

Relative Adrenal Insufficiency among Egyptian patients with liver Cirrhosis

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Abstract

Background: Cirrhotic patients are at increased risk for refractory shock and mortality due to relative adrenal insufficiency (RAI), which occurs when the adrenal cortex does not secrete enough cortisol in response to peripheral demand. This is particularly true in severely sick patients.

Aim and objectives: To evaluate and measure RAI in Egyptian cirrhotic patients.

Patients and methods: This study was carried out from November 2023 to November 2024 at the Internal Medicine Department of Sayed Galal University Hospital on 90 patients with liver cirrhosis from Egypt.

Results: Hepatitis C affects 78 people (86.67%), non-alcoholic fatty liver disease (5.56%), hepatitis B (4.44%), autoimmune illness (2.22%), and alcohol (1.11%) are the causes of liver cirrhosis. The Child-Pugh score was significantly higher in the RAI group than in the normal adrenal function group. The child Pugh score class A was significantly lower in the relative adrenal insufficiency group than in the normal adrenal function group.

Conclusion: RAI showed a high prevalence among Egyptian patients with liver cirrhosis (43.33%). Also, RAI was associated with liver disease severity, lower Hb, WBCs, platelets, albumin, Na level, and cortisol level, and higher serum creatinine, BUN, AST, ALT, and total bilirubin.

Keywords: RAI; Egyptian patients; Liver cirrhosis

1. Introduction

Cirrhotic patients are at increased risk for refractory shock and mortality due to relative adrenal insufficiency (RAI), which occurs when the adrenal cortex does not secrete enough cortisol in response to peripheral demand. This is particularly true in severely sick patients.¹

Blood cortisol levels rise as a result of hypothalamic-pituitary-adrenal axis activation, which is a significant compensatory mechanism in critical disease. Nevertheless, when circulating cytokines such as TNF-alpha and IL-6 are present, pituitary hyporesponsiveness may lower blood cortisol levels.²

There was a high incidence of RAI in patients

with liver cirrhosis who had severe sepsis or septic shock in the initial trials (51% to 77%), and these patients had a bad prognosis.³

Recent studies suggest that RAI may be a characteristic of liver disease and can be observed in non-critically ill patients with cirrhosis, with a prevalence ranging from 7 to 49%.^{4,5}

The risk of serious sepsis, type-1 hepatorenal syndrome (HRS), and short-term mortality is increased in patients with RAI, and their circulatory and renal functions are impaired to a greater extent.⁶

The aim of the current research was to evaluate and measure RAI in Egyptian cirrhotic liver patients.

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2. Patients and methods

Following permission from our institution's ethical committee, a total of ninety Egyptian patients diagnosed with liver cirrhosis and seen in the internal medicine department of Sayed Galal University Hospital between November 2023 and November 2024 participated in this study.

Inclusion criteria:

Subjects must be Egyptian nationals, of either sex, and at least 18 years old, with a history of liver cirrhosis confirmed by clinical, laboratory, and abdominal ultrasonography findings; they must also be hemodynamically stable, meaning their mean arterial pressure (MAP) is greater than 60 mm Hg, and they must not be using vasopressors.

Exclusion criteria:

Exclusion criteria include patient refusal, hepatocellular carcinoma, viral markers for HBV, HIV infection, hemodynamic instability (defined as MAP less than 60 mm Hg or vasopressor dependency on test day), history of hypothalamic-pituitary or adrenal disease, current or past use of corticosteroids or other drugs affecting steroidogenesis (e.g., etomidate, ketoconazole), and pregnancy.

Methods:

All patients were subjected to the following:

Full medical history. Full clinical examination, including signs of CLD:

This included jaundice, manifested by yellowing of the skin and sclerae. Patients exhibited signs of ascites, including abdominal distension and shifting dullness on percussion. Spider angiomas (telangiectasia), palmar erythema, and clubbing of the fingers may also be present, reflecting changes in circulation and skin microvasculature. Additionally, hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen) may be detected.

Routine laboratory investigations:

Laboratory tests that measure liver function include AST, ALT, ALP, GGT, Albumin, INR, PT, and Total and direct Bilirubin. serum creatinine (mg/dL), sodium, potassium, total cholesterol (mg/dL), HDL (mg/dL), LDL (mg/dL), baseline cortisol (nmol/L), and hepatitis C and HIV (mg/dL).

Serum creatinine assessment principle:

In a biolabo setup, time-dependent testing, the content of creatinine in a sample is directly correlated with the intensity of the colored molecule that results from its reaction with picrate in an acidic environment. We used Jaffe's Kinetic technique to measure serum creatinine.⁷

$$\text{Creatinine (mg/dl)} = \frac{(E2C - E1C)}{E2STD - E1STD} \times \text{Conc.STD}$$

Creatinine standard Blood and serum: Between 0.9 and 1.3 mg/dl (80 and 115 pmol/l) in men's serum and 0.6 and 1.1 mg/dl (53 and 97

pmol/l) in women's. Both sexes should aim for 800-2000 mg/24 h (7.1-17.7 mmol/24 h) of urine, while women should aim for 600-1800 mg/24 h (7.1-15.9 mmol/24 h).

In the morning following admission, patients underwent an ACTH stimulation test in the following manner:

At 8-9 AM, after blood samples were taken to establish baseline levels of cortisol, 250 milligrammes of synthetic adrenocorticotrophic hormone (Synacthen) was administered intravenously. At 30 and 60 minutes later, cortisol levels were re-measured. The serum was chilled to -80°C after separation. The day of the brief Synacthen test (SST) was used to gather routine hematological, lipid, biochemistry, and coagulation profiles.

After 60 minutes of SST, the adrenal function of each patient was assessed by monitoring their basal and peak cortisol levels. The indwelling intravenous catheter was implanted at least 15 minutes after samples were taken to prevent a stress-induced spike in cortisol. A conventional radioimmunoassay was used to measure serum cortisol levels.

In this study, a TC peak of 18µg/dl (497 nmol/L) and a delta cortisol level of more than 9µg/dl were considered typical responses to SST. Results from a peak cortisol level below 18µg/dL and/or a delta cortisol level below 9µg/dL were regarded as indicative of RAI in patients.⁸

Imaging includes Abdominal Ultrasound:

The abdominal ultrasound was conducted using a Toshiba alpio 500 transducer, which is 3-5MHz in frequency.

Ethical considerations:

The study adhered to all protocols set out by the Al-Azhar University Ethical Committee, and all participants were required to provide either written or verbal agreement. The privacy of the participants and the confidentiality of the data were adequately protected.

Statistical analysis:

We used SPSS v26 (IBM Inc., Chicago, IL, USA) to complete the statistical analysis. The normality of the data distribution was assessed using the Shapiro-Wilks test and histograms. We used an unpaired Student's t-test to compare the two groups' quantitative parametric variables, which were given as means and standard deviations (SD). Median and interquartile range (IQR) were used to present quantitative non-parametric data, which were examined using the Mann-Whitney test. Qualitative variables were examined using the Chi-square test or Fisher's exact test when appropriate, and were provided as frequency and percentage (%). It was deemed statistically significant if the two-tailed P-value was less than 0.05

3. Results

At Sayed Galal University Hospital's Internal Medicine Department, researchers studied 90 Egyptians suffering from liver cirrhosis.

Table 1. The demographic information of the groups under study.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
AGE(YEARS)	Mean±SD	52.9±10.35	50.86±11.45	0.386
	Range	30-69	24-71	
SEX	Male	28(71.79%)	39(76.47%)	0.614
	Female	11(28.21%)	12(23.53%)	

Age and sex were insignificantly difference between both groups, (table 1; figures 1&2).

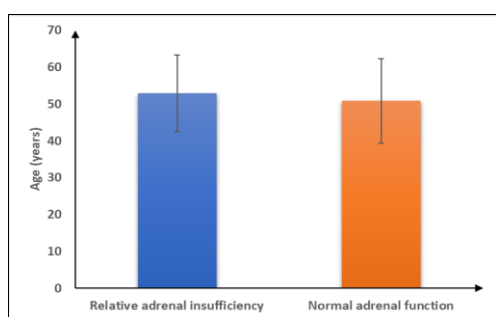


Figure 1. Ages of the groups under study.

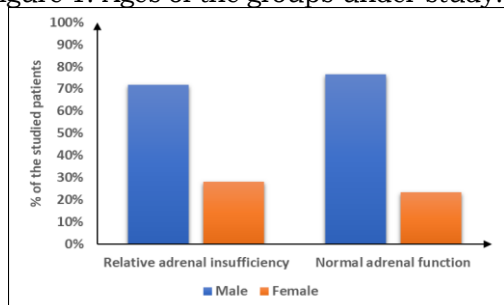


Figure 2. The sex of the groups under study.

Table 2. Child Pugh scores for the groups under study.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
CHILD PUGH SCORE	Median	8	6	<0.001 *
	IQR	7-8	5-8	
CHILD PUGH SCORE CLASSES	Class-A	7(17.95%)	31(60.78%)	<0.001 *
	Class-B	27(69.23%)	20(39.22%)	
	Class-C	5(12.82%)	0(0%)	

*:Significant as p-value<0.05.

The relative adrenal insufficiency group's kid Pugh score was substantially greater than that of the normal adrenal function group (P-value<0.001). The relative adrenal insufficiency group's kid Pugh score class-A was considerably lower than that of the normal adrenal function group (P-value<0.001),(table 2; figure 3).

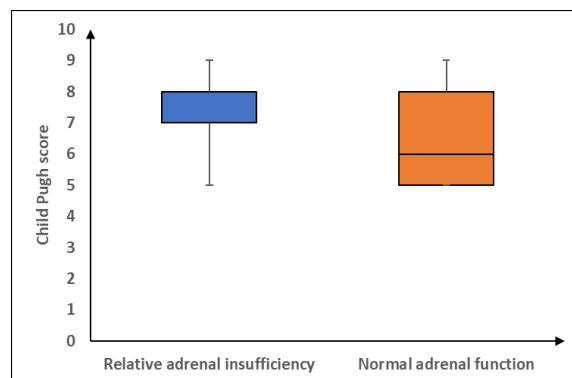


Figure 3. Child Pugh score of the studied groups.

Table 3. Liver function tests of the studied groups.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
AST(IU/L)	Mean±SD	74.08±30.23	46.73±17.43	<0.001*
	Range	31-165	29-89	
ALT(IU/L)	Mean±SD	72.64±40.04	54.86±15.85	0.005*
	Range	32-193	32-94	
TOTAL BILIRUBIN(MG/DL)	Mean±SD	1.94±0.51	1.61±0.38	<0.001*
	Range	1-3.2	1.2-2.5	
ALBUMIN(MG)	Mean±SD	3.18±0.47	3.55±0.42	<0.001*
	Range	2.3-3.9	2.6-4	
INR	Mean±SD	1.73±0.49	1.51±0.58	0.058
	Range	0.8-2.8	0.8-2.5	

*:Significant as p-value<0.05, ALT:Alanine aminotransferase, AST:Aspartate aminotransferase, INR:International normalized ratio.

The relative adrenal insufficiency group had considerably greater levels of AST, ALT, and total bilirubin than the normal adrenal function group (P-value<0.05), while the relative adrenal insufficiency group had significantly lower levels of albumin (P-value<0.001). The difference in INR between the groups with normal adrenal function and those with relative adrenal insufficiency was negligible, (table 3; figure 4).

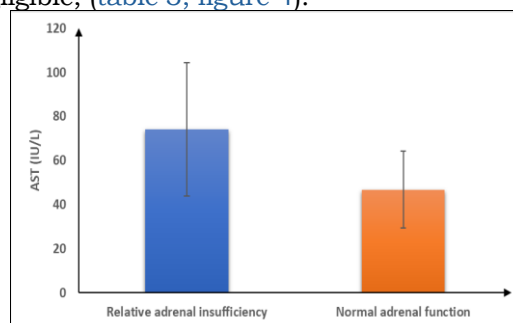


Figure 4. AST of the studied groups.

Table 4. Lipid profile test of the studied groups.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
CHOLESTEROL(MG/DL)	Mean±SD	200.21±45.48	204.47±32.16	0.604
	Range	130-360	123-280	
TRIGLYCERIDES(MG/DL)	Mean±SD	117.46±32.95	116.73±20.31	0.896
	Range	57-207	70-165	
LDL(MG/DL)	Mean±SD	115.73±38.07	116.29±26.24	0.934
	Range	47-227	59-171	
HDL(MG/DL)	Mean±SD	60.97±17	63.18±15.9	0.529
	Range	28-95	32-96	

*:Significant as p-value<0.05, LDL:Low-density

lipoprotein, HDL:High density lipoprotein.

Cholesterol, triglycerides, LDL and HDL were insignificantly different between relative adrenal insufficiency group and normal adrenal function group,(table 4; figure 5).

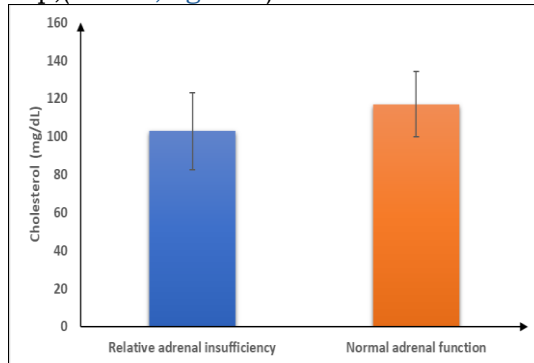


Figure 5. Cholesterol of the studied groups.

Table 5. Kidney tests of the studied groups.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
SERUM CREATININE(MG/DL)	Mean±SD	1.26±0.36	1.1±0.25	0.014*
	Range	0.6-2	0.7-1.7	
BUN(MG/DL)	Mean±SD	41.72±15.24	32.59±12.44	0.002*
	Range	20-77	20-60	

BUN:Blood urea nitrogen.

Serum creatinine and BUN were significantly higher in relative adrenal insufficiency than normal adrenal function(P-value<0.001),(table 5; figure 6).

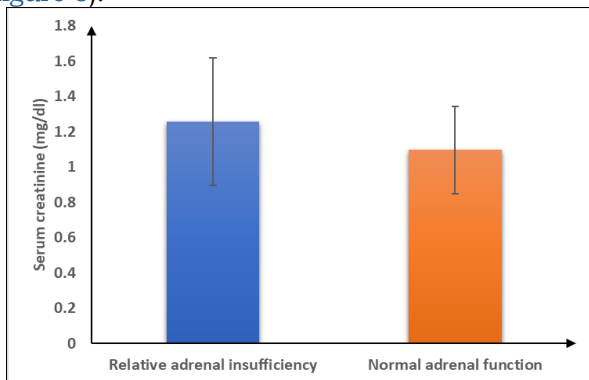


Figure 6. Serum creatinine of the studied groups.

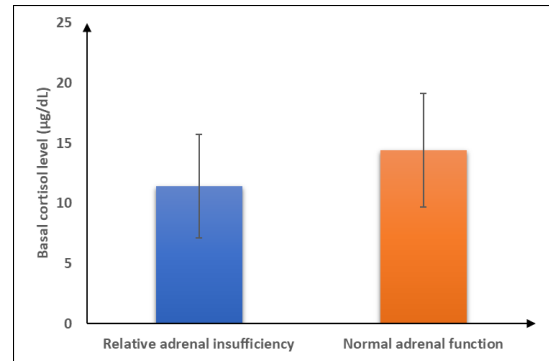
Table 6. Cortisol level of the studied groups.

		RELATIVE ADRENAL INSUFFICIENCY (N=39)	NORMAL ADRENAL FUNCTION (N=51)	P-VALUE
BASAL CORTISOL LEVEL	Mean±SD	11.44±4.28	14.43±4.72	0.003*
	Range	5-22	7-31	
30-MINUTES CORTISOL LEVEL POST-ACTH(μG/DL)	Mean±SD	15.72±4.3	27.63±4.72	<0.001*
	Range	9-26	20-40	
60-MINUTES CORTISOL LEVEL POST-ACTH(μG/DL)	Mean±SD	18.59±4.12	36.18±5.3	<0.001*
	Range	11-27	24-46	
DELTA CORTISOL LEVEL(μG/DL)	Mean±SD	4.28±1.12	13.14±1.78	<0.001*
	Range	3-6	9-16	

*:Significant as p-value<0.05

Compared to normal adrenal function, basal cortisol levels, 30- and 60-minute post-ACTH cortisol levels, and delta cortisol levels were

considerably lower in cases of relative adrenal insufficiency (P-value<0.05),(table 6; figure 7).



Figure(7):Baseline cortisol level of the studied groups.

Table 7. RAI of the studied patients.

RAI	(N=90)	
	Yes	No
	39(43.33%)	51(56.67%)

RAI:Relative adrenal insufficiency.

RAI was present in 39(43.33%) patients, (table 7; figure 8).

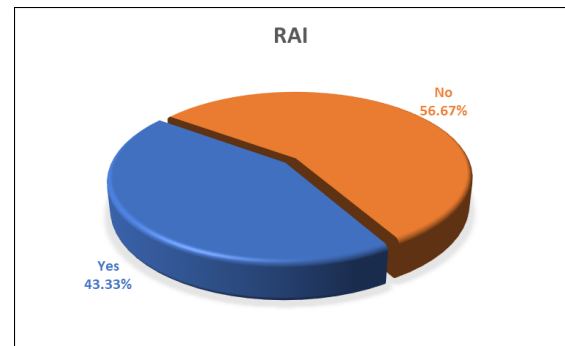


Figure 8. RAI of the studied patients.

4. Discussion

In reaction to stress or physical sickness, the adrenal gland releases glucocorticoids, a class of corticosteroids. Their principal role is to increase levels of anti-inflammatory proteins, which in turn decreases the body's inflammatory response.⁸

Insufficient production of cortisol and other glucocorticoid hormones by the adrenal gland is known as adrenal insufficiency.^{9,10}

In the current study, age ranged from 24 to 71 years with a mean value(±SD) of 51.7(±10.97) years. There were 67(74.44%) males and 23(25.56%) females.

This agreed with Siramolpiwat et al.,¹¹ They examined the frequency of RAI and its predictive value in 115 cirrhotic patients who were not in critical care. They found that men made up 66% of the group and that the average age was 59.9±16 years.

The results showed that hepatitis-C in

78(86.67%) patients, non-alcoholic fatty liver disease in 5(5.56%) patients, hepatitis-B in 4(4.44%) patients, autoimmune disease in 2(2.22%) patients, and alcohol in 1(1.11%) patient were the causes of liver cirrhosis.

Supporting our results, Fede et al.,⁶ looked at adrenal insufficiency in cirrhosis patients who did not have infection or hemodynamic instability by studying 101 consecutive patients with cirrhosis. They found that alcoholic liver disease was the cause of cirrhosis in 25% of cases and viral liver disease in 47%.

Possible explanations for these discrepancies with our findings include cultural and environmental factors.

The median (IQR) Child Pugh score in this research was 7 (range: 6-8). Class-A was the Child Pugh score for 38 patients (42.22%), class-B for 47 patients (52.22%), and class-C for five patients (5.56%).

Consistent with what we found, Siramolpiwat et al.,¹¹ found that 30.4% had a Child Pugh score of C, 53.9% had a class B, and 15.7% had a class A.

In our study, Hb ranged from 8 to 14.6g/dl with a mean value (\pm SD) of 10.9(\pm 1.34) g/dl. WBCs ranged from 1 to 11.1 \times 10⁹/L with a mean value (\pm SD) of 6.9(\pm 2.14) 10⁹/10⁹/L. Platelets ranged from 55 to 304 10⁹/L with a mean value(\pm SD) of 150.9(\pm 54.34) 10⁹/L.

However, Elfaramawy,¹² observed that the mean platelet count was 201.3 \times 10³/mL, and the mean leukocyte count was 5.9 \times 10³/mL.

In the present study, the AST ranged from 29 to 165U/L with a mean value(\pm SD) of 58.6(\pm 27.32) U/L. The ALT ranged from 32 to 193U/L with a mean value(\pm SD) of 62.6(\pm 30.07) U/L. The total bilirubin ranged from 1 to 3.2mg/dL with a mean value(\pm SD) of 1.8(\pm 0.47) mg/dL. The albumin ranged from 2.3 to 4mg with a mean value(\pm SD) of 3.4(\pm 0.48) mg. INR ranged from 0.8 to 2.8 with a mean value(\pm SD) of 1.6(\pm 0.55).

In this context, Piano et al.,¹³ showed that median (IQR) albumin was 3.1 g/dL, median INR was 1.5 and median bilirubin was 3.6 mg/dL.

Also, Elfaramawy,¹² noted that the mean AST was 126.7 IU/L, ALT was 101.3 IU/L, albumin was 3.3gm/dL, total bilirubin was 7.7 mg/dL, and INR was 1.2 in cirrhotic children.

In this study, cholesterol ranged from 123 to 360mg/dL with a mean value(\pm SD) of 202.6(\pm 38.32) mg/dL. The triglycerides ranged from 57 to 207mg/dL with a mean value(\pm SD) of 117.04(\pm 26.37) mg/dL. The LDL ranged from 47 to 227mg/dL with a mean value(\pm SD) of 116.05(\pm 31.71) mg/dL. The HDL ranged from 28 to 96 mg/dL with a mean value(\pm SD) of 62.2(\pm 16.33) mg/dL.

However, Fede et al.,⁶ observed that total

cholesterol was 130(mg/dl), LDL was 80 mg/dl, and HDL was 29mg/dl.

Regarding our results, serum creatinine ranged from 0.6 to 2mg/dL with a mean value(\pm SD) of 1.2(\pm 0.31) mg/dL. BUN ranged from 20 to 77mg/dL with a mean value(\pm SD) of 36.5(\pm 14.38) mg/dL. However, in Elfaramawy, 12 study, they found that mean creatinine was 0.4 mg/dL.

Our results revealed that Na level ranged from 124 to 138mEq/L with a mean value(\pm SD) of 131.5(\pm 2.88) mEq/L. K level ranged from 3.5 to 4.6mEq/L with a mean value(\pm SD) of 3.97 \pm 0.31 mEq/L.

This agreed with Elfaramawy,¹² , the average sodium level in cirrhotic individuals was 132.1 mEq/L and the average potassium level was 3.8 mEq/L.

In the current study, basal cortisol level ranged from 5 to 31 μ g/dL with a mean value(\pm SD) of 13.1(\pm 4.75) μ g/dL and was significantly higher at 30 30-minutes and 60 minutes post-adrenocorticotrophic hormone than baseline. Peak cortisol level ranged from 20 to 40nmol/L with a mean value(\pm SD) of 27.8(\pm 4.83) μ g/dL. Delta cortisol level ranged from 3 to 16 μ g/dL with a mean value(\pm SD) of 9.3(\pm 4.67) μ g/dL. Near our results, Fede et al.,⁶ found that basal cortisol level was 11.2(7.7-16.4) μ g/dl.

In our study, RAI was present in 39(43.33%) patients. Supporting our results, Wentworth et al.,¹⁴ conducted a systematic review and meta-analysis on 22 studies comprising 1991 patients with cirrhosis. They showed that the pooled prevalence of RAI was 37%.

In the same line, Siramolpiwat et al.,¹¹ found that RAI prevalence was 30.4% in patients with liver cirrhosis.

This study revealed that the child Pugh score was significantly higher in the RAI group than in the normal adrenal function group. The child Pugh score class-A was significantly lower in the relative adrenal insufficiency group than in the normal adrenal function group.

This came in line with Wentworth et al.,¹⁴ who demonstrated that RAI prevalence varied according to Child-Pugh classification; patients classified as Child-Pugh C had the highest prevalence (64%), followed by those classified as Child-Pugh B (39%), and Child-Pugh A (27%).

Compared to the group with normal adrenal function, the group with RAI had much reduced hemoglobin, white blood cell, and platelet counts.

On the other hand, Siramolpiwat et al.,¹¹ found no statistically significant difference in white blood cell count or platelet count between the RAI group and the control group. The primary cause of cirrhosis in this study was chronic alcohol drinking; therefore, the gap could be due to differences in baseline characteristics.

Albumin levels were considerably lower in the

RAI group compared to the normal adrenal function group, whereas AST, ALT, and total bilirubin were significantly higher in the RAI group. Neither the RAI group nor the group with normal adrenal function showed a statistically significant difference in INR.

Supporting our results, Siramolpiwat et al.,¹¹ the albumin level was considerably lower in the group who received RAI compared to the group that did not. They did find that there was no statistically significant difference in AST, ALT, and total bilirubin levels between the groups that received RAI and those that did not.

When comparing normal adrenal function to relative adrenal insufficiency, we found that the latter was characterized by much higher serum creatinine and BUN levels.

Consistent with our results, Acevedo et al.,⁵ discovered that RAI was linked to elevated BUN.

While there was no statistically significant difference in K levels between the two groups, the present investigation found that Na levels were substantially lower in RAI compared to normal adrenal function.

Consistent with what we found, Acevedo et al.,⁵ found that the sodium level in RAI was much lower than in normal adrenal function.

All three of these cortisol levels—basal, 30 and 60 minutes post-ACTH, and delta—were considerably lower in RAI compared to normal adrenal function, according to our findings.

Consistent with what we found, Siramolpiwat et al.,¹¹ discovered that compared to the non-RAI group, patients with RAI had noticeably lower delta blood cortisol levels.

Limitations:

We did not evaluate serum-free cortisol; the sample size was limited, the study only involved one location, and there was no healthy control group.

4. Conclusion

RAI showed a high prevalence among Egyptian patients with liver cirrhosis (43.33%). Also, RAI was associated with liver disease severity, lower Hb, WBCs, platelets, albumin, Na level, and cortisol level, and higher serum creatinine, BUN, AST, ALT, and total bilirubin.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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