Prevalence of Adenocortical Insufficiency in Patients with Liver Cirrhosis, Liver Cirrhosis with Septic Shock and in Patients with Hepatorenal Syndrome

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Abstract: Critical illness is accompanied by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is highlighted by increased serum corticotropin and cortisol levels. In patients with severe sepsis, the integrity of the HPA axis can be impaired by a variety of mechanisms. These patients typically have an exaggerated proinflammatory response and are considered to be relatively corticosteroid insufficient. This complex syndrome is referred to as critical illness-related corticosteroid insufficiency (CIRCI) which manifests with insufficient corticosteroid mediated down regulation of inflammatory transcription factors. Similar to type II diabetes (relative insulin deficiency), CIRCI arises due to corticosteroid tissue resistance together with inadequate circulating levels of free cortisol. Numerous papers have reported a high incidence of adrenal failure in critically ill patients, including those with end stage liver disease and liver transplant recipients. The term hepatoadrenal syndrome e.i, Adrenocortical insufficiency in patients with liver cirrhosis has been used to describe such an association between liver disease and adrenal failure and the definition of this term extends beyond the occurrence of sepsis, which is a frequent complication of liver failure. Aim of work to assess: The prevalence of hepatoadrenal syndrome (HAS) among the Egyptian cirrhotic patients, the prevalence of HAS among those complicated with septic shock or hepatorenal syndrome and to find significant predictors for HAS. Patients and methods: Our study was a cross sectional study, conducted on 45 patients admitted to the liver intensive care unit and hepatology ward of Theador Bilharz Research Institute (TBRI) in the period between November 2009 and February 2010, who were fulfilling the criteria of Child Pugh classification. Patients were divided into three groups. Group A included 15 patients with liver cirrhosis, with neither septic shock nor hepatorenal syndrome, Group B included 15 patients with liver cirrhosis and septic shock, but not associated with hepatorenal syndrome, Group C included 15 patients with hepatorenal syndrome. The adrenal function of all patients was assessed by the conventional dose, short synacthen test (250 ug.iv) which was performed within the first 24 h of admission. Blood samples to measure plasma cartisol levels were obtained before and 30 minutes after synacthen administration. Results: Our study revealed that adrenocortical insufficiency (ACI) was found in 33 patients out of the 45 patients subjected to this study (73.3%).Receiver Operating Characteristic (ROC) curve was done and showed that the MELD score may be a good predictor for ACI in liver cirrhosis patients. ROC curve showed also that the serum bilirubin may be a good predictor for ACI in liver cirrhosis patients. Conclusion: Adrenocortical insufficiency is common in patients with cirrhosis and in patients complicated with hepatorenal syndrome. According to our study MELD score and serum bilirubin level may be good predictors for Hepatoadrenal Syndrome. Recommendation: We recommend To make further studies with greater number of patients to detect hepatoadrenal syndrome and to study its effect on the prognosis, the complication of liver cirrhosis and mortality.

[Mohamed Badr Mohamed, Gamal Hamed, Ayman Heikal and Hisham Darwish. Prevalence of Adenocortical Insufficiency in Patients with Liver Cirrhosis, Liver Cirrhosis with Septic Shock and in Patients with Hepatorenal Syndrome. Journal of American Science 2011;7(6):391-400]. (ISSN: 1545-1003). http://www.americanscience.org.

Key words: Liver cirrhosis, child classification, hepatoadrenal syndrome, hepatorenal syndrome, adrenal dysfunction, adrenocortical insufficiency, relative adrenal insufficiency, MELD score

1. Introduction

Critical illness is accompanied by the activation of the hypothalamic pituitary-adrenal (HPA) axis, which is highlighted by increased serum corticotropin and cortisol levels *[1-3]*.

The activation of the HPA axis is a crucial component of the host's adaptation to severe stress. Cortisol is essential for the normal function of the immune system, maintenance of vascular tone, and various cellular functions. In patients with severe sepsis, the integrity of the HPA axis can be impaired by a variety of mechanisms *[1-4]*.

These patients typically have an exaggerated proinflammatory response and are considered to be relatively corticosteroid insufficient. Until recently, the exaggerated proinflammatory response that characterizes patients with systemic inflammation has focused on suppression of the HPA axis and adrenal failure. However, experimental and clinical data suggest that corticosteroid tissue resistance may also

play an important role. This complex syndrome is referred to as critical illness-related corticosteroid insufficiency (CIRCI) which is defined as inadequate corticosteroid activity for the severity of the illness of a patient. CIRCI manifests with insufficient corticosteroid mediated down regulation of inflammatory transcription factors. Similar to type II diabetes (relative insulin deficiency), CIRCI arises due to corticosteroid tissue resistance together with inadequate circulating levels of free cortisol *[5]*.

Recently, the concept of relative adrenal insufficiency (RAI) has been used to describe a subnormal adrenal response to adrenocorticotropin in severe illness, in which the cortisol levels, even though high in terms of absolute value, are inadequate to control the inflammatory situation *[1]*.

The short corticotropin stimulation test i.e the short synacthem test (SST), is most commonly used to evaluate the appropriateness of the adrenal response in this setting. Numerous papers have reported a high incidence of adrenal failure in critically ill patients, including those with end stage liver disease and liver transplant recipients *[6]*.

The term *hepatoadrenal syndrome* has been used to describe such an association between liver disease and adrenal failure and the definition of this term extends beyond the occurrence of sepsis, which is a frequent complication of liver failure *[6]*.

Aim of the work

- To detect the prevalence of hepatoadrenal syndrome (HAS) in patients with live cirrhosis and in those complicated with septic shock or hepatorenal syndrome.
- To find out significant predictors for hepatoadrenal syndrome (HAS)

2. Patients and Methods

Our study was a across sectional study, conducted on 45 patients (21 males and 24 females) admitted to the liver intensive care unite and hepatology word of Theador Bilharz Research Institute (TBRI) in the period between November 2009 and February 2010, who were fulfilling the criteria of child Pugh classification. Patients were divided into three groups. **Group A** included 15 patients with liver cirrhosis, with neither septic shock nor hepatorenal syndrome, **Group B** included 15 patients with liver cirrhosis and septic shock, but not associated with hepatorenal syndrome, **Group C** included 15 patients with hepatorenal syndrome.

All patients were subjected to:

1. Full clinical evaluation,
2. Routine lab. Investigation,
3. Model for End stage Liver Disease (MELD) scoring.

The adrenal function of all patients was assessed by the conventional dose, short synacthen test (250 ug,iv .), which was performed within the first 24 hrs of admission.

Informed consent for participation in the study was obtained according to the guidelines of the institutional review boards for human subjects at the participating study centers.

Inclusion criteria:

1- Liver cirrhosis patients by:

I. Full clinical assessment.
II. Child. pugh classification.
III. Abdominal ultrasonography

2-Cirrhotic patient with septic shock is considered present when:

I: Two or more of the following criteria are met :

1. Body temperature > 38°C or < 36°C
2. Tachycardia >90/minute
3. Hyperventilation: respiratory rate >20/minute or arterial hypocapnia < 32 mmHg
4. White blood cell count > 12,000/dL or <4,000/dL or immature forms > 10%

II: Source Of Infection.

III: Sepsis associated with circulatory failure characterized by persistent arterial hypotension (decrease of systolic blood pressure below 90 mmHg or >40 mmHg from baseline, or mean arterial pressure <60 mmHg, despite adequate fluid resuscitation) unexplained by other causes. [7]

Refractory circulatory failure was defined as a persistent or growing metabolic acidosis despite adequate vasoactive support over an observation period of 6–12hours, and was judged to be present if there was a base excess below 5 mmol/l at the end of this period ***[8].***

3- Hepatorenal syndrome:

Diagnostic Criteria of Hepatorenal Syndrome in Cirrhosis [9]

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement of serum creatinine e.g decrease to a level of 1.5 mg%, after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1gm/kg/d up to maximum of 100 g/day.
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography.

-Urine volume <500 mL/day **[10]**

-Urine sodium <10 mEq/L **[10]**

Exclusion criteria:

- History of long term steroid therapy.

All patients were subjected to the following:

1- Child–Pugh classification and score using full detailed history and clinical evaluation (Table 1 & 2).
2- MELD (Model of End stage Liver Disease) score using full detailed history and clinical evaluation. ***MELD= 3.78 [Loge serum bilirubin (mg/dL)] ± 11.2 [loge INR] ± 9.57 [Loge serum creatinine (mg/dL)] ± 6.43***
3- **Full chemistry** including total lipid profile, liver function tests, renal functional tests Complete blood count, Prothrombin time (PT), Prothrombin Count (PC) and INR.
4- Urinary Na.
5- Abdominal ultrasonography
6- Synacthen test was performed within the first 24 hours of admission.

Synthetic adrenocorticotropic hormone (250 µg, Synacthen), was given intravenously. Blood samples to measure plasma cortisol levels were obtained before and 30 minutes after synacthen administration.

According to the serum cortisol level one of the following three conditions could be detected:

1. Baseline serum cortisol level >35 g/dL, this means that functional hypoadrenalism is unlikely.
2. Baseline serum cortisol level <15 g/dL, this means that functional hypoadrenalism is likely.
3. If the baseline serum cortisol level is between 15-35 g/dL, at this situation the increase in plasma cortisol will be the determining factor, as if the increment is ≤ 9 mg/dL, hypoadrenalism is likely, while if the increment is ≥9 mg/dL, functional hypoadrenalism is unlikely ***(11).***

Table (1): Showing Child Pugh Score (12, 13)

Measure	*1 point*	*2 points*	*3 points*	*Units*
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	mol/l (mg/dL)
Serum albumin	>3.5	2.8-3.5	<2.8	g/L
INR	<1.7	1.7-2.2	>2.2	-
Ascites	None	Improved by medication	Refractory	-
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	-

Note: The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15. Child Pugh class is either A (a score of 5 to 6), B (3 to 9), or C (10 or above). Decompensation indicates cirrhosis with a child Pugh score of 7 or more (class B). This level has been the accepted criterion for listing for liver transplantation.

Table (2): Child Pugh Score Interpretation (12, 13)

Points	*Class*	*Life expectancy*	*Preoperative Mortality*
5-6	A	15-20 years	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 years	82%

3. Results :

Demographic Data:1. Age distribution:

The mean age of ***group A*** patients was 52.8±10.97 year, ***group B*** patients was 60.2±8.99 year, and ***group C*** patients was 59.33±8.65 year. There was no significant statistical difference in age between the three group (Table 3).

2. Adrenocartical insufficiency distribution:

Our study revealed that adrenocartical insufficiency (ACI) was found in 33 patients out of the 45 patients subjected to this study (73.3% vs 26.7%) respectively (Figure 1).

Table (3): Showing age distribution

Group	No. Of Patients	Age (years)	P-Value
A	15	52.8± 10.97	***0.081***
B	15	60.2 ±8.99	
C	15	59.33 ±8.65	

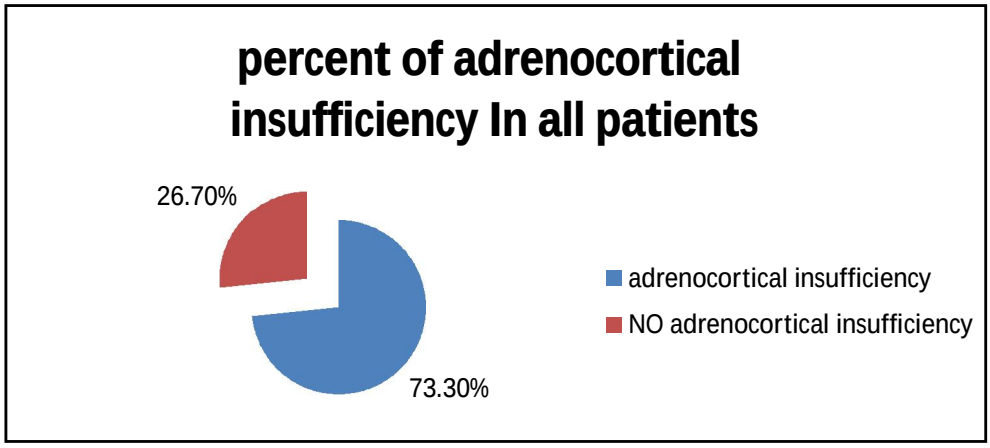

Fig (1): Percentage of adrenocortical insufficiency In all patients

The prevalence of adrenocartical insufficiency (ACI) varied between the three groups, being found 53.5% in ***group A*** patients, 86.7% in ***group B***, and 73.3% in ***group C***. there was no significant statistical difference in adrenocortical insufficiency between the three groups (P: 0.092), also there was no statistical difference between each two groups as follow, between group A and group B (P: 0.54), between group A and group C (P: 0.123) and between group B and group C (P: 0.5)as seen in table (4).

Table (4): adrenocortical insufficiency–distribution

Adrenocortical insufficiency		Group A	Group B	Group C	total
No	No.	7	2	3	12
	%	46.7%	13.3%	20%	26.7%
Yes	No.	8	13	12	33
	%	53.3%	86.7%	80%	73.3%

3. Child-pugh classification distribution:

According to child pugh classification, ***group A*** had 6 patients (40%) with child A, 4 patients (26.7%) with child B and 5 patients (33.3%) with child C, regarding patients in both ***group B*** and ***C*** they were all fulfilling the criteria of child C classification (Table 5).

Table (5) child-pugh classifications –distribution

	CHILD A		CHILD B		CHILDC	
	No.	%	No.	%	No.	%
Group A	6	40%	4	26.7%	5	33.3%
Group B	0	0%	0	0%	15	100%
Group C	0	0%	0	0%	15	100%

4. MELD score distribution:

Regarding MELD score, the mean score was highest in ***group C*** patients (33.93±3.08), followed by ***group B*** patients (28.67±5.23), and in ***group A*** patients it was (15.87±8.25).

There was a statistically significant difference in MELD score between each two groups of the three groups, group A and B < 0.001, group A and C < 0.001, and group B and C P: 0.003 (Table 6) .

Table (6): showing MELD score distribution

Group	Number of Patients	Mean ± SD	P-Value
A	15	15.87± 8.25	A,B<0.001 A,C<0.001 B,C=0.003
B	15	28.67 ±5.23	
C	15	33.93 ±3.08	
Total	45	26.16±9.6	

II. Relation between significant predictors and Adrenocortical Insufficiency:

1. Child Score and adrenocortical insufficiency:

There was a statistically significant relationship between child score and adrenocortical insufficiency (ACI), as the 33 patients diagnosed to have ACI had child score of 12.52±2.35, while the other 12 patients who did not have ACI, had a child score of 9.75±3.91 with a P value: 0.049 (Table 7).

Table (7): Mean±SD of Child score in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	Number of patients	Mean ± SD Of Child Score	P-Value
Yes	33	12.52± 2.35	0.049
No	12	9.75± 3.91	

2. MELD score and adrenocortical insufficiency:

There was a highly statistically significant correlation between MELD score and ACI, as the 33

patients diagnosed to have ACI, had a MELD score of 28.66±8.05, while the other 12 patients who did not have ACI, had a MELD score of 19.25±10.45, with a P value: 0.008 (Table 8).

Table (8): Mean±SD of MELD score in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	*Number Of Patients*	*Mean ± SD Of Meld Score*	*P-Value*
No	12	19.2500± 10.45	0.008
Yes	33	28.66± 8.05	

3. Serum Bilirubin level and Adenocortical Insufficiency:

There was a highly statistically significant correlation between serum bilirubin level and ACI, as the 33 patients diagnosed to have ACI, had a serum bilirubin level of 50.1±3.072 mg/dL, while the other 12 patients who did not have ACI, had a serum bilirubin level of 2.04±1.35 mg/dl with a p value: 0.002 (Table 9).

Table (9): Mean±SD of serum Bilirubin level in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	Number Of Patients	MEAN ± SD Of Serum Bilirubin Level Mg/Dl	P-Value
No	12	2.40± 1.35	0.002
Yes	33	5.01± 3.072	

4. Serum creatinine level and adrenocortical insufficiency:

There was a highly statistically significant correlation between serum creatinine level and ACI, as the 33 patients diagnosed to have ACI, had a serum creatinine level of 3.033±1.45 mg/dL while the other 12 patients who did not have ACI, had a serum creatinine level of 2±1.5 mg%, with a P value of 0.027, (Table 10).

Table (10): Mean±SD of serum creatinine level in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	Number OF Patients	MEAN ± SD Of Serum Creatinine Level mg/dL	P-Value
No	12	2± 1.5	0.027
Yes	33	3.0333 ± 1.45	

5. Serum SGOT/AST and adenocortical insufficiency:

On evaluating the relationship between serum SGOT/AST and ACI in patients subjected to this study, it was found that the 33 patients diagnosed with ACI, had serum SGOT/AST level of 82.848±93.34 mg/dL, while the 12 patients who did not have ACI had serum SGOT/AST level of 31.66±13.79 mg/dL with a highly significant statistical P value of 0.003 (Table 11).

Table (11): Mean±SD of serum SGOT/AST level in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	Number of Patients	MEAN ± SD Of Serum SGOT Level mg/dL	P-Value
No	12	31.66± 13.792	0. 003
Yes	33	82.848± 93.34	

6. Serum albumin level and adrenocortical insufficiency:

On evaluating the relationship between serum albumin level and ACI, it was found that the 33 patients diagnosed to have ACI, had albumin serum level of 2.433±0.612 mg/dL, while the 12 patients who did not have ACI, had albumin serum level of 2.958±0.59 gm/dL with a significant P value: 0.014 (Table12).

Table (12): Mean±SD of serum albumin level in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	Number of Patients	Mean ± Sd Of Serum Albumin Level mg/dL	P-Value
No	12	2.9583±.0.59766	0.014
Yes	33	2.4333±0.612	

7. Blood urea nitrogen (BUN) and adrenocortical insufficiency:

The 33 patients diagnosed to have ACI, had a BUN level of 50.9±24.08 gm/dL, while the 12 patient who did not have ACI, had BUN level of 30.83±22.43 mg/dL with a P value: 0.012., (Table 13).

Table (13) Mean±SD of serum BUN level in patients with and without adrenocortical insufficiency

Adrenocortical Insufficiency	*Number Of Patients*	*Mean ± Sd Of Serum Bun Level mg/dL*	*P-Value*
No	12	30.83± 22.433	0.012
Yes	33	50.9± 24.089	

III. Logistic regression analysis:

In statistics, logistic regression is used for prediction of the probability of occurrence of an event by fitting data to logic function e.i logistic curve. This study was done to find out the most significant predictor for ACI from the obtained data as child classification, serum SGOT/AST, serum bilirubin, Ascidis, serum creatinine, serum albumin, and MELD score.

All these data were analyzed by the logistic regression analysis and only MELD score was found to be a very significant predictor for ACI with a P value: 0.007 (Table 14).

Tab (14): Showing logistic regression analysis for significant variables

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1	MELD	.107	.040	7.193	1	.007	1.113
	Constant	-1.598	.994	2.584	1	.108	.202
					Score	df	Sig.
Step 1	Variables	Ascites			.058	2	.972
		Ascites (1)			.015	1	.901
		Ascites (2)			.054	1	.816
		Creatinine.0.61.3mgdl			.439	1	.508
		Albumin3.55.5gdl			..622	1	.430
		CHILDClassification			.082	2	.965
		CHILDClassification(1)			.064	1	.801
		CHILDClassification(2)			.055	1	.815
		SGOT737mgdl			2.012	1	.156
		Bilirubin0.21			2.219	1	.136

IV. Receiver operating characteristic (ROC) curve for adrenocortical insufficiency:

ROC curve is a graphical plot of sensitivity by plotting the fraction of true positives out of the positives (TPR= true positive rates) vs. the fraction of false positives out of the negatives (FNR= false negative rate), in other words sensitivity vs specificity. It was found that MELD score and serum bilirubin could be good screening tests for ACI in patients with liver cirrhosis, (Figure 2).

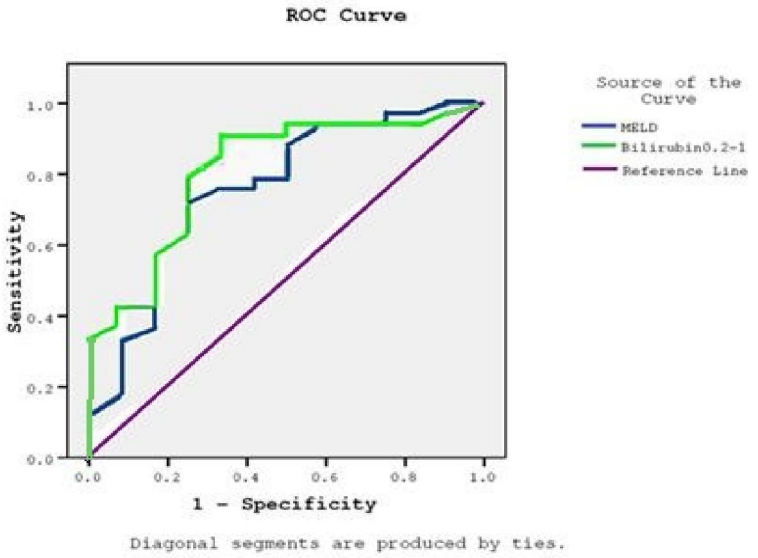

Figure (2) ROC curve for adrnocortical insufficiency the area under the MELD score curve was 0.761, and that under the serum bilirubin curve was 0.811.

Cutoff level interpretation:

1. MELD Score:

Regarding MELD cut off score of 18.5, it had a sensitivity for predicting ACI of 0.879, and a specificity of 0.5. But with a higher MELD cutoff score of 25.5 the sensitivity declined to 0.727 and the specificity raised to 0.75 (Table 15).

2. Serum bilirubin levels:

The interpretation of the serum bilirubin level, showed a cutoff level of 2.75mg/dL, it had a sensitivity for predicting ACI of 0.909 and a specificity of 0.667. But with a higher cutoff serum bilirubin level the sensitivity declined to 0.788 and the specificity raised to 0.75 (Table16).

Table (15) Showing MELD score cut off levels

Positive if Greater Than or Equal To	Sensitivity	Specificity
18.5000	.879	.500
22.5000	.788	.583
24.5000	.758	.667
25.5000	.727	.750

Table (16) Showing bilirubin cut off levels

Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	Specificity
Bilirubin0.2-1	2.7500	.909	.667
	2.9500	.788	.750

3.The serum cortisol level before and 30 minutes after the conventional-dose (250 g IV) short synacthen test:

The whole population of patients had a mean serum cortisol level before synacthen test of 17.9±6.94, g/dL, P value: 0.44, while the mean serum cortisol level 30 minutes after synacthen test was 22.65±8.96 g/dL P value: 0.539, with a median increment 4.1 g/dL (Table17).

From the previously mentioned data, there was no significant statistical difference between the three groups of patients.

Table (17): Showing synacthen tests results and shows P value between serum cortisol 0 min and 30 min after synacthen test

The whole population of patients	Serum cortisol	Mean±SD g/dL	P value	Median increment
	0 min.	17.9±69.4	0.44	4.1 g/dL
	30 min. after ACTH	22.65±89.6	0.539	

4. Discussion:

Our study was a cross sectional study, conducted on 45 patients diagnosed to have liver cirrhosis admitted to the hepatology intensive care unit & hepatology ward at Theodor Bilharz Research Institute (TBRI) they included 21 males (46.7%) & 24 females (53.3%).

- Group A included 15 patients with liver cirrhosis neither complicated with sepsis nor hepatorenal syndrome.
- Group B included 15 patients with liver cirrhosis complicated with septic shock.
- Group C included 15 patients with hepatorenal syndrome.

All patients had been subjected to full history taking, clinical examination, several laboratory investigations, and statistically comparative studies.

Our study found that the prevalence of adrenocortical insufficiency (ACI) was 73% in all patients. The prevalence of adrenal insufficiency varied between the three groups, being found 53.5% of patients with liver cirrhosis only, 86.7% in liver cirrhosis associated with septic shock and 73.3% in patients with hepatorenal syndrome.

This goes with what Marik et al., found in 2005, as they conducted a study on 340 patients suffering for liver disease. Adrenal insufficiency was found in 72 %. of the patients. The prevalence of ACI varied between the groups, being seen in 66% of ACLF (acute on top of chronic liver failure) patients, 33% of ALF (acute liver failure) patients, and 61% of patients who had undergone liver transplantation in the past [6]. In the study conducted by harry et al., (14) on 20 patients, 69% of the patients had adrenal insufficiency. In another study conducted by Harry et al., (15) in they found that out of the 45 patients subjected to the study, 62% patients had ACI. In 2006 Fernandez et al.,(16) studied 25 patient's with liver disease, they found that 63% had ACI .

But in another study conducted by Tsai et al., (17) on 101 patient with liver cirrhosis complicated with severe sepsis and septic shock, they found that not more than 51.4% of the patients had ACI. This difference in ACI prevalence between our study and that one, might be due to the type of patients population subjected in both studies as we included patients with hepatorenal syndrome while Tsai et al., (17) studied only cirrhotic patients complicated with severe sepsis and septic shock.

Our study found that patients who had ACI, had a mean child score of 12.52±1.6, compared to 4.75±3.9 in those who did not have ACI, P value: 0.049. This goes with what Tsai et al., (17), as patients with ACI had a mean child score of 12.7±2.2, while those who did not have ACI, had a mean child score of 11±2.7 with a statistical significant P value: 0.022. Also they found a relation between the cortisol increment and Child-Pugh scores, suggesting that adrenal dysfunction is related to liver function reserve.

Regarding MELD score, our study found that patients with ACI had a mean MELD score of 28.6±8 compared to 19.2±10 in those without ACI (statistically significant P value: 0.008). This is in agreement with Tsai et al.,(17). who found that patients with ACI had a mean MELD score of 15.2±5.2 and in patients without ACI the mean MELD score was 10.4±6 with statistically significant P value < 0.001.

Logistic regression analysis was done to search for significant predictors ACI, only MELD

was found to be a significant predictor for ACI with a P value of 0.007.

ROC curve was done and showed that the MELD score may be a good predictor for ACI in liver cirrhosis patients. The area under the MELD curve was 0.76 and a MELD cutoff score of 25.5 had a sensitivity of 0.727 and specificity of 0.75, was shown while a MELD cut off score of 18.5, had a sensitivity of 0.879 and specificity of 0.500. This differs from the study Tsai et al., [17] who found in 2006 that MELD cutoff level of 12 had a sensitivity of 72.22% and specificity of 65.95%. Despite the difference in MELD score cutoff levels, MELD score could be a good predictor with a considerable sensitivity and specificity as with high score values the specificity in detecting ACI increase as the MELD score gets higher the ACI could prevail.

On evaluating serum blood urea nitrogen we found that patients with ACI had a mean serum BUN level of 50.9±24.089 mg/dl, compared to 30.03±22.43 in patients without ACI who statistically significant P value of 0.012. This does not go with Tsai et al. [17], who found in 2006, that patients with ACI had a mean serum BUN level of 58.1±47.5 mg/dL, and in patients without ACI, the mean was 43.6±40.3 mg/dL with no statistical significant p value: 0.103.

Regarding serum creatinine level, our study found that patients with ACI had a mean serum creatinine level of 3.03±1.45 mg/dl, compared to 2±1.5 in patients without ACI, with a statistically significant P value of 0.027. These findings are in agreement with Tsai et al., [17] who found that the patients with ACI had mean serum creatinine level of 3.2±2.7 mg/dl and in patients without ACI the mean was 1.9±1.6 mg/dl which showed statistical significant P value: 0.004.

On the other hand Fernandez et al., [18], found that the mean serum creatinine level in patients without ACI was 2.5±2.4 mg/dL compared to 1.9±1.1 in those suffering from ACI. This disagreement might be due to the number of patient in their (25 patients vs 45 patients in our study). Also it may be due to the patients clinical status in our study, as most of them were complicated with hepatorenal syndrome while in Fernandez et al.,(18) study patients were complicated with septic shock.

On evaluating the serum Bilirubin level, our study found that there was a correlation relation between ACI and Bilirubin. Patients with ACI had a mean serum bilirubin level of 5.01±3.072 mg/dl compared to 2.4±1.35 in those without ACI statistically significant P value of 0.002. This is agreement with Tsai et al., [17] who found a significant relation between ACI and serum Bilirubin P< 0.001.

ROC curve was done and showed that the serum bilirubin may be a good predictor for ACI in liver cirrhosis patients, as the area under the curve of bilirubin was 0.811. With a serum bilirubin cutoff level of 2.75 mg/dl a sensitivity of 0.909 and specificity of 0.667 were shown. When the bilirubin had a cutoff level of 2.95 mg/dl, the sensitivity was 0.788 and specificity was 0.75. This is in agreement with Tsai et al., [17], the that serum bilirubin was an independent factor in predicting adrenal insuffiency in critically ill patients with cirrhosis and severe sepsis.

Evolutionary endocrinology provides an example of tissue corticosteroid resistance. New world monkeys (eg, squirrel monkey and cotton-top tamarin) over-express FK binding protein-51 (a GR chaperone), resulting in decreased nuclear translocation of the glucocorticoid-GR-α complex [19, 20]. In addition, these monkeys have a transcriptionally incompetent GR [20]. To overcome this inherent corticosteroid resistance, these primates have elevated circulating levels of both free and total cortisol relative to those in old world monkeys (eg, humans) [19]. Tissue corticosteroid resistance is a well known manifestation of chronic inflammatory diseases such as COPD, severe asthma, systematic lupus erythematosus, ulcerative colitis, and rheumatoid arthritis [21-24]. Emerging data suggest that corticosteroid tissue resistance may develop in patients with acute inflammatory diseases, such as sepsis and acute lung injury (ALI) [25].

In a sheep model of ALI induced by Escherichia coli endotoxin, Liu et al [26] demonstrated decreased nuclear GR-α binding capacity and increased expression of phospholipase A2 (PLA2) despite increased serum cortisol levels. These authors demonstrated similar findings in the liver cytosol following a burn injury in rats, which were partially reversed by TNF-α and IL-1β neutralizing antibodies [27]. Kino et al [28] and Kino and Chrousos [29] have demonstrated that TNF-α inhibits the transcriptional activity of the GR-α by interfering with its interaction with p160 type nuclear receptor coactivators. In an ex vivo model, Meduri et al [25] compared the cytoplasmic to nuclear density of the GR-complex in patients with ARDS whose conditions improved with that in patients that did not improve. These authors demonstrated a markedly reduced nuclear density of the GR-complex in patients who did not improve, while the cytoplasmic density was similar in patients who improved and in those who did not. This experiment provides further evidence that the nuclear glucocorticoid-GR activity may be impaired in critically ill patients despite adequate cytoplasmic (serum) levels of cortisol.

Conclusion:

Adrenocortical insufficiency (hepatoadrenal syndrome), is commonly present in patients with cirrhosis and in patients complicated with hepatorenal syndrome. In patients with liver cirrhosis adrenal dysfunction is associated with renal dysfunction, it occurs more frequently in patients with more severe liver disease and correlates with disease severity scores. According to our study MELD score and serum bilirubin level may be good predictors for hepatoadrenal syndrome.

Recommendation:

1. We recommend making further researches on hepatoadrenal syndrome and to study its effect on prognosis and complication of liver cirrhosis.
2. Further clarification is needed in terms of whether glucocorticoid supplements in this subset of patients can improve hemodynamic impairment, multiple organ dysfunction and outcomes.

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5/12/2011