown. Cirrhosis prevalence was estimated at 0.15% in the USA[2]. This may underestimate the high prevalence of undiagnosed cirrhosis in both NASH and hepatitis C. Similar numbers have been reported from Europe and numbers are even higher in most Asian and African countries where chronic viral hepatitis B or C are frequent [3]. Chronic liver disease and cirrhosis result in about 35,000 deaths each year in the United States. Cirrhosis is the ninth leading cause of death in the United States and is responsible for 1.2% of all US deaths [4].CLD can give rise to complications due to portal hypertension, synthetic dysfunction, pulmonary/renal/neurological involvement or due to development of hepatocellular carcinoma. Among these, hypoalbuminemia and coagulopathy are sensitive markers of synthetic dysfunction [1].

II. Adrenal Insufficiency

Cirrhosis has been linked to abnormalities in the endocrine system, including adrenal insufficiency, abnormal sex hormone metabolism, thyroid disease, and osteoporosis[5].

The recognition that adrenal insufficiency worsens outcomes in sepsis, a syndrome characterized by physiologic abnormalities also seen in liver failure, has led to the evaluation of adrenal dysfunction in patients with liver disease. Multiple studies have demonstrated the presence of relative adrenal insufficiency in critically ill patients with both compensated and decompensated cirrhosis, with reported frequencies of 10% to 92% [7-12].The wide range in frequency is a reflection of the absence of a standardized test to diagnose the entity in the cirrhotic population [13]. The presence of relative adrenal insufficiency has been associated with greater hemodynamic instability and increased mortality [9-14]. In 2 studies, glucocorticoid therapy improved survival, but in 2 others such therapy was associated with increased mortality secondary to GI bleeding and nosocomial and opportunistic infections [8,10,15]. Two proposed pathophysiologic mechanisms for relative adrenal insufficiency include (1) impaired adrenal cortisol synthesis from cholesterol during stress, secondary to inadequate hepatic cholesterol production as a result of liver disease, and (2) increased circulating levels of endotoxins and pro inflammatory cytokines [6,16,17]. No standardized diagnostic criteria have been developed to define relative adrenal insufficiency, and whether a subset of critically ill patients with liver disease may benefit from glucocorticoid treatment remains an area of active investigation.

Liver cirrhosis is a major cause of mortality World Wide [18,44,45,], since cirrhosis and severe illness including sepsis has many hemodynamic abnormalities such as hyper dynamic circulatory failure, decrease peripheral vascular resistance, increase cardiac output, decrease responsiveness to vasopressor, increased level of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha) and it has been consequently reported that AI is common in critically ill cirrhotic patients [19,46,47].

In a healthy, unstressed person, cortisol is secreted according to a diurnal pattern under the influence of corticotropin released from the pituitary gland. Corticotropin secretion, in turn, is under the influence of hypothalamus. These effects are due to increased production of corticotropin -releasing hormone and corticotropin and a reduction in negative feedback from cortisol [5,48,49,50]. Stimulation of the hypothalamic–pituitary–adrenal axis in this context is caused by elevated levels of circulating cytokines, as occur in cirrhosis. Adrenal responsiveness to exogenous corticotropin is normally maintained during acute illness. In addition, during critical illness, levels of corticosteroid-binding globulin decrease rapidly leading to increased levels of circulating free corticosteroids. These changes in cortisol action appear to be important adaptive mechanisms regulating the inflammatory response [20,51,52,53].

During severe illness, many factors can impair the normal corticosteroid response [54]. These factors include preexisting conditions affecting the hypothalamic–pituitary–adrenal axis, but corticosteroid

insufficiency can also occur during the course of acute illness. Adrenal cortisol synthesis can be impaired by multiple mechanisms, including that in cirrhosis patients [54,55,56].

AI may also be presented in stable cirrhosis patients without sepsis or encephalopathy [19,57,58].

The term Hepatoadrenal syndrome define AI in patients with advanced liver disease with sepsis or other complications and suggested it could be a feature of liver disease with a different pathogenesis of septic shock [19,21,22,23].

The prevalence of AI in cirrhosis patients varies widely according to stage of liver disease (compensated and decompensated), with or without sepsis. [59,60]

III. Aims and objectives:

The aim is to observe serum cortisol and ACTH level and to see prevalence of AI in chronic liver disease patients along with to understand pathophysiology of AI in CLD if feasible.

IV. Materials and methods:

It is a hospital based observational cross-sectional study involving 50 patients carried out in the department of General Medicine of Medical College and Hospital, Kolkata from August 2020 to October 2021. The study population was all patient of CLD with variable etiologies attending inpatient and outpatient department of General Medicine and Gastromedicine, Medical College, Kolkata. Patients were selected on the basis of certain inclusion and exclusion criteria given below after permission from departmental ethical committee(IEC) and taking informed consent, data collection was done and collected data were noted in a proforma. They were evaluated based on clinical history, physical examination findings and certain investigation parameters such as complete hemogram, liver function test, coagulation parameters and serum cortisol and ACTH level and also USG whole abdomen with SPD. The data collected were analysed with a suitable statistical analysis software package.

INCLUSION CRITERIA:

1. Individuals with CLD of both gender, aged > 12 years, as diagnosed by CPS criteria, irrespective of therapy status.
2. Patients who gave multilingual informed consent.

EXCLUSION CRITERIA:

1. Non consenting adults
2. Patient with history of steroid treatment.

The patients were studied on the following variables-

1. Clinical sign and symptoms.
2. Blood for CBC, LFT, PT-INR
3. USG Whole Abdomen with SPD,
4. Serum cortisol level
5. Serum ACTH level.

Data analysis was performed with a commercially available statistical analysis software package (SPSS 16.0for windows; SPSS; Chicago, IL, USA) with Microsoft Office Word and Excel to generate graphs and tables.

V. RESULTS AND ANALYSIS:

All patients, included in our study, were selected according to the inclusion and exclusion criteria mentioned above. After taking clearance of Institutional Ethical committee and consent from the patient, the study was conducted. Necessary blood samples were collected. All laboratory parameters and demographic variables were entered in a pre-designed proforma. Data were compiled using Microsoft Office Excel software. Tables and diagrams showing demographic variables were made by using Microsoft Office Excel and Word software.

Table 1 : shows the distribution of Age of CLD patients

	Age	Frequency	Percent
	20- 35 Years	9	18.0
	36- 50 years	24	48.0

	> 50 years	17	34.0
	Total	50	100.0
	Mean Age	46.18	
	SD	10.123	

From Table 1 it is observed that most of the CLD patients are in the age group 36-50 years (48.0%) followed by greater than 50 years (34.0%) . The same distribution has been also shown in the following graph .

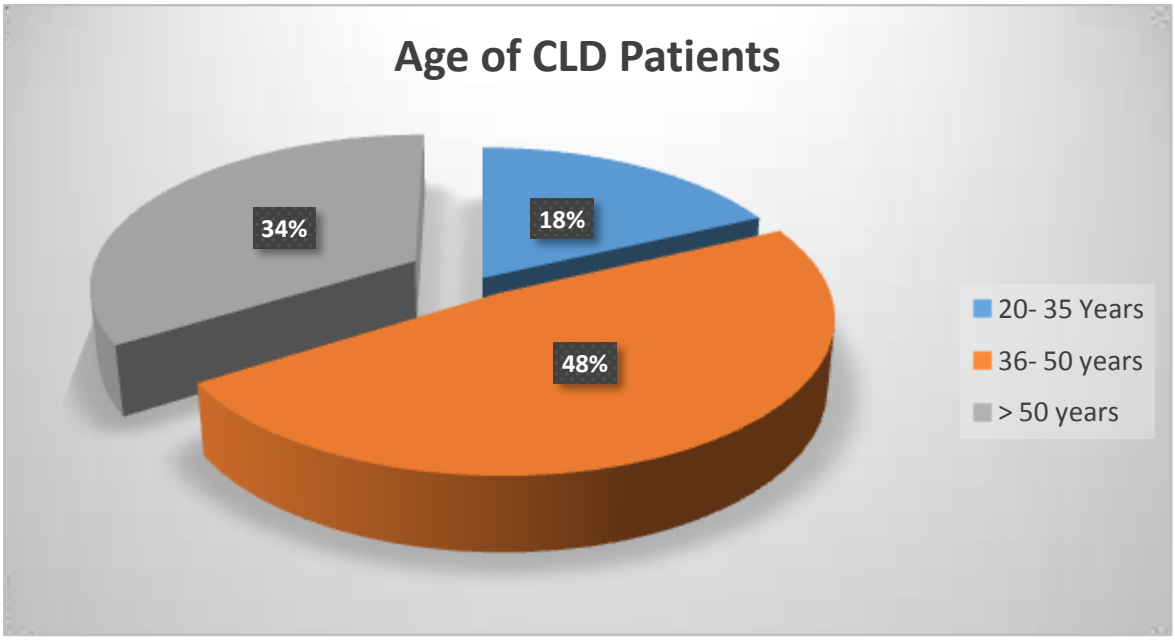

Fig 1 : Pie diagram shows the distribution of Age of CLD patients

Table 2 : shows the distribution of Sex of CLD patients

SEX		Frequency	Percent
Valid	Female	12	24.0
	Male	38	76.0
	Total	50	100.0

From Table 2 it is observed that most of the CLD patients are Male (76.0%) followed by Female (24.0%) . The same distribution has been also shown in the following graph .

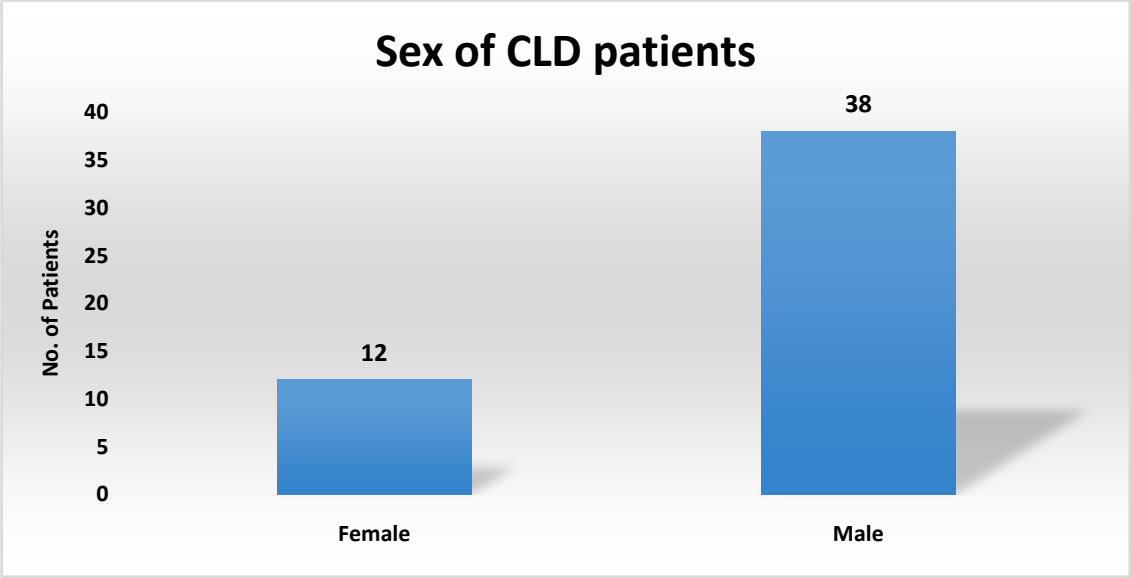

Fig 2 : Bar diagram shows the distribution of Sex of CLD patients

Table 3 : shows the distribution of Etiology of CLD patients

	ETIOLOGY	Frequency	Percent
	ALCOHOL	21	42.0
	HEPATITIS B	7	14.0
	CRYPTOGENIC	22	44.0
	Total	50	100.0

From Table 3 it is observed that Etiology of the most of the CLD patients are CRYPTOGENIC (44.0%) followed by ALCOHOL (42.0%) and HEPATITIS B is only 14.0% and the same distribution has been also shown in the following graph .

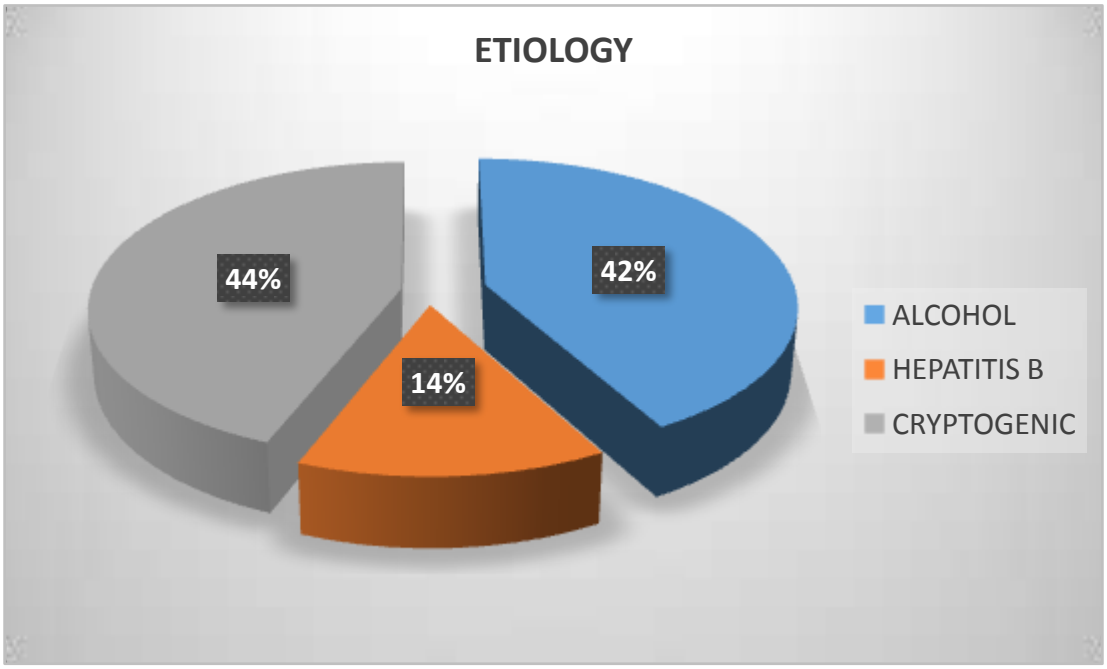

Fig 3 : Pie diagram shows the distribution of ETIOLOGY of CLD patients

Table 4 : shows the distribution of COMPENSATED AND DECOMPENSATED of CLD patients

		Frequency	Percent
	COMPENSATED	13	26.0
	DECOMPENSATED	37	74.0
	Total	50	100.0

From Table 4 it is observed that no. of patients according to cps score , most of the CLD patients are DECOMPENSATED (74.0%) followed by COMPENSATED (26.0%) and the same distribution has been also shown in the following graph .

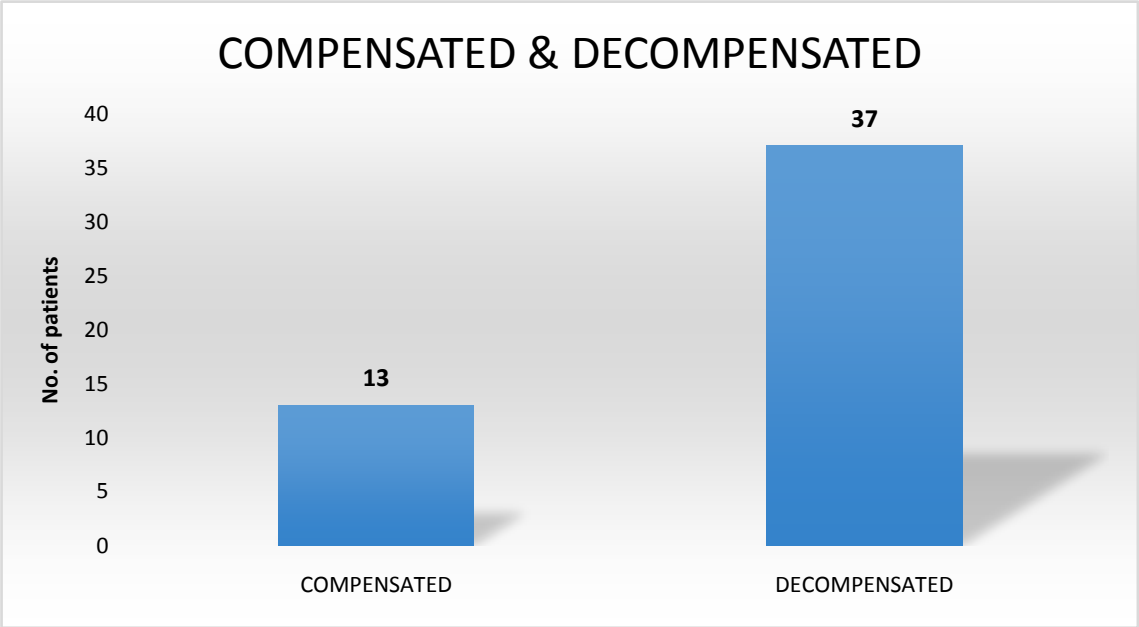

Fig 4 : Bar diagram shows the distribution of COMPENSATED AND DECOMPENSATED of CLD patients

Table 5 : shows the distribution of Age & SEX with COMPENSATED AND DECOMPENSATED of CLD patients

SEX				=1 AND =2 COMPENSATED	=1 AND =2 DECOMPENSATED	Total
Female	AGE	20-35 Years	Count	0	3	3
			% of Total	0.0%	25.0%	25.0%
		36-50 Years	Count	0	3	3
			% of Total	0.0%	25.0%	25.0%
		>50 Years	Count	2	4	6
			% of Total	16.7%	33.3%	50.0%
	Total		Count	2	10	12
			% of Total	16.7%	83.3%	100.0%
Male	AGE	20-35 Years	Count	0	6	6
			% of Total	0.0%	15.8%	15.8%
		36-50 Years	Count	7	14	21
			% of Total	18.4%	36.8%	55.3%
		>50 Years	Count	4	7	11
			% of Total	10.5%	18.4%	28.9%
	Total		Count	11	27	38
			% of Total	28.9%	71.1%	100.0%
Total	AGE	20-35 Years	Count	0	9	9
			% of Total	0.0%	18.0%	18.0%
		36-50 Years	Count	7	17	24
			% of Total	14.0%	34.0%	48.0%
		>50 Years	Count	6	11	17
			% of Total	12.0%	22.0%	34.0%
	Total		Count	13	37	50
			% of Total	26.0%	74.0%	100.0%

From Table 5 it is observed that For Female , total compensated is 16.7 % and decompensated is 33.3% whereas for male , total compensated is 28.9 % and decompensated is71.1 % according to age category .

Table 6 : shows the distribution of cps of CLD patients

distribution of **cps**		Frequency	Percent
	A	13	26.0
	B	27	54.0
	C	10	20.0
	Total	50	100.0

From Table 6 it is observed that no. of patients according to cps score , the distribution of cps score are class A 26% , B is 54% and C is 20% and the same distribution has been also shown in the following graph .

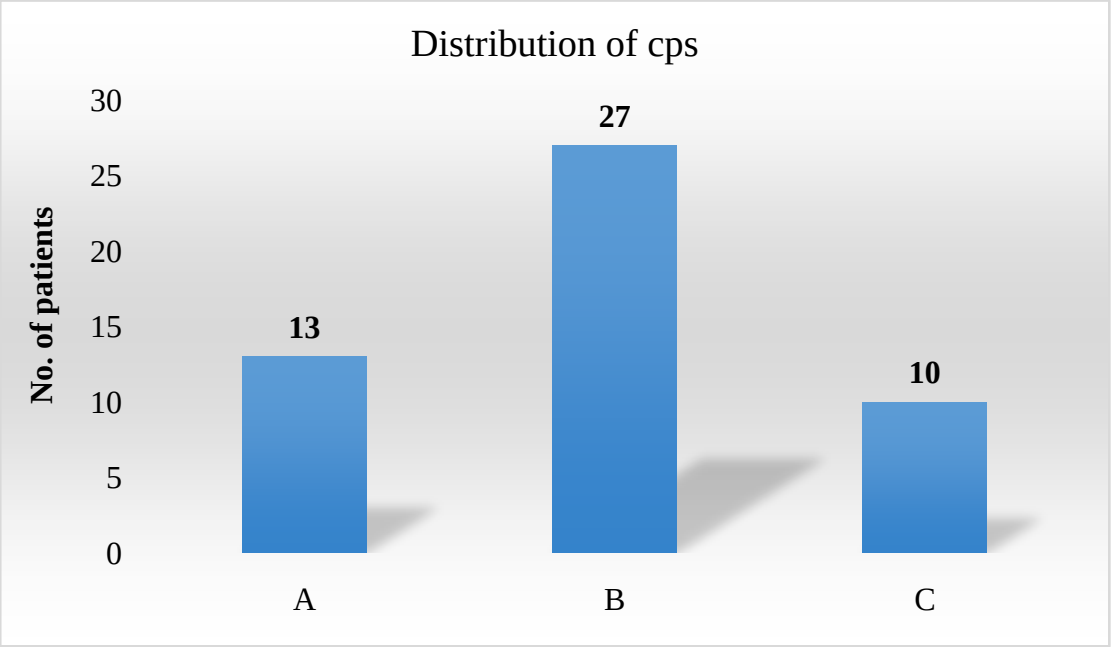

Fig 5 : Bar diagram shows the distribution of distribution of cps of CLD patient

Table 7 : shows the distribution of ENCP of CLD patients

ENCP		Frequency	Percent
Valid	NONE	40	80.0
	MINIMAL	7	14.0
	ADVANCED	3	6.0
	Total	50	100.0

From table 7 it is observed that most of the patients are not having ENCEPHALOPATHY i.e. NONE is 80% , MINIMAL is 14% and ADVANCED is only 6% . The same has been shown in the following graph .

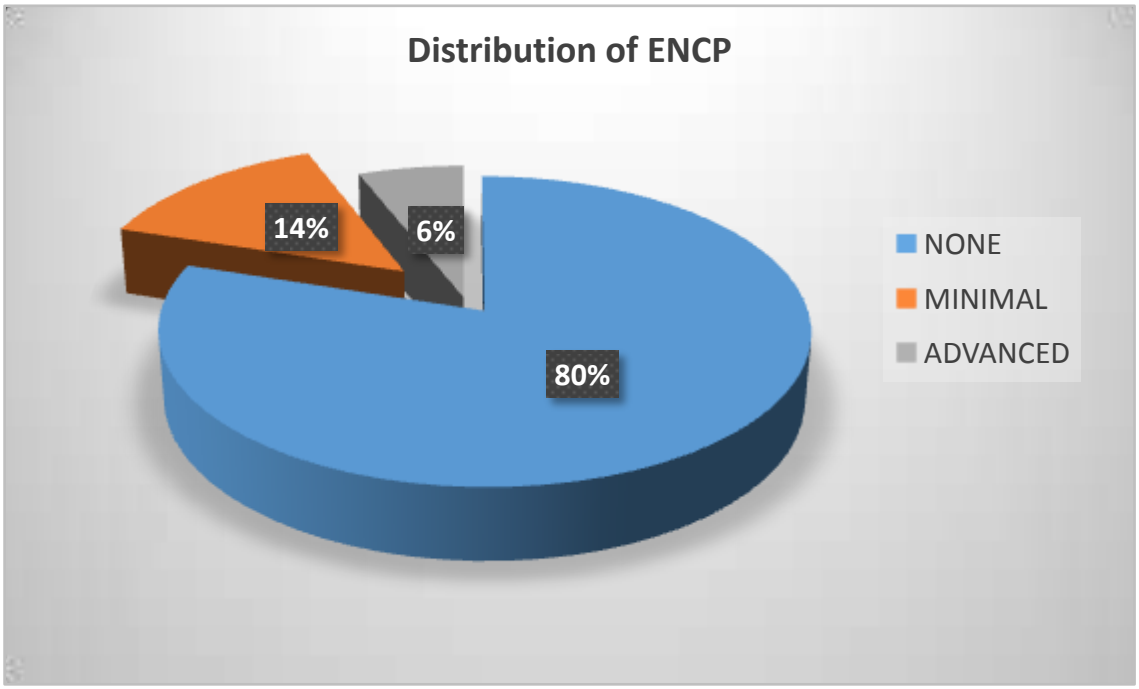

Fig 6 : Pie diagram shows the distribution of distribution of ENCP of CLD patient

Table 8 : shows the Albumin range of CLD patients

Albumin range		Frequency	Percent
	< 2.5	12	24.0
	> 2.5	38	76.0
	Total	50	100.0

From table 8 it is observed that most of the patients Albumin range greater than 2.5 is 76% followed by less than 2.5 is only 24% . The same has been shown in the following graph .

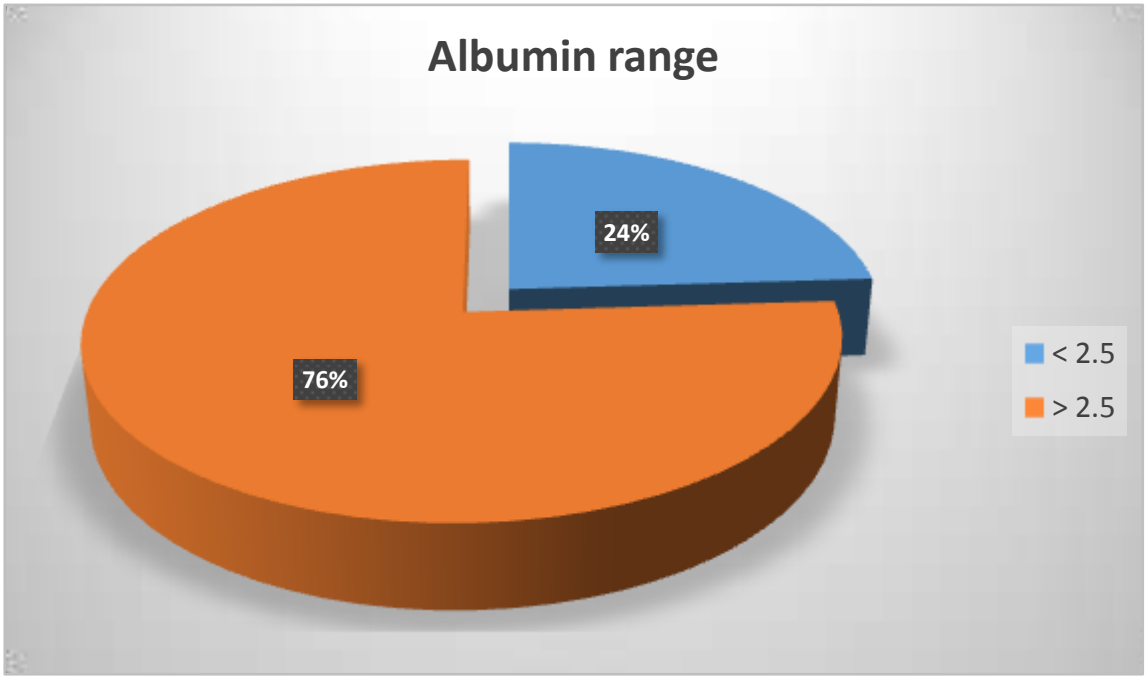

Fig 7 : Pie diagram shows the distribution of distribution of Albumin range of CLD patient

Table 9 : shows the Albumin with relate to Cortisol of CLD patients

ALB with CORTISOL		Frequency	Percent
	AI	22	44.0
	No AI	28	56.0
	Total	50	100.0

ALB	CORTISOL	Patient no.	AI/NO AI
<2.5	<10	8	AI
	>10	4	NO AI
>2.5	<15	14	AI
	>15	24	NO AI

From table 9 it is observed that most of the patients Albumin with relate to cortisol having no AI 56% whereas AI is 44% . The same has been shown in the following graph . From lower table it is observed that patient with Albumin < 2.5 mg/dl and serum cortisol <10 having AI i.e. 8 and serum albumin > 2.5 but serum cortisol <15 i.e. 14 patients having AI. Rest of 28 patients do not having AI.

ACTH	CORTISOL	Patient no.	AI/NO AI
<46	<10	19	AI
	>10	1	NO AI
>46	<15	3	AI
	>15	27	NO AI

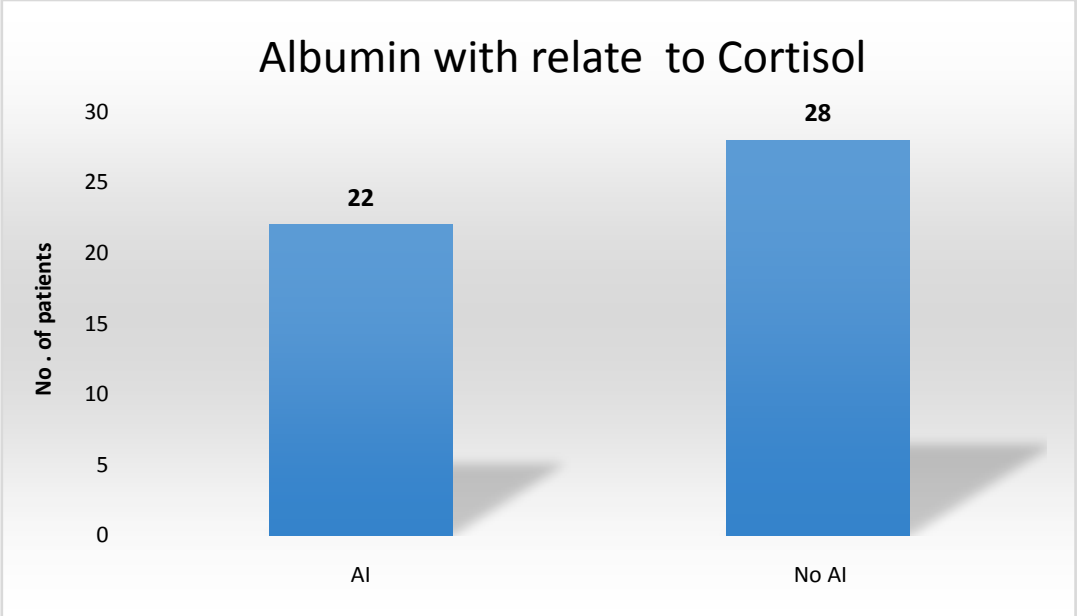

Fig 8 : Bar diagram shows the distribution of distribution of Albuminwith relate to cortisol of CLD patient

Table 10 : shows the distribution of ACTH with relate to Cortisol of CLD patients

ACTH_Cortisal,		Frequency	Percent
	AI	22	44.0
	No AI	28	56.0
	Total	50	100.0

From table 10 it is observed that most of the patients ACTH with relate to cortisol having no AI 56% whereas AI is 44% . From the lower table it has been concluded that patients with Acth level of < 46 with cortisol <10 and ACTH >46 but cortisol < 15 comes under AI i.e. 22 patients . The same has been shown in the following graph .

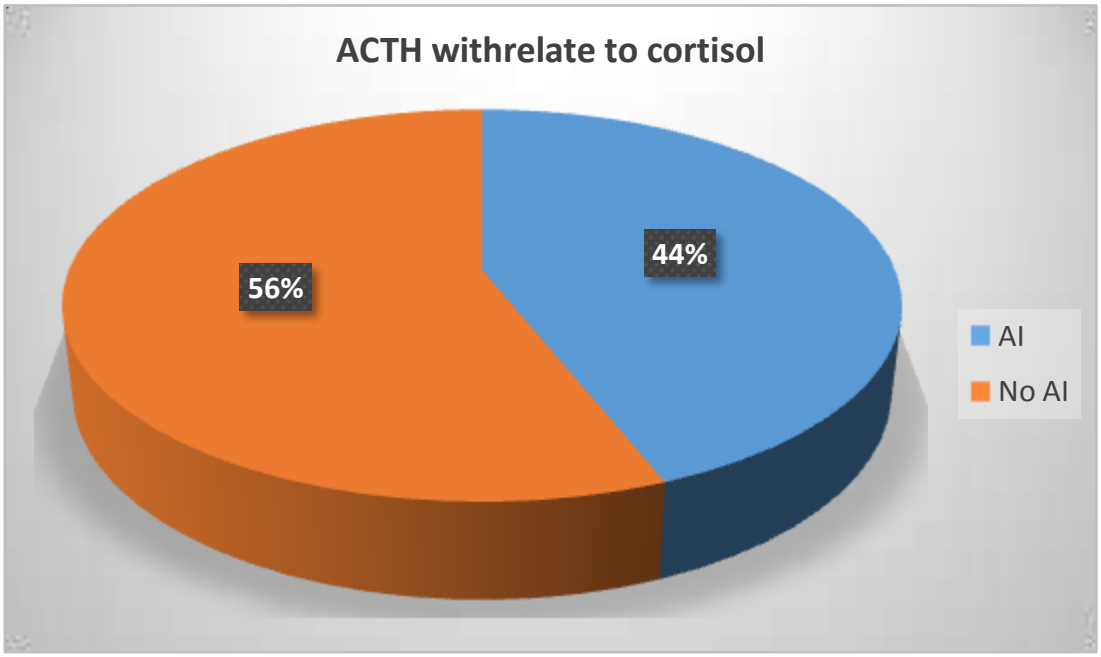

Fig 9 : Pie diagram shows the distribution of distribution of ACTH relate to cortisol of CLD patient

Table 11 : shows the distribution of AI according to cps in total of CLD patients

Distribution of cps			AI	No AI	Total
	A	Count	3	10	13
		% of Total	6.0%	20.0%	26.0%
	B	Count	11	16	27
		% of Total	22.0%	32.0%	54.0%
	C	Count	8	2	10
		% of Total	16.0%	4.0%	20.0%
Total		Count	22	28	50
		% of Total	44.0%	56.0%	100.0%

From table 11 it is observed that the distribution of AI according to cps score in total , AI is 44% and No AI is 56% .

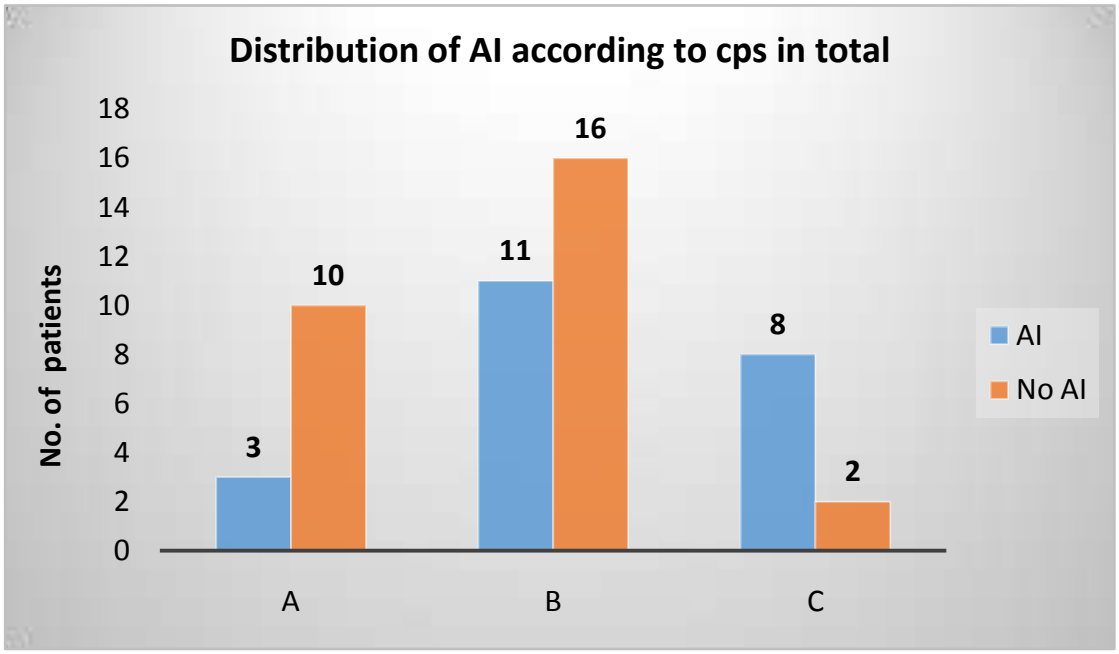

Fig 10 : Multiple Bar diagram shows the distribution of Distribution of AI according to cps in total of CLD patient .

Table 12 : shows the distribution of AI according to cps (Severity) of CLD patients

Distribution of cps	AI	Total	Percentage (AI)
A	3	13	23%
B	11	27	40%
C	8	10	80%
Total	22	50	44%

From table 12 it is observed that the distribution of AI according to cps score in class A is 3 out of 13, in class B AI is 11 out of 27 and in class C AI is 8 out of 10 which shows percentage distribution of 23% in class A, 40% in class B and 80 % in class C.

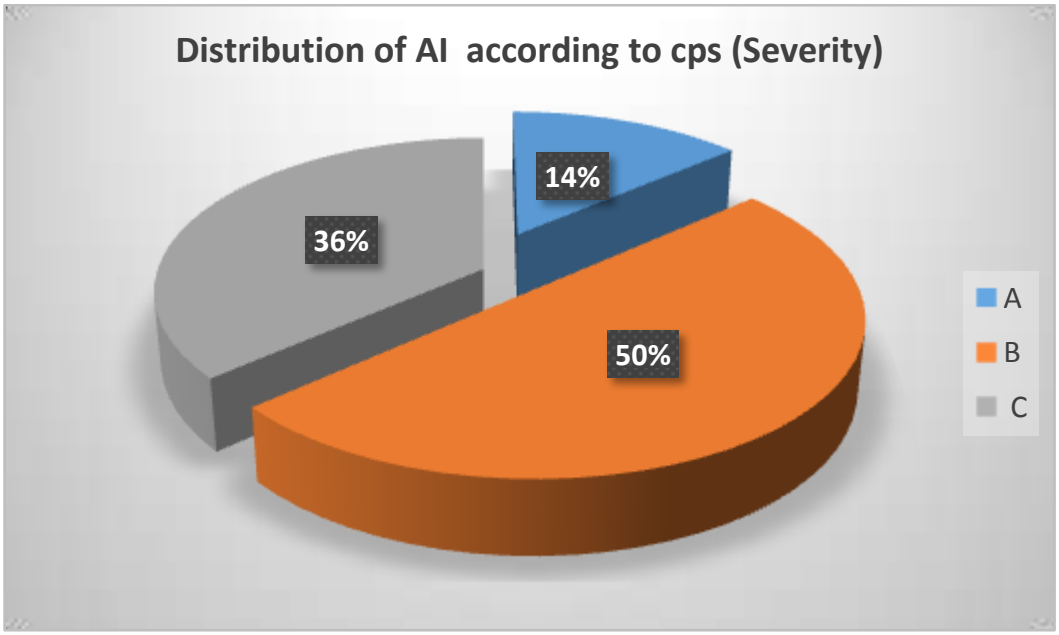

Fig 11 : Pie diagram shows the distribution of distribution of AI according to cps of CLD patient

Table 13 : shows the correlation of CPS (A/B/C) with Sr. cortisol of CLD patients

Descriptive Statistics				
	Mean	Std. Deviation	Correlation coefficient (r)	P-value
sr. CORTISOL <15mcg/dl	18.398	12.2436	-0.436	0.002
CPS	8.00	2.157		

From the above table- 13 it is observed that the correlation between cps score with Sr, cortisol is -0.436 . there is statistically significant relationship between CPS score with Sr, cortisol as the p-value is 0.002 which is less than 0.05 , at 5% level of significance . so, there is negative significant relationship between them .

Table 14 : shows the correlation of compensated & Decompensated with Sr. cortisol of CLD patients

Descriptive Statistics				
	Mean	Std. Deviation	Correlation coefficient (r)	P-value
sr. CORTISOL <15mcg/dl	18.398	12.2436	- 0.133	0.358
COMPENSATEDAND DECOMPENSATED	1.74	.443		

From the above table- 14 it is observed that the correlation between compensated & Decompensated with Sr, cortisol is -0.133 . there is statistically no significant relationship between cps score with Sr, cortisol as the p-value is 0.358 which is higher than 0.05 , at 5% level of significance . so, there is negative relationship between them .

Table 15 : shows the correlation of platelets with Sr. cortisol of CLD patients

Descriptive Statistics				
	Mean	Std. Deviation	Correlation coefficient (r)	P-value
sr. CORTISOL <15mcg/dl	18.398	12.2436	0.157	0.277
PLT	157640.00	81919.762		

From the above table- 15 it is observed that the correlation between platelets with Sr, cortisol is -0.157 . there is statistically no significant relationship between cps score with Sr, cortisol as the p-value is 0.358 which is higher than 0.05 , at 5% level of significance . so, there is positive relationship between them .

Table 16 : shows the correlation of Hb with Sr. cortisol of CLD patients

Descriptive Statistics				
	Mean	Std. Deviation	Correlation coefficient (r)	P-value
sr. CORTISOL <15mcg/dl	18.398	12.2436	-0.179	0.214
HB	9.630	2.2654		

From the above table- 16 it is observed that the correlation between Hb with Sr, cortisol is -0.179 . there is statistically no significant relationship between cps score with Sr, cortisol as the p-value is 0.214 which is higher than 0.05 , at 5% level of significance . so, there is negative relationship between them .

VI. Discussion

The aim of our study was to observe adrenal insufficiency in patients with chronic liver disease by measurement of serum cortisol as well as serum ACTH.

It is observed that most of the CLD patients are in the age group 36-50 years (48.0%) followed by greater than 50 years (34.0%) . The mean age of our study population was 46.18 years with standard deviation of 10.123 years. So most of the patients are distributed in range of 36- 50 years of age. It is observed that most of the CLD patients are Male (76.0%) followed by Female (24.0%). Which signifies more prevalence of liver disease in male than female. Although alcoholism is most common cause of liver disease in our population , it is observed that Etiology of the most of the CLD patients are CRYPTOGENIC (44.0%) followed by ALCOHOL (42.0%) and HEPATITIS B is only 14.0%. other etiologies includes autoimmune hepatitis, NASH related CLD and others which was not included in this observational study.

Among the sample patient it is observed that number of patients according to Child Pugh Score , most of the CLD patients are DECOMPENSATED (74.0%) which includes Class B and Class C followed by

COMPENSATED (26.0%) which mainly cover Class A. On basis of sex distribution it is observed that For Female , total compensated is 16.7 % and decompensated is 33.3% whereas for male , total compensated is 28.9 % and decompensated is71.1 % according to age category . It is observed that number of patients according to Child Pugh Score , the distribution of patients are class A has total 13 patients i.e. 26% , Class B includes 27 patients i.e. 54% and Class C includes 10 patients out of 50 i.e. 20% Among all patients either compensated or decompensated it is observed that 80% of the patients do not have encephalopathy but has other features, 14% of them had minimal encephalopathy and only 6% have advanced encephalopathy. The patients we sampled, it is observed that most of the patient's Albumin range was greater than 2.5 mg/dl in 76% followed by less than 2.5mg/dl in only 24%.

Patient with Albumin < 2.5 mg/dl and serum cortisol <10 having AI i.e. 8 and serum albumin > 2.5 but serum cortisol <15 i.e. 14 patients having AI. Rest of 28 patients do not having AI. It has been concluded that patients with ACTH level of < 46 with cortisol <10 and ACTH >46 but cortisol < 15 comes under AI i.e. 22 patients

It is observed that the distribution of AI according to Child Pugh Score in total , AI is 44% and No AI is 56% . Based on Child Pugh Score there are 13 patients in class A, among them 3 has AI. Class B has 27patients, 13 among them has AI. Class C includes 10 patients and 8 out of them have AI which is 14%, 50% and 36% respectively.

It is observed that the distribution of AI according to cps score in class A is 3 out of 13, in class B AI is 11 out of 27 and in class C AI is 8 out of 10 which shows percentage distribution of 23% in class A, 40% in class B and 80 % in class C. It is observed that the correlation between Child Pugh Score with Serum cortisol is -0.436 . There is statistically significant relationship between Child Pugh Score with Serum cortisol as the p-value is 0.002 which is less than 0.05 , at 5% level of significance . So, there is negative significant relationship between them . It is observed that the correlation between platelets with Serum cortisol is -0.157 . There is statistically no significant relationship between Child Pugh score with Serum cortisol as the p-value is 0.358 which is higher than 0.05 , at 5% level of significance . So, there is positive relationship between them .It is observed that the correlation between Hb with serum, cortisol is -0.179 . There is statistically no significant relationship between Child Pugh score with Serum cortisol as the p-value is 0.214 which is higher than 0.05 , at 5% level of significance . So, there is negative relationship between them .

Multiple studies have demonstrated the presence of relative adrenal insufficiency in critically ill patients with both compensated and decompensated cirrhosis, with reported frequencies of 10% to 92%.The wide range in frequency is a reflection of the absence of a standardized test to diagnose the entity in the cirrhotic population. The presence of relative adrenal insufficiency has been associated with greater hemodynamic instability and increased mortality.

VII. Conclusion And Summary:

Our study deals with Adrenal Insufficiency in compensated and decompensated cirrhotic patients by measurement of serum cortisol along with serum ACTH levels at 8-9 am as study tools and other necessary laboratory test and imaging required.

In our study we have observed that majority of the patient were males. Overall the disease is more common in males at the age group of 36-50 years. In our study high percentage of patients were decompensated according to Child Pugh Score and among decompensated which includes class B and class C, Adrenal Insufficiency is present in 40% and 80% respectively, suggesting that most decompensated cirrhosis patients are having more chance of Adrenal Insufficiency.

From study we also observed the correlation between Child Pugh Score with Serum cortisol is -0.436 . There is statistically significant relationship between Child Pugh Score with Serum cortisol as the p-value is 0.002 which is less than 0.05 , at 5% level of significance .

VIII. LIMITATIONS OF THE STUDY:

This is a cross sectional study. Therefore, it does not accurately represents course of the disease. A good number of patients are treated at the medicine and gastroenterology department. A large sample size would have increase the power of the study. This was a single centre study. A multi-centric study would have been more desirable. This study was carried out in tertiary care centre where the patients were mostly referred from other hospitals. We have measured serum ACTH and serum cortisol level in known case of Chronic Liver Disease patients in relatively small population, hence there is a need for further longitudinal, multi-centric studies in these subcontinent to support our findings. we have measured cortisol and ACTH sample at 8-9 am duration only, these levels needs to be measured with dexamethasone overnight test at midnight plasma cortisol. We have looked for Adrenalin Insufficiency in some etiologies for Chronic liver Disease, how these parameters are related in case of mixed etiologies needs further evaluation.

ETHICAL CLEARANCE:
Ethical clearance for the study was taken from the Institution Ethics Committee.

FUNDING:
The study subjects did not bear any financial burden related to this study. All procedures and all investigations were performed at the institute, in close collaboration with Department of General Medicine & Biochemistry, Medical College, Kolkata.

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