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Research Article

Adrenal Insufficiency Is A Common Finding In Chronic Hepatitis C Patients Regardless Of Cirrhosis.

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Abstract

EA and YZ were concerned with the design of the study; ME and HM were responsible about statistical analysis; HM performed the PCR and laboratory parameters; NM was responsible for radiological examination and EA, MF and AH analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Background: Chronic hepatitis C virus (HCV) infection is a real public health issue and a major contributor to liver-related morbidity and death because of its propensity for liver fibrosis, cirrhosis, and cancer. Several extra-hepatic illnesses that affect the kidneys, skin, salivary glands, eyes, thyroid, joints, neurological system, and immune system have also been linked to HCV infection. Adrenal insufficiency (AI) was demonstrated in patients with cirrhosis and liver failure.

Objective: We aimed to detect serum cortisol levels and ACTH levels in patients with HCV and liver cirrhosis and study the relationship between liver function and adrenal insufficiency.

Methods: Our study included 240 HCV patients subdivided into four groups: Group 1: Included 60 with chronic HCV without cirrhosis. Group 2: It included 60 patients with HCV-related compensated cirrhosis. Group3: included 60 patients with HCV decompensated cirrhosis, and Group 4 included 60 healthy volunteers.

Results: ACTH level was significantly higher in all HCV groups than in the control group ($p<0.001$), also, delta cortisol was significantly lower in all HCV groups than in the control group groups ($p=0.021$). The prevalence of AI among patients with decompensated cirrhosis, compensated, and chronic hepatitis was 25%, 15%, and 11.7%, respectively.

Conclusion: AI could be encountered in patients with chronic HCV without liver cirrhosis and is typical in cirrhotic individuals without signs of sepsis or hemodynamic disturbance.

Keywords : *Adrenal cortex hormones, Hepatitis C virus, liver cirrhosis, liver failure, ACTH.*

INTRODUCTION

Hepatitis C virus (HCV) is related to numerous autoimmune endocrinal disorders, particularly thyroid, yet additionally affects the hypothalamus, pituitary, and kidneys[1]. Metabolism of hormones occurs mainly in the liver. In this manner, hepatic disorders were related to different endocrine diseases[2]. Adrenal insufficiency (AI) was demonstrated in patients with cirrhosis and liver failure. Additionally, AI in liver diseases is due to low production of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and high level of endotoxins in the blood[3]. The precursors of all adrenal hormones and cortisol binding globulin are stored in the liver. Cortisol is the primary glucocorticoid (GC) hormone synthesized, secreted in the adrenal cortex, and regulated by adrenocorticotropic hormone (ACTH), which is released from the pituitary gland[4]. AI may occur in both stable and critically ill cirrhotic patients (sepsis, septic shock, and gastrointestinal bleeding). AI was related to liver disease severity. It is not associated with the cause of cirrhosis[5]. The relationship between the HCV virus and whether it affects the gland directly is unclear. Our study

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aimed to detect serum cortisol levels and ACTH levels in patients with chronic HCV and liver cirrhosis and investigate the relationship between liver function and AI.

MATERIALS AND METHODS

Study subjects

This case-control hospital-based study was conducted from June 2018 to June 2019. Our study included 240 patients and included four groups. Group I included 60 chronic HCV patients. and Group II included 60 HCV-related compensated cirrhosis patients. Group III: it included 60 HCV decompensated cirrhosis patients. Group VI: It included 60 people (healthy volunteers). Patients with autoimmune diseases, chronic hepatitis rather than HCV infection, patients who received corticosteroids, and patients with other causes of adrenal dysfunction rather than CHC were excluded from our study.

Clinical and Laboratory Assessment

Diagnosis of HCV-related chronic hepatitis was based on the positivity of anti-HCV antibodies by EIA for ≥ 6 months and confirmed by detecting HCV RNA by PCR. Diagnosis of liver cirrhosis was based on clinical symptoms and signs of a liver cell failure, portal hypertension, and relevant findings in abdominal ultrasound and grade of fibrosis in elastography and standard laboratory data. Adrenal CT was done to exclude the presence of adenoma, hemorrhage, hyperplasia, or calcifications as a cause of AI. Ultrasound elastography was done using Toshiba Alpio 500. Complete blood count was determined by an automated cell counter (Celltac ES, Nihon Kohden Corporation, Automated hematology analyzer, Japan). INR: fully automated coagulometer (STAGO Diagnostic -STAGO – France). Using a fully automated clinical chemistry auto-analyzer equipment (Auto-analyzer Selectra proM, ELITech Group, clinical chemistry automation systems, Finland), RBG, renal function tests, and liver function tests were assessed. MINI VIDAS (automated immunoassay system based on the Enzyme-Linked Fluorescent Assay (ELFA) principles- bioMérieux- France) was used to assess the viral markers. Real-time polymerase chain reaction (PCR) was used to identify HCV RNA by DT-Lite 48 (DNA –technology, Russia). The EIA method assigned ACTH (the kit was supplied by Abcam-china, catalog no. ab267814). The measure of serum cortisol by EIA technique (Abcam-china supplied h=kit, catalog no. ab108665). Basal ACTH, basal cortisol, and delta cortisol levels (Peak cortisol – basal cortisol) were assessed in all patient groups and control group, while serum cortisol after injection of synthetic ACTH (ACTH stimulation test) was assessed in patients only.

Statistical analysis

Mean±SD and range were used to express quantitative parametric measures. Numbers and percentages were used to express categorized data. Analysis of variance (ANOVA) was utilized to compare parametric data among groups, followed by an LSD post hoc test to detect differences among groups. The Student t-test was used to compare two independent groups for parametric data, and the Chi-square test or Fisher's exact test was used to compare categorical variables. Pearson correlation was used to detect correlations between the parameters. A P-value of 0.05 or less was considered significant, whereas values of 0.01 and 0.001 were considered highly significant.

RESULTS

Decompensated cirrhotic group (group III) had the highest age with a mean of (61.8±5.8) years. Hypotension was higher among the decompensated cirrhotic group (30%). The lowest ranges of Hb and platelet were detected in the decompensated group. The mean platelet number was significantly lower among decompensated group than in other groups (P=129.3±68.8). There was a significant increase in INR and bilirubin in decompensated group vs. others and a significant decrease in serum albumin (P<0.001). PCR of compensated cirrhosis and decompensated cirrhosis were (165450, 312513, and 325026), respectively. There was a statistically significant difference among groups regarding creatinine level (P<0.001) (**Table 1**).

A statistically significant difference was found between (decompensated cirrhosis &control group) in peak cortisol levels (**Table 2&Figure 1**). The percentage of AI prevalence was (25%, 15%, and 11.7%) among (decompensated cirrhosis, compensated, and chronic hepatitis) respectively (**Table 3&Figure 2**). When comparing various characteristics among the AI group (N=31) and the normal adrenal function group (N=149), a statistically significant difference was found regarding age (p<0.001) and occupation (p 0.028). Hb level, platelet count, and serum albumin were also significantly lower in the group with AI Vs. the normal one (P<0.001). INR also showed a significantly higher level in the AI group vs. the normal one. Also, ALT, Total bilirubin, and creatinine showed significantly higher in the AI group than in the normal one (**Table 4**). There was a significant difference regarding ACTH, baseline morning serum cortisol, and Peak and Delta Cortisol between AI and normal adrenal function groups, with means of 125.5±33.6 for baseline morning serum cortisol, While 372.29±72.03 for peak cortisol and 246.8±51.1 for delta cortisol in AI group (**Table 5**). A significant fair negative correlation between baseline morning serum cortisol and (age and ACTH), A significant fair negative correlation between Peak and (age, creatinine, and ACTH), A significant fair, positive correlation between delta cortisone and serum albumin, and a significant fair negative correlation between delta cortisone

and (Hb and creatinine) were detected in CHC patients (**Table 6**). In compensated cirrhosis, there was a significant fair negative correlation between baseline morning serum cortisol and age. However, there was a significant moderate positive correlation with Hb. Also, there was a significant fair negative correlation between peak cortisone and (Age & total bilirubin) in the same group.

Additionally, there was a significant fair, positive correlation between delta cortisone &Hb. (**Table 7**). In compensated cirrhosis, there was a significant fair negative correlation between (baseline morning serum cortisol and (INR &ACTH), a significant fair, positive correlation between baseline morning serum cortisol and (platelets, AST, and direct bilirubin), significant fair negative correlation between Peak and (INR, ALT, and ACTH), and a significant fair, positive correlation between Delta cortisone and (platelets &serum) (**Table 8**).

Figure 1. baseline and peak cortisol values among study groups.

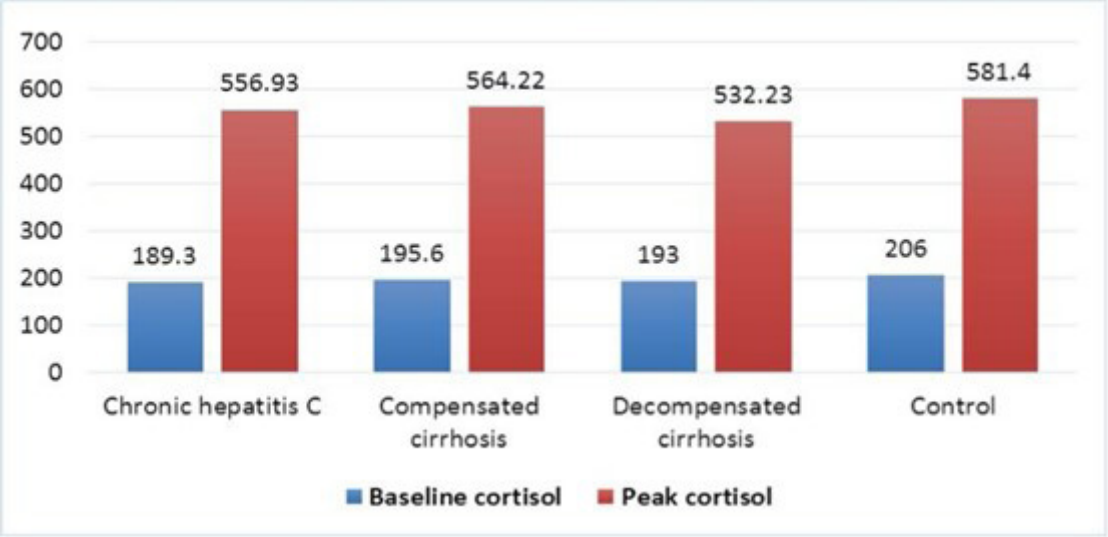

Figure 2. prevalence of adrenal insufficiency among different studied groups.

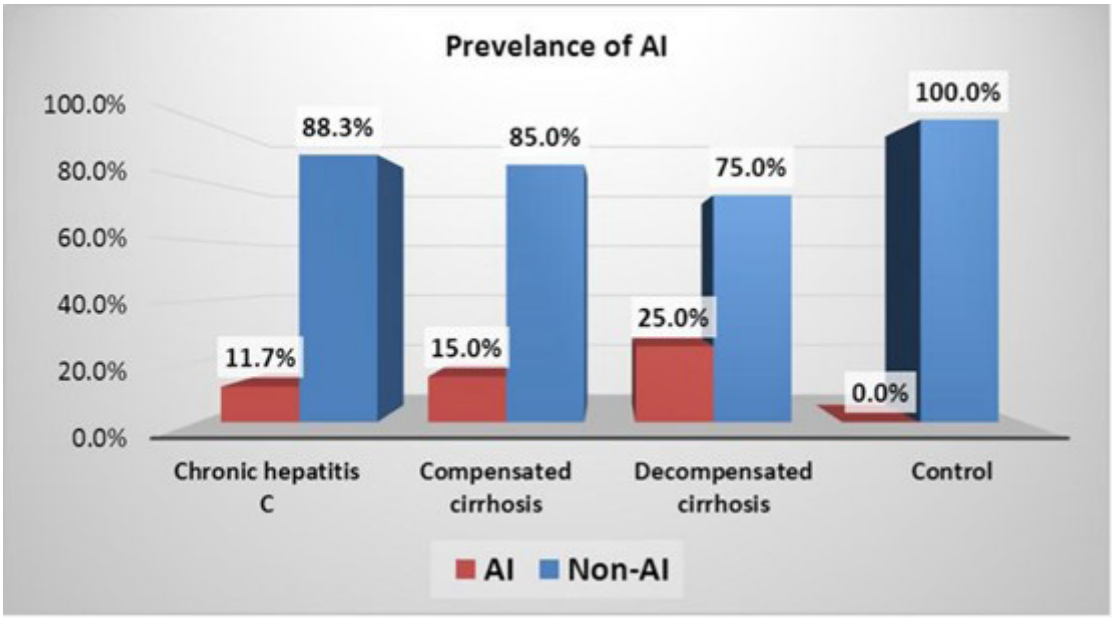

Table 1. Sociodemographic, clinical characters and laboratory among different study groups.

	Chronic hepatitis C (I)	Compensated cirrhosis (II)	Decompensated cirrhosis (III)	Control (C)	p value
	(n=60)	(n=60)	(n=60)	(n=60)	
Age (years) Mean±SD (Range)	 37.6±13.6 (18-65)	 37.3±13.8 (18-65)	 61.8±5.8 (47-75)	 30.8±9.6 (18-50)	 <0.001*
Sex Male Female	 21 (35.0%) 39 (65.0%)	 36 (60.0%) 24 (40.0%)	 44 (73.3%) 16 (26.7%)	 25 (41.7%) 35 (58.3%)	 <0.001*
Occupation Employed Unemployed	 31 (51.7%) 29 (48.3%)	 33 (55.0%) 27 (45.0%)	 26 (43.3%) 34 (56.7%)	 54 (90.0%) 6 (10.0%)	 <0.001*
Smoking Smoker Non-smoker	 21 (35.0%) 39 (65.0%)	 21 (35.0%) 39 (65.0%)	 20 (33.3%) 40 (66.7%)	 13 (21.7%) 47 (78.3%)	 0.324
Hypertension Hypotensive Normotensive Hypertensive	 8 (13.3%) 48 (80.0%) 4 (6.7%)	 12 (20.0%) 48 (80.0%) 0 (0.0%)	 18 (30.0%) 34 (56.7%) 8 (13.3%)	 0 (0.0%) 60 (100%) 0 (0.0%)	 <0.001*
INR Mean±SD (Range)	 1.12±0.19 (1-1.76)	 1.18±0.17 (1-1.8)	 1.46±0.36 (1-2.2)	 0.99±0.05 (0.9-1.1)	 <0.001*
Serum albumin Mean±SD (Range)	 4.5±0.5 (3.5-5.9)	 3.7±0.1 (3.5-3.9)	 2.6±0. 6(1.6-3.8)	 4.5±0.6 (3.5-5.7)	 <0.001*
ALT Mean±SD (Range)	 45.5±26.3 (20-128)	 72.9±28.2 (18-99)	 46.3±26.3 (15-111)	 16.6±2.9 (11-20)	 <0.001*
AST Mean±SD (Range)	 45.3±24.5 (18-103)	 75.7±24.8 (29-98)	 50±24.9 (16-115)	 15.7±3.4 (10-20)	 <0.001*
T.BIL Mean±SD (Range)	 0.68±0.22 (0.11-1.2)	 0.93±0.06 (0.87-1)	 1.45±0.56 (0.4-2.1)	 0.51±0.2gv8 (0.18-1.2)	 <0.001*
D.BIL Mean±SD (Range)	 0.23±0.16 (0.1-0.7)	 0.37±0.19 (0.1-0.6)	 0.92±0.44 (0.1-1.8)	 0.28±0.24 (0.1-0.9)	 <0.001*
PCR Median (IQR)	 165450 (32800-520000)	 312513 (45600-757500)	 325026 (55684-925000)	 0.414	 -
HB Mean±SD (Range)	 12.8±1.4 (10.2-15.4)	 12.9±1.4 (10.2-14)	 9.5±2 (4.5-12.5)	 12.8±1 (12-15.4)	 <0.001*
TLC (x103) Mean±SD (Range)	 6.4±1.9 (1.9-9.3)	 8.3±2.2 (4.5-11.3)	 5.8±2.5 (2.5-13.4)	 5.8±1.5 (4-11)	 <0.001*
PLT (x103) Mean±SD (Range)	 250.9±83.2 (53-427)	 241.8±70 (186-370)	 129.3±68.8 (54-274)	 256.1±65.4 (150-450)	 <0.001*
Creatinine Mean±SD (Range)	 0.9±0.2 (0.6-1.3)	 0.9±0.2 (0.6-1.3)	 1±0.2 (0.6-1.5)	 0.7±0.3 (0.4-1.5)	 <0.001*

Table 2. Hormone profile at baseline and post Synacthen test. Anova test for comparison between different groups

	Chronic hepatitis C (I)	Compensated cirrhosis (II)	Decompensated cirrhosis (III)	Control (C)	p value
	(n=60)	(n=60)	(n=60)	(n=60)	
Baseline					
ACTH (nmol/L) Mean±SD (Range)	 71.5±12.6 (55-110)	 72.2±11.6 (40-90)	 88.6±25.5 (38-123)	 48.5±10 (24-72)	 <0.001*
Baseline cortisol (nmol/L) Mean±SD (Range)	 189.3±54.4 (102-353)	 195.6±45.4 (110-310)	 193±52.6 (90-300)	 206±68.7 (140-385)	 0.401
Post SST					
Peak cortisol (nmol/L) Mean±SD (Range)	 556.93±97.38 (312-751)	 564.22±96.41 (323-750)	 532.23±111.9 (282-714)	 581.4±84.52 (500-860)	 0.053
Delta cortisol (nmol/L) Mean±SD (Range)	 367.7±69.7 (200-520)	 368.6±78.6 (213-550)	 339.2±70.6 (170-434)	 375.4±51.7 (289-520)	 0.021*

Table 3. Prevalence of adrenal insufficiency in different groups.

Diagnosis and definition of AI	Chronic hepatitis C (I)	Compensated cirrhosis (II)	Decompensated cirrhosis (III)	Control (C)	p value
	(n=60)	(n=60)	(n=60)	(n=60)	
Basal cortisol <138 nmol/L)	5 (8.3%)a	7 (11.7%)a	12 (20.0%)a	0 (0.0%)b	0.003*
Peak cortisol <500 nmol/L)	7 (11.7%)a	9 (15.0%)a	15 (25.0%)a	0 (0.0%)b	0.001*
Δ cortisol <250nmol/L)	5 (8.3%)	5 (8.3%)a	8 (13.3%)a	0 (0.0%)b	0.021*
ATCH >72	 11 (18.3%)	 35 (58.3%)	 45 (75.0%)	 0 (0.0%)	 <0.001*

Each superscript letter denotes a subset of group whose column proportions do not differ significantly from each other at the .05 level. A Chi square test and Fisher's exact test was used to compare between proportions.

Table 4. Demographic, clinical data and Biochemical profiles of AI and normal adrenal function groups.

	patients with AI (SST)	patients with normal adrenal function (SST)	p value
	(N=31)	(N=149)	
Age Mean±SD (Range)	 62±7 (36-75)	 46.6±15.5 (18-75)	 <0.001*
Sex Male Female	 18 (58.1%) 13 (41.9%)	 108 (51.7%) 101 (48.3%)	 0.506
Occupation Employed Unemployed	 13 (41.9%) 18 (58.1%)	 131 (62.7%) 78 (37.3%)	 0.028*
Smoking Smoker Non-smoker	 14 (45.2%) 17 (54.8%)	 61 (29.2%) 148 (70.8%)	 0.073
Hypotensive Normal Hypertensive	8 (25.8%) 23 (74.2%) -	18 (8.6%) 181 (86.6%) 10 (4.8%)	 0.089
HB Mean±SD (Range)	 10.7±2.7 (4.5-15.1)	 10.7±2.7 (5.3-15.4)	 <0.001*

TLC Mean±SD (Range)	 6.6±2.1 (4-11.3)	 6.6±2.3 (1.9-13.4)	 0.985
platelet Mean±SD (Range)	 169.7±81.9 (65.8-370)	 226.9±87.6 (53-450)	 0.001*
INR Mean±SD (Range)	 1.36±0.31 (1-2.1)	 1.16±0.27 (0.9-2.2)	 <0.001*
Serum albumin Mean±SD (Range)	 3.5±0.9 (2.2-5.2)	 3.9±0.9 (1.6-5.9)	 0.033*
ALT Mean±SD (Range)	 59.4±30.3 (15-111)	 43.2±30.2 (11-128)	 0.006*
AST Mean±SD (Range)	 54.3±28 (16-115)	 45.5±30.4 (10-115)	 0.134
Total bilirubin Mean±SD (Range)	 1.1±0.52 (0.27-2)	 0.86±0.47 (0.11-2.1)	 0.012*
Direct bilirubin Mean±SD (Range)	 0.58±0.42 (0.1-1.3)	 0.43±0.38 (0.1-1.8)	 0.05
Creatinine Mean±SD (Range)	 1±0.3 (0.6-1.5)	 0.9±0.2 (0.4-1.5)	 0.007*

*A p-value of <0.05 is considered statistically significant. Subgroup analysis of AI and non-AI patients according to the peak cortisol criteria (>500 nmol/L). Independent sample t- test was used.

Table 5. Hormonal profile of AI and normal adrenal function groups.

	AI (SST)	**Normal adrenal function (SST)**	**p value**
	(N=31)	**(N=149)**	
ACTH Mean±SD (Range)	 89.3±20.3 (51-123)	 67.4±20.2 (24-120)	 <0.001*
ACTH			<0.001*
≤72	7 (22.6%)	142 (67.9%)	
>72	24 (77.4%)	67 (32.1%)	
Baseline morning serum Cortisol Mean±SD (Range)	 125.5±33.6 (90-220)	 206.4±50.8 (112-385)	 <0.001*
Peak cortisol Mean±SD (Range)	 372.29±72.03 (282-500)	 586.34±67.6 (500-860)	 <0.001*
Delta cortisol Mean±SD (Range)	 246.8±51.1 (170-368)	 379.9±53.4 (280-550)	 <0.001*

Table 6. Correlation analysis for basal serum cortisol, post-cosyntropin cortisol, and delta fraction versus rest of the parameters among chronic hepatitis C patients (n=60).

Chronic hepatitis C	base line morning serum cortisol		Peak		DeltaC	
	r	p	r	p	p	R
Age	-0.277	0.032*	-0.284	0.028*	-0.181	0.167
HB	0.022	0.865	-0.215	0.099	-0.318	0.013*
MCV	-0.29	0.025*	-0.385	0.002*	-0.312	0.015*
TLC	-0.061	0.643	-0.181	0.167	-0.205	0.116
Platelet	0.201	0.124	0.16	0.223	0.066	0.615
INR	-0.063	0.633	-0.188	0.15	-0.214	0.101
Serum albumin	0.122	0.354	0.301	0.019*	0.326	0.011*
ALT	-0.117	0.374	-0.054	0.679	0.015	0.909
AST	-0.179	0.171	-0.087	0.51	0.019	0.888
Total bilirubin	0.365	0.004*	0.36	0.005*	0.218	0.095
Direct bilirubin	-0.053	0.687	-0.207	0.113	-0.248	0.056
Creatinine	-0.149	0.255	-0.314	0.015*	-0.322	0.012*
ACTH	-0.358	0.005*	-0.266	0.04*	-0.092	0.483

Interpretation for correlation: (+ve) value of r means positive correlation (-ve) value of r means negative correlation if r: Up to 0.25 (weak correlation), if r: 0.25 to 0.50 (fair correlation), if r: 0.50 to 0.75(moderate correlation),If r :0.75 to 1 (strong correlation) andSignificant correlation if P value < 0.05.

Table 7. Correlation analysis for basal serum cortisol basal, post-cosyntropin cortisol, and delta fraction versus rest of the parameters among patients with compensated cirrhosis (n=60).

Compensated cirrhosis	base line morning serum Cortisol		Peak		DeltaC	
	r	p	r	p	p	R
Age	-0.349	0.006*	-0.256	0.048*	-0.112	0.393
HB	0.5	<0.001*	0.496	<0.001*	0.32	0.013*
MCV	-0.271	0.037*	-0.216	0.098	-0.108	0.41
TLC	0.369	0.004*	0.357	0.005*	0.225	0.084
Platelet	0.12	0.361	0.067	0.61	0.013	0.92
INR	-0.078	0.553	-0.038	0.77	-0.002	0.988
Serum albumin	0.378	0.003*	0.252	0.052	0.09	0.494
ALT	0.03	0.821	-0.039	0.768	-0.065	0.622
AST	0.134	0.308	0.038	0.771	-0.03	0.818
Total bilirubin	-0.514	<0.001*	-0.44	<0.001*	-0.243	0.061
Direct bilirubin	-0.217	0.096	-0.246	0.058	-0.177	0.176
Creatinine	-0.024	0.853	0.123	0.35	0.165	0.208
ACTH	-0.232	0.075	-0.015	0.911	0.116	0.379

Table 8. Correlation analysis for basal serum cortisol basal, post-cosyntropin cortisol, and delta fraction versus rest of the parameters among patients with decompensated cirrhosis (n=60).

Decompensated cirrhosis	base line morning serum Cortisol		Peak		DeltaC	
	r	p	r	p	p	R
Age	-0.085	0.52	-0.159	0.224	-0.19	0.147
RBS	-0.3	0.02*	-0.267	0.039*	-0.2	0.125
HB	0.043	0.746	0.13	0.324	0.174	0.185
MCV	-0.039	0.768	0.004	0.973	0.036	0.785
TLC	-0.051	0.697	-0.039	0.768	-0.023	0.859
Platelet	0.353	0.006*	0.312	0.015*	0.339	0.008*
INR	-0.39	0.002*	-0.352	0.006*	0.12	0.363
Serum albumin	0.323	0.012*	0.256	0.048*	0.319	0.013*
ALT	-0.287	0.026*	-0.278	0.032*	-0.144	0.272

AST	0.266	0.04*	0.155	0.238	0.048	0.718
Total bilirubin	0.156	0.233	0.076	0.564	0.004	0.977
Direct bilirubin	0.311	0.016*	0.214	0.101	0.108	0.413
Creatinine	0.008	0.952	0.053	0.689	0.078	0.556
ACTH	-0.315	0.014*	-0.255	0.049*	-0.169	0.195

DISCUSSION

AI in liver cirrhosis and failure is a condition of decreased cortisol response in critical illness or stress in the absence of structural defects in the hypothalamic-pituitary-adrenal axis[6]. This condition occurs mainly in the critical illness in addition to hemodynamically unstable liver cirrhosis patients suffering from sepsis where corticosteroids may decrease mortality. Other studies have reported that AI is common in patients with stable cirrhosis without sepsis. This study aimed to assess AI incidence in patients with stable cirrhosis, decompensated cirrhosis, and chronic HCV.

AI occurs because of the low production of total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol in cases of liver cirrhosis with an elevation in circulating lipopolysaccharides levels[7]. There is disagreement on the proper assays and normal values to assess adrenal function in the context of liver disease; as a result, normal ranges and methods need to be standardized.. The use of total cortisol to evaluate adrenal function overestimates AI in patients with cirrhosis because of low levels of cortisol-binding protein, so direct free cortisol measurement or its surrogates might be used to detect AI[8]. Additionally, there are problems with adreno-cortico-tropic-hormone (ACTH) stimulation tests[9].

In our study, we found that hypotension was discovered in decompensated cirrhosis 30%, over-compensated group 20%, and chronic hepatitis 13.3%. Hypotension is an established complication in patients with cirrhosis due to portal hypertension, which causes splanchnic and systemic vasodilatation [10]. According to our results, the hypotension may be due to the AI, which is more predominant in the decompensated group than in other groups. Our results showed that the prevalence of AI according to basal cortisol level (<138 nmol/L) is 20% in decompensated cirrhosis while 11.7% in compensated cirrhosis and 8.3% in CHC patients, While according to peak cortisol level <500 nmol/L) is 25% in decompensated cirrhosis and 15% in compensated, and 11.7%, while delta cortisol <250nmol/l is 13.3% in decompensated and 8.3%in compensated and CHC. This result is in agreement with Kharb et al. (2013)[11]. They found an increase in the percentage of patients with adrenal dysfunction with the progression of liver disease as evaluated by Child-Pugh staging. They also detected that the AI had improved after liver transplantation. Trifan and his colleagues (2013) showed that the prevalence of AI was higher in patients with liver cirrhosis and acute diseases as in cases of septicemia and septic shock unlike other chronic diseases[12]. In addition, cirrhosis with AI was accompanied by a worse prognosis and higher complications than cirrhotic patients without AI.

Additionally, (Acevedo et al., 2013) showed that AI was 26% in decompensated cirrhotic patients, and in cirrhotic patients with septic shock, the occurrence of AI was 76%[13]. AI occurrence in hemodynamically stable patients with cirrhosis has been recently raised. Fede et al., 2011[14] reported that AI was detected in hemodynamically stable patients with cirrhosis. Orozco et al. (2016) demonstrated that AI is frequent in patients with stable cirrhosis and is related to liver disease severity[15]. Compared to healthy controls, cortisol binding globulin (CBG) was considerably reduced in cirrhotic patients. Total cortisol is decreased with hypoalbuminemia or low CBG, while free cortisol, which is in charge of glucocorticoid action on peripheral organs, stays normal[16].

We found a significantly higher level of INR, Alt, and total bilirubin in the AI group than the normal one and significantly lower Hb level, Serum albumin, and Platelet count in the group with AI Vs. the normal one. This is in agreement with Kim et al. (2017)[6] & Park et al. (2018)[5], who found that serum albumin level was lower. INR was higher in patients with AI than in those without AI, and Kharb et al. (2013)[11] concluded that worsening of liver functions in liver disease predicts the occurrence of AI. We found a significant correlation between basal cortisol and total bilirubin with a significant r-value of 0.365, p= 0.004, and ACTH in chronic HCV patients with an r-value of 0.358, p-value < 0.005. In patients with compensated cirrhosis significant correlation was found between basal cortisol and hemoglobin level (p<0.001), serum albumin (p < 0.003), and total bilirubin (p <0.001) and also between peak cortisol level and hemoglobin level P<0.001 and total bilirubin P<0.001. Finally in patients with decompensated cirrhosis we found significant correlation between basal cortisol and platelet count with p< 0.006, INR (p < 0.002), serum albumin (p < 0.012) and ACTH (P < 0.014) , and between peak cortisol level and platelet count (p < 0.015) , INR (p < 0.006) , serum albumin p < 0.048) . This is in agreement with (Park et al., 2018)[5], who found that Peak serum cortisol levels had a significant correlation with bilirubin and AST, and also with (Jang et al.,2014)[17], who concluded that patients with AI associated with severe liver failure. Additionally, CTP and MELD scores were greater in individuals with AI, and these values showed a negative correlation with delta cortisol. (Chawlani et al., 2015)[18] reported that between individuals with and without AI,

serum albumin, platelet count, INR, transaminases, alkaline phosphatase, creatinine, MELD score, and CTP score were comparable. Also, the finding of (Paz-Delgadillo et al.,2017)[19], stated that Individual factors such as encephalopathy, ascites, serum albumin, bilirubin, INR, and creatinine did not substantially differ across the groups. According to a study by (Annane et al., 2000)[20], there are significant correlations between the survival rate and the prevalence of AI in sepsis. Acevedo et al., 2013[13] could not discover any relationship between disease severity and relative AI in patients with decompensated cirrhosis but not severely ill.

Evaluating HPA axis must be done through biochemical tests, while imaging studies such as adrenal CT are helpful for the localization of tumors or lesions. After a laboratory diagnosis of either deficiency or excess glucocorticoid production, imaging studies can help the hormonal evaluation[21].

Our result revealed that AI was demonstrated in patients with chronic HCV without liver cirrhosis. AI is also common in patients with cirrhosis without a proof of sepsis or hemodynamic instability. AI should be energetically pursued in patients with liver cirrhosis. HCV may have a role in the development of AI in chronic HCV patients.

Declaration

Ethical Approval and Consent to participate: Informed and written consent was obtained from all individual participants included in the study, and also, for publication of the work. Institutional Review Board, Faculty of Medicine, Minia University reviewed and approved the research protocol and consent forms;.

Availability of data and materials: This published article contains all the data analyzed during this work

Competing interests: All authors declare no Conflict of interest

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