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RESEARCH ARTICLE

Prevalence of adrenal dysfunction in patients with liver cirrhosis

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Abstract

Background and aim: Adrenal insufficiency represents an essential topic with great variation in its prevalence in the spectrum of chronic liver diseases. So we a***ssessed the prevalence of*** adrenal insufficiency (AI) ***&*** relative adrenal insufficiency (RAI) ***in patients with liver cirrhosis.*** **Patients and methods**: In a cross-sectional hospital- based observational study, 80 patients previously diagnosed as hepatitis C and or B-induced liver cirrhosis were recruited from the inpatient unit of the internal medicine department, AL Kasr Al Aini Hospital, Cairo University. Patients were subdivided into 3 groups, (A): patients with compensated liver cirrhosis, (B): patients with decompensated liver cirrhosis without infections and group (C): patients with decompensated liver cirrhosis with infections. Hormonal assessment of adrenal function including adrenocorticotropin (ACTH) stimulation test and serum total cortisol was estimated by ELISA.
Results: The average serum basal total cortisol level, cortisol after stimulation and delta cortisol was significantly low in group(C) with mean (8.56±1.40, 17.52±2.94, 9.38±2.91) respectively as compared with other groups, P value <0.001. The cortisol level after ACTH was inversely correlated with child -Turcotte-Pugh and model of the end-stage liver disease (MELD) score in decompensated liver cirrhosis. **Conclusion:** (AI) presented in (80%) of patients with decompensated liver cirrhosis with infections and (RAI) presented in (56.7%) of patients with decompensated liver cirrhosis without infections. Ascites, spontaneous bacterial peritonitis, high Child and MELD score, low levels HDL and LDL cholesterol were predictors of AI and require regular evaluation of adrenal function.

Introduction

Liver cirrhosis is one of the major causes of mortality all over the world, usually with severe sepsis as the end stage [1].
Liver has different functions in the body, one of its important functions, its role in the hormone metabolism. So diseases of the liver have been associated with several endocrine disorders [2].
Liver is a site for synthesis and storage of precursors of all adrenal hormones and cortisol binding globulin (CBG), so it is not surprising that dysfunction of adrenal gland has been developed in different spectrum of liver diseases [3].
Adrenal insufficiency (AI) is defined as deficient production or action of glucocorticoides resulting from either a structural damage of adrenal gland (primary adrenal failure) or an impairment of the hypothalamic-pituitary axis or secondary adrenal disease [4].
In critically ill patients, there is relative adrenal insufficiency (RAI) which is an inadequate glucocorticoid activity relative to the severity of illness [5].

Adrenal insufficiency (AI) is frequent in cirrhotic patients with critical illness; also it may be occurred in cases with stable cirrhosis in absence of sepsis and in patients under go liver transplantation [1].
There is great variation in prevalence of AI in cirrhotic patients depending on the stage of the liver disease (compensated or decompensated, with or without sepsis), the criteria for diagnosis and the methodology used to define AI [1].
The use of corticosteroids in cirrhotic patients with septic shock and AI are doubtful, some researches documented favorable results [6], while others didn't document any benefit results [7].

Objective of the study

Assessment of the adrenal functions and the prevalence of adrenal insufficiency ***(AI) &*** relative adrenal insufficiency (***RAI) in patients with liver cirrhosis (compensated & decompensated).***

Methods:

Subjects:

In a cross-sectional hospital- based observational study, 80 patients previously diagnosed as hepatitis C and or B-induced liver cirrhosis were recruited from the inpatient unit of the internal medicine department, AL Kasr Al Aini Hospital, Cairo University, from May 2013 to May 2014. Patients were subdivided into 3 groups, group (A): patients with compensated liver cirrhosis, group (B): patients with decompensated liver cirrhosis without infections and group (C): patients with decompensated liver cirrhosis with infections. All subjects had established HCV and or HBV infection, previously proved by PCR of HCV-RNA and HBV DNA.

Exclusion criteria:

Patients on steroids or had received therapy with corticosteroids. Patients were taking lipid modulating therapy within the last 3 months. Patients with alcoholic liver disease or admitted for post-operative care including liver transplantation or being treated with total parental nutrition. Patients had diabetes mellitus, hypertension, autoimmune, metabolic, cardiovascular, cerebrovascular stoke and kidney diseases.

Ethical aspects:

Research protocols were approved by the medical ethics committee of Al Kasr Al Ainy medical school, Cairo University. All participants provided a written informed consent after the research protocols were carefully explained to them. Informed consent was obtained from all the study participants and their approval taken by signature.

Methods:

All subjects underwent a complete screening panel, including history taking and physical examination. Blood samples were withdrawn for routine laboratory investigations (complete blood picture, AST, ALT, albumin, Billirubin, urea, creatinine, INR) and abdominal ultrasound was performed. The degree of liver decompensation was evaluated using the model of the end-stage liver disease **(**MELD) score [8] and Child-Turcotte-Pugh score (CPTS) [9-10].

Hormonal assessment of adrenal function of all subjects was done as patient's blood was collected in fasting state and serum was separated and stored at -80°C. Adrenocorticotropin (ACTH) stimulation test was performed in all patients using 250 microgram of tetracosactrin given intramuscularly and serum samples were collected after 60 minutes. Serum total cortisol was estimated by ELISA kits supplied by IBLINTERNATIONALGMBH Flughafenstrasse 52a D-22335 Hamburg, Germany.

In our study, **Adrenal insufficiency (AI)** was defined when the baseline total serum cortisol level is < 9.05µg/dl = 250nmol/L [11].

Relative adrenal insufficiency(RAI) was defined when:

A delta cortisol (defined as the difference between peak and basal cortisol) < 9.05µg/dl = 250nmo/L [12].

To convert values of serum cortisol from µg/dl to nmo/L multiply it with 27.59.

Calculation of model of the end-stage liver disease score

It was calculated according to the following equation [8]***:***

MELD score =9.6 x log creatinine (mg/dl) +3.8x log bilirubin (mg/dl) + 11.20 xlog international normalized ratio +6.4.

Child-Turcotte-Pugh score

A numerical score was given for each of the variables signifying liver decompensation [9] as follows:

Variables	Numerical score		
	1	2	3
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin (mg/dl)	<2	2-3	>3

Albumin (mg/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time (extra seconds above control)	1-3	4-6	>6

Child A 5-6
Child B 7-9
Child C 10-15 [10]

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing 2 groups when normally distributed and Mann Whitney *U* test for independent samples when not normally distributed.

Comparison of numerical variables between more than two groups was done using one way analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons in normally distributed data and Kruskal Wallis test in non-normal data. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P value less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The demographic data of our cirrhotic patients involved in the study was represented as mean ± SD in (Table I). We found that spontaneous bacterial peritonitis (SBP) was the main cause of infection in group C.

According to grades of liver cirrhosis, CPTS and MELD score were high in group C (Table II).

The base line laboratory data of the three groups was shown in (Table III). Total cholesterol, HDL and LDL cholesterol were higher in group A with statistically significant difference in comparison with other groups (table IV, figure 1)

The average serum basal total cortisol level, cortisol after stimulation and delta cortisol were significantly low in group(C) as compared with other groups (table V, Figure 2). .

There was neither adrenal insufficiency (AI) nor relative adrenal insufficiency (RAI) in group A but the highest percentage of AI was noted in group C while RAI was more in group B (Figure 3).

Ascites, spontaneous bacterial peritonitis (SBP), high Child and MELD score, low levels HDL cholesterol and LDL cholesterol were predictors of AI (Figure 4, 5) (Table VI).

Table (I): The demographic characteristics of the studied groups

Using ANOVA test	**Group A Compensated liver cirrhosis**	**Group B Decompensated liver cirrhosis without infections**	**Group C Compensated liver cirrhosis with infection**	**Total**	**P value**
Age	50.80±12.56	53.53±6.76	45.57±11.12	53.24±10.11	0.432
Sex female	8 (40.0%)	12 (40.0%)	16 (53.3%)	36 (45.0%)	
male	12 (60.0%)	18(60.0%)	14 (46.7%)	44 (55.0%)	0.510
Jaundice					
Yes	0 (0.0%)	15 (50.0%)	30 (100.0%)	45 (56.3%)	<0.001*
Encephalopathy					
Yes	0 (0.0%)	11 (36.7%)	17 (56.7%)	28 (35.0%)	<0.001*
Ascites					
Yes	0 (0.0%)	30 (100.0%)	30 (100.0%)	60 (75.0%)	<0.001*
Lower limb edema					
Yes	0 (0.0%)	30 (100.0%)	30 (100.0%)	60 (75.0%)	<0.001*

SBP **Yes**	0 (0.0%)	(0.0%)0	27 (90.0%)	27 (33.8%)	<0.001*
UTI **Yes**	0 (0.0%)	0 (0.0%)	3 (10.0%)	3 (3.8%)	0.074

(SBP) Spontaneous bacterial peritonitis, (UTI) Urinary tract infection,* P value is statistically significant

Table (II): Comparison between Child-Pugh & MELD scores of liver cirrhosis among the studied groups

	Group A	**Group B**	**Group C**	**P value**
Child score	5.50±0.51	8.73±1.29	9.23±1.16	<0.001*
MELD score	7.23±0.87	15.78±6.18	17.16±6.16	<0.001*

* P value is statistically significant

Table (III): The baseline laboratory data of the studied groups

	Group A	**Group B**	**Group C**	**P value**
Serum Billirubin (total) (up to 1 mg/dl)	0.83±0.24	2.53±2.45	3.07±3.41	0.012
Serum Bilirubin (direct) (up to 0.2 mg/dl)	0.36±0.17	1.20±1.43	1.53±2.06	0.033
ALT (up to 45Iu/l)	30.60±5.03	47.00±8.71	48.73±10.34	<0.001*
AST (up to 45Iu/l)	28.05±7.23	51.47±10.46	52.80±10.87	<0.001*
ALP (30-120IU/l)	45.70±17.65	95.90±40.23	94.57±59.47	<0.001*
Serum Albumin (3.5-5.2g/dl)	4.2±0.49	2.3±0.63	2.4±0.54	<0.001*
INR	1.05±0.04	1.67±0.43	1.76±0.46	<0.001*
Blood Urea (10-50mg/dl)	27.85±8.97	59.07±40.97	62.96±53.23	0.010
Serum Creatinine (0.5-1.5mg/dl)	0.7±0.3	1.1±0.5	1.66±1.7	0.044
Hb (12.2-15.1 g/dl)	12.41±0.82	9.23±2.06	10.17±1.84	<0.001*
TLC (4.000-11.000 /cmm^3)	6.76±2.22	8.60±5.89	11.75±14.33	0.177
Platelets (150.000-400.000cmm^3)	250.650±83.13	122.633±73.88	140.633±92.66	<0.001*

ALT alanine aminotransferase, AST aspartate aminotransferase, ALP alkaline phosphatase, INR international normalized ratio, Hb haemoglobin, TLC total leucocytic count

Table (IV): Lipid profile of the studied groups

	Group A	Group B	Group C	P value
Cholesterol	168.40±20.52	105.73±33.71	94.73±44.66	<0.001*
HDL	46.60±4.61	26.57±12.14	16.33±10.61	<0.001*
LDL	114.75±23.52	54.00±20.96	44.67±26.54	<0.001*

HDL high density lipoprotein cholesterol, LDL low density lipoprotein cholesterol.

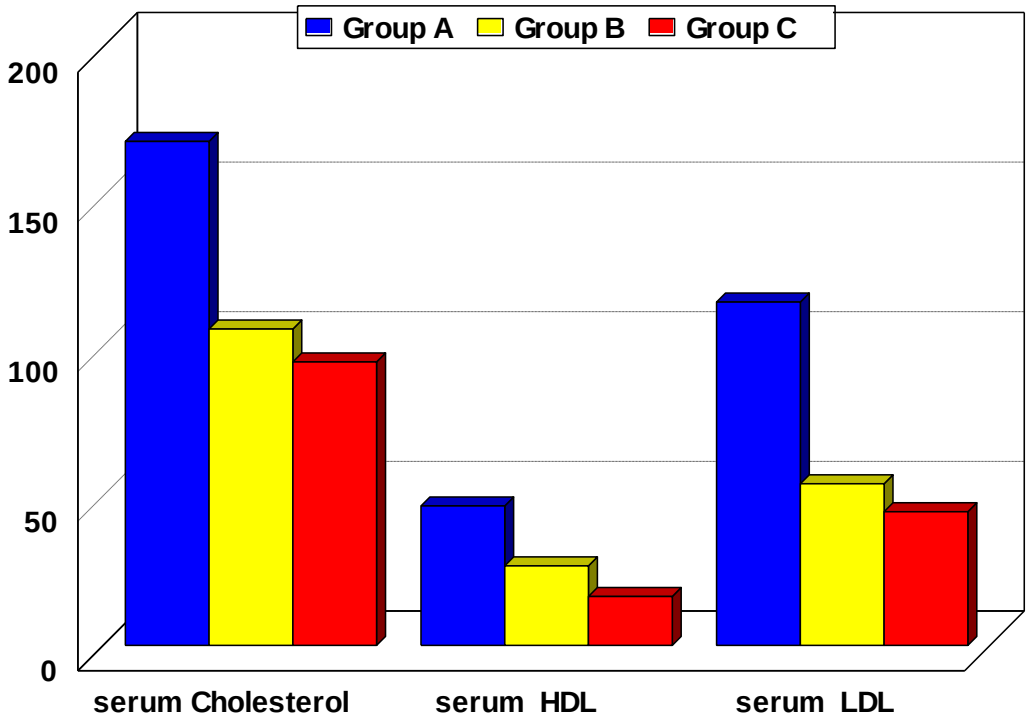

Fig (1): Comparison of the lipid profile of the three groups

Table (V): The cortisol level among the three groups

	Group A	**Group B**	**Group C**	P value
Baseline Cortisol	17.76±1.8	12.2±2.44	8.56±1.40	<0.001*
Cortisol after stimulation	34.08±2.2	20.62±4.02	17.52±2.94	<0.001*
Delta cortisol	16.33±2.30	8.43±2.62	9.38±2.91	<0.001*

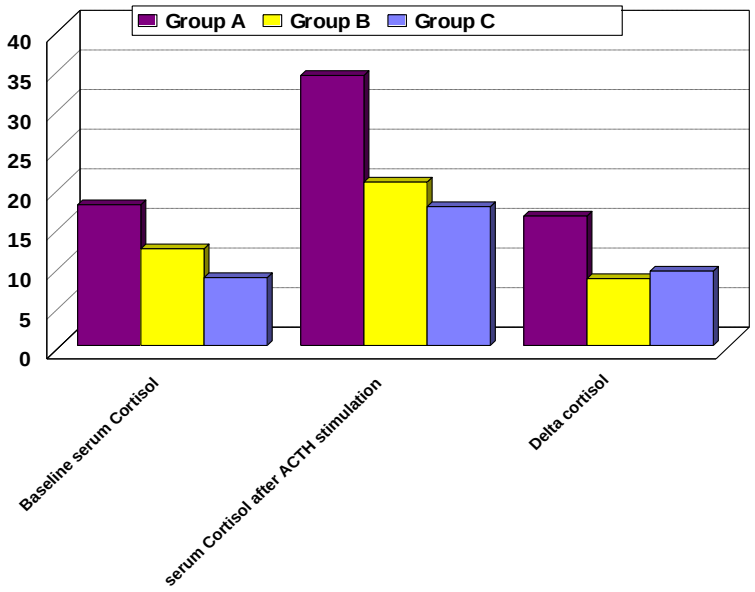

Fig (2): Comparison of serum cortisol level among the three groups

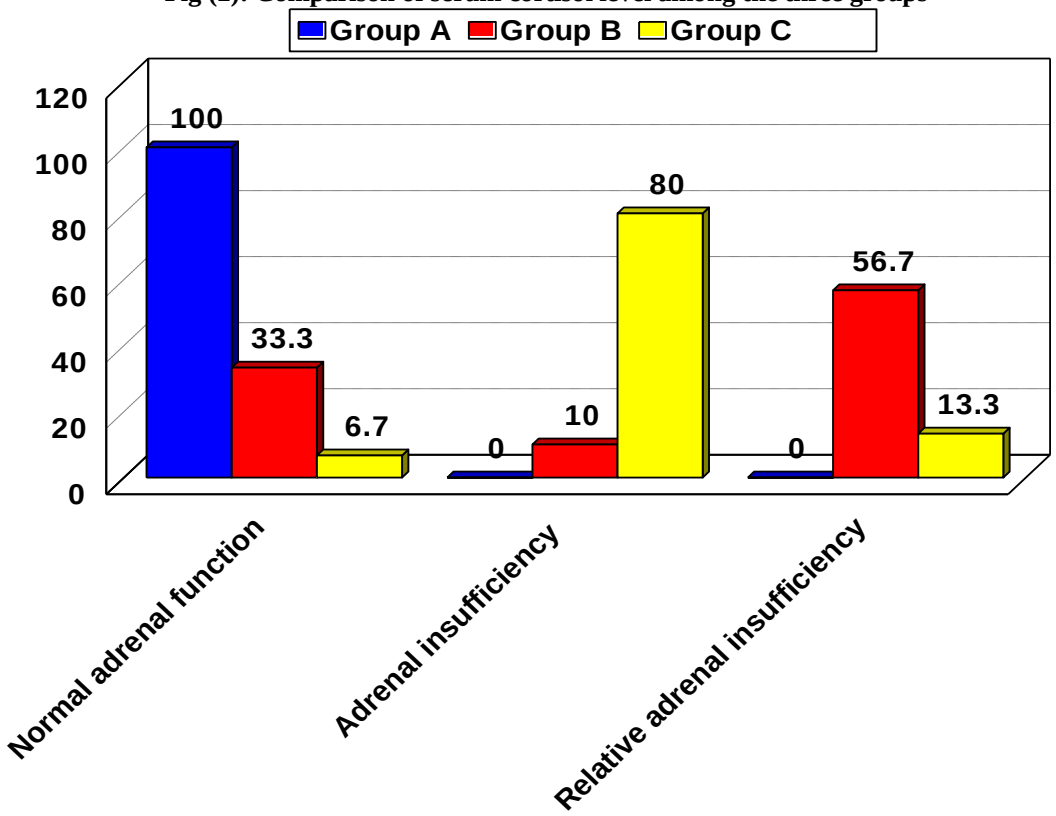

Fig (3): The percentage of the adrenal function among the three groups

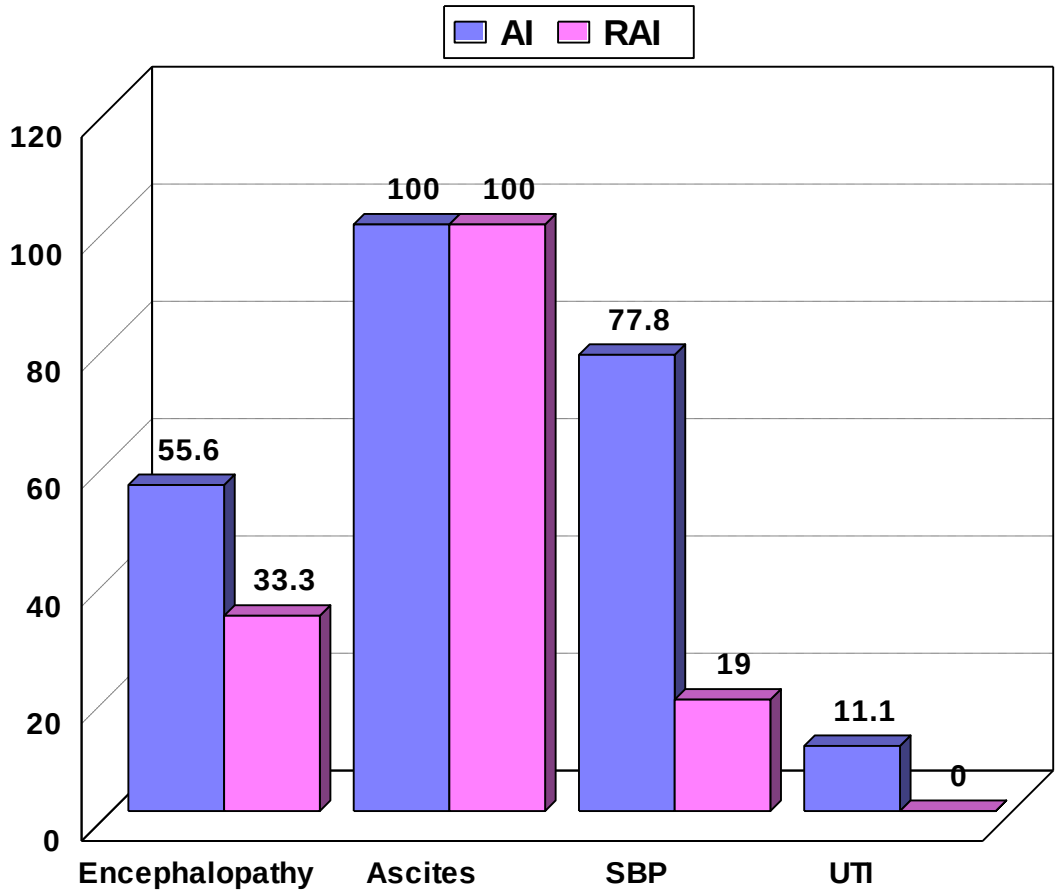

Fig (4): Comparison between AI and RAI regarding the clinical data in all cases

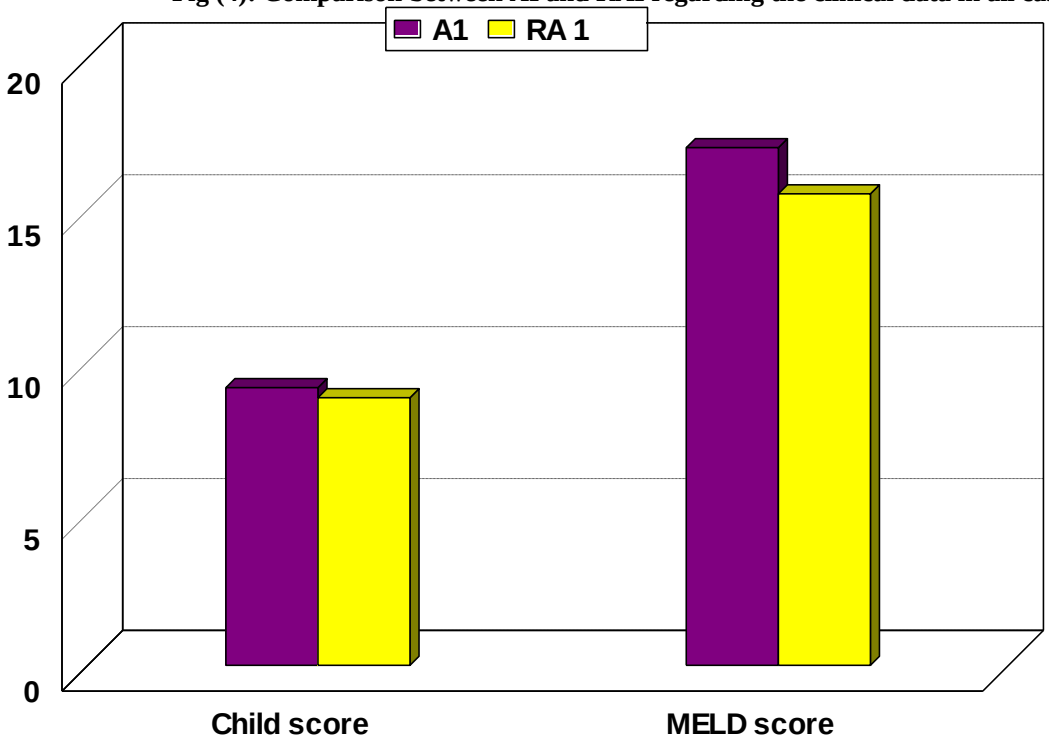

Fig (5): Comparison between AI & RAI in all cases regarding Child & MELD scores

Table (VI): laboratory predictors of AI & RAI in all groups

	AI	RAI	Total	P value
serum billirubin (total) (up to 1 mg/dl)	3.13±3.62	2.67±2.63	2.93±3.2	0.62
serum billirubin (direct) (up to 0.2 mg/dl)	1.59± 2.17	1.33 ± 1.596	1.48± 1.927	0.65
ALT (up to 45Iu/l)	48.70± 8.853	47.05±10.9	47.98 ± 9.75	0.57
AST (up to 45Iu/l)	50.89±10.07	52.67±12.539	51.67±11.127	0.59
ALP(30-120IU/l)	98.07±63.104	92.52±42.31	95.65 ±54.52	0.73
serum albumin (3.5-5.2g/dl)	2.16±0.513	2.21±0.725	2.18±0.608	0.76
INR	1.75±0.472	1.60±0.363	1.69± 0.430	0.22
blood urea (10-50mg/dl)	62.21±51.71	56.71±31.87	59.81±43.80	0.67
serum creatinine (0.5-1.5mg/dl)	1.64±1.86	1.14±0.672	1.4±1.47	0.25
Hb	10.04±1.97	9.490±1.914	9.800±1.9	0.34
TLC	12.07±15.02	8.381±4.184	10.456±11.64	0.28
Platelets	143.82±98.87	121.962±68.30	134.254 ±86.67	0.28
Serum Cholesterol (50-200mg/dl)	96.33 ±47.37	110.76 ±34.81	102.65 ±42.53	0.63
serum HDL (35-55mg/dl)	17.00 ±11.99	25.57 ±12.69	20.75 ±12.91	0.02*
serum LDL (40-226mg/dl)	47.48 ±28.97	51.19 ±21.89	49.10 ±25.92	0.02*

Discussion

Dysfunction of adrenal gland has been reported in all spectrums of liver diseases [13, 7, 6].

AI is documented in cirrhotic patients with sepsis and septic shock and it is associated with raised mortality [14].Diagnosis of AI in cirrhotic patients with critical illness on clinical bases is impossible due to absence of typical addisonian features [6]**.** So that diagnosis of AI in cirrhotic patients made on laboratory assay of serum basal total cortisol and one hour after IM injection of 250 µg tetracosactrin.

Mechanisms of AI in liver cirrhosis are not clearly known, but it may include decreased synthesis in total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol, in addition high levels of proinflammatory cytokines and circulating endotoxin (e.g., lipopolysaccharide) [15-16], however no recent consensus defining AI [14].

In the present study we found that only (10%) of patients ***in group*** B and majority of patients (80%) in group C had AI.

In agreement with these results, **Tsai et-al 2006** [17] found that AI occurred in 51.48% of cirrhotic patients with critical illness and patients with severe sepsis. Also they documented that patients with AI had a higher hospital mortality rate as compared with those with normal adrenal function [17].

The study done by Kharb et al 2013 [18] found that AI was presented in 40% of patients with chronic liver disease**.** Several authors have documented that AI ranging from 33-68% in chronic liver disease patients [13].

Acevedo et al 2010[19] evaluated the prevalence of AI in 198 cirrhotic patients [10 cases with compensated cirrhosis, 188 with decompensation and complications as hepatic encephalopathy (HE), (SBP), ascites, gastrointestinal bleeding, hepatorenal syndrome] they found AI presented in 64% of patients. Mortality was similar between cirrhotic patients with or without AI. The same researches assessed RAI (delta cortisol <250 nmo/l after SST), study was done on 166 patients with advanced cirrhosis, they found that 26% of cases had RAI [20].

In our study we didn't find AI or RAI in patients with compensated cirrhosis. This may be explained as all patients were Child A, small number, different level of serum basal total cortisol used for diagnosis AI. These were in contrary with study done by **Fede et al, 2011**[13] who reported that AI was found in 38% of 101 patients with stable cirrhosis.

In our study all cases with AI had ascites (100%) and majority of cases had SBP (77.8%). These results were in agreement with **Triantos et al 2011**[21]who reported that AI is common in compensated and

decompensated cirrhosis without sepsis as in cases with variceal bleeding (30-48%) and ascites (26-64%). Ascites was important predictor for AI [14].

Our results showed that bilirubin (total, direct), INR, were high, while albumin was low in cases with AI but not statistically significant. This was in agreement with what was published in 2013 by **Kharb, et al** [18] who found that higher total bilirubin, INR and albumin were predictors of AI which has also been observed by others [17-13].

In our study RAI presented in (56.7%) ***of group*** B and in (13.3%) in group C.

In the study done by **Fernandez et al** [6] found RAI in 68% in cirrhotic patients with sepsis.

Also the study done by **O'Beirne et al** [22] showed that the cases with liver cell failure particularly those with sepsis had a high prevalence of RAI, and the degree of adrenal dysfunction proportionate with the severity of liver disease [21]. This may partially explained as majority of patients with decompensated cirrhosis with infections had AI (80%) and our cases were not in sepsis.

In fact, cortisol transport protein (cortisol binding globulin and albumin) are often decreased in cirrhotic patients, causing a reduced bound fraction of cortisol, where as concentration of free cortisol, which is active fraction of cortisol, remains unchanged. Some studies showed that measurement of serum total cortisol (performed at 8 am before and after corticotropin injection) greatly overestimate the prevalence of AI [11].

In our study the cortisol level after ACTH was inversely correlated with child and MELD score in decompensated liver cirrhosis.

These results were in agreement with results done by **Tsai et-al** [17] who reported that the cortisol response to corticotropin was inversely correlated with various diseases severities, MELD and CPT scores [17].

Also these results were in agreement with results done by **Kharb, et al** [18] who concluded that the values of stimulated cortisol were reduced in patients with chronic liver diseases (CPTS C and B), and this was improved after liver transplantation. This suggests that after liver transplantation liver functions improve; there may also be recover of LDL and HDL synthetic function of the liver which causing recovery of adrenal function [18].

In spite of disparity in the prevalence of AI among several studies, this may be due to different criteria used to diagnose AI, dysfunction of adrenal gland occurred in patients with compensated and decompensated liver cirrhosis not only from sepsis but may also resulting from bleeding and ascites [14]. So that AI may be a feature of liver disease alone without relation to critical illness. However researches are in need of agreement on the convenient tests and the accepted normal value in evaluation of adrenal function in patients with liver disease. Hypothalamic pituitary adrenal dysfunction in liver disease needs more exploration [14].

Liver is vital organ for synthesize, storage, transport and decompose of lipid along with synthesis and secretion of endogenous lipoprotein; synthesis of rate limiting enzyme of lipoprotein metabolism to control mutual conversion and metabolism between a variance of lipoprotein; and absorbing and removing metabolites of lipoprotein through lipoprotein receptors on the surface of liver cells to keep equilibrium of total cholesterol (TC) and triglyceride (TG) metabolism [23]. Some papers have shown that the lipid level was an essential parameter to reflect liver damage which can be used to detect condition and evaluate the prognosis of the patients [24].

In our study, the serum cholesterol, LDL and HDL were significantly lowered in decompensated liver cirrhosis than compensated liver cirrhosis with statistically significant difference.

These results were in agreement with the study done by **Abbasi, et al,** [25] and **Cicognani et-al** [26] that found hypocholestremia in decompensated chronic liver diseases and showed significant association with Child Pugh score. It may raise significance of CPTS in evaluation of severity and prognosis in patients with chronic liver disease [25].

Also the study done by **Jiang et al, 2010** [27] found that the serum triglyceride, LDL, HDL and total cholesterol (TC) were reduced with high MELD score and MELD> or =18 and TC< or =2.8 mmol/L are two important indexes to predict the prognosis of patients with decompensated cirrhosis [27].

Conclusion

AI represented essential topic in spectrum of chronic liver disease, it presented in (80%) of patients in group C and RAI presented in (56.7%) ***of group*** B.

Ascites, Spontaneous bacterial peritonitis, high Child and MELD score, low levels of serum protein, serum albumin, high levels of total cholesterol, HDL cholesterol, LDL cholesterol, serum bilirubin and INR were predictors of AI and require regular evaluation of adrenal function.

Further studies are required to confirm role of use of steroid in improving outcome in patients with liver disease, in particularly at stressful condition and critical illness. Also standardization of criteria used for diagnosis of AI among spectrum of liver disease.

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