

# Assessment of Adrenal Function in Cirrhotic Patients with Spontaneous Bacterial Peritonitis

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## Abstract

**Background:** One of the subjects that has become a big issue in recent years is adrenal Insufficiency in cirrhotic patients, it is evidenced that there is an argument association between cirrhotic patients with spontaneous bacterial peritonitis and adrenocortical dysfunction. **Aim:** to assess adrenal function in chronic liver disease patients with spontaneous bacterial peritonitis to measure hepato-adrenal syndrome problem in our patients. **Subjects and Methods:** cross sectional analytic study was carried out including 160 persons divided into 4 groups, 40 patients for each. Group1(healthy or control group), Group2 (Patients with compensated liver disease), Group 3 (patients with cirrhotic liver disease and sterile ascites and Group 4( patients with cirrhotic liver disease and spontaneous bacterial peritonitis), Then serum cortisol level was assessed for each group at 8a.m , 8p.m and post synacthen test then the comparison was held to assess adrenal function among them. **Results:** Our study revealed statistically significant differences between the comparative groups with pre and post synacthen test where adrenal insufficiency was clear. P-value was (0.001), mean value of total neutrophilic count ( $p < 0.001$ ), relation between adrenal insufficiency and Child-Pugh score ( $p = < 0.001$ ). **Conclusion:** Spontaneous bacterial peritonitis plays a very major role in adrenal insufficiency.

**Key words:** Adrenal function, liver cirrhosis, peritonitis

## Introduction

One of the subjects that has become a big issue in recent years is adrenal Insufficiency (AI) in cirrhotic patients. It can be found in both stable and unstable cirrhotic patients<sup>(1)</sup>. Cirrhosis with terminal events, such as sepsis, because of debate whether the use of corticosteroids in treatment would be beneficial<sup>(2)</sup>. It is well known that the risk of infection is enhanced in cirrhotic patients and that Sepsis is one of the common causes of

mortality in cirrhosis<sup>(3)</sup>. Same pathological processes have a role in both cirrhosis and sepsis such as low Mean arterial pressure, low peripheral vascular resistance, high cardiac output, and reduced sensitivity to vasopressin with increased levels of proinflammatory cytokines may induce AI<sup>(4,6)</sup>. The cause of AI is not definite, it is associated to decreased synthesis of total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol in the liver in cirrhotic patients

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and high level of circulating endotoxins, such as proinflammatory cytokines and lipopolysaccharides (4,5). Use of corticosteroid therapy for treating cirrhotic patients with septic shock and AI are controversial, some studies reporting favorable results<sup>(7)</sup>. while other study<sup>(8)</sup> has shown no benefit.

## Subjects and Methods

**Study design:** The study was a cross sectional analytic study which carried out at University hospital inpatient and outpatient clinic of internal medicine department. The Target populations were divided in to four groups: Group I was including healthy subjects (control group), Group II was including those with compensated liver disease (diagnosed by lab tests and abdominal ultrasound), Group III was including those with cirrhotic liver disease and sterile Ascites (diagnosed by lab tests and abdominal ultrasound) and Group IV was including those with cirrhotic liver disease and spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis

was diagnosed by presence of polymorphonuclear cell in ascitic fluid more than 250cells/c.c. Then serum cortisol level was measured for each group at 8a.m, 8p.m and post synacthen test and the comparison was held to assess adrenal function in between them by ELISA kit (R&D systems Inc., USA). Exclusion criteria included those with hematemesis, melena, hepatorenal syndrome and hepatic encephalopathy. The study was approved by medical ethical approval committee and faculty of Medicine review board. Informed written consent was obtained from patients and control groups.

## Statistical Analysis

The database was established on excel files. Data were imported to SPSS software to process data. Significance of statistical difference was measured by two tests. For character variables: Chi-square test ( $X^2$ ), Fisher exact  $X^2$  and Yates correction  $X^2$ . For numerical variables: t-test was used. Results were presented in tables and graphs.

**Table 1:** sociodemographic data of study groups

	G 1	G 2	G 3	G 4	Total
<b>Sex</b>					
Male	24	24	26	32	106(66.25%)
Female	16	16	14	8	54(33.75%)
<b>Age</b>					
<20 year	2	0	0	0	2(1.25%)
20-40 years	29	11	0	0	40(25%)
41-60 years	6	17	31	37	91(56.88%)
>60 years	3	12	9	3	27(16.8%)

## Results

The number of subjects included in the study was 160 subjects divided into 4 groups, 40 subjects each. Table 1 shows

sociodemographic data of study groups where the males represented 66.25% and females were 33.75% within an age group between 40 and 60 years old. Table 2 shows adrenal insufficiency between groups 2, 3 and 4 where the

higher percentage was in group 4 (77.5%). Table 3 shows the relation between adrenal insufficiency and Child-

Pugh score where the more increase in Child-Pugh score, the more adrenal insufficiency is noted.

**Table 2:** adrenal insufficiency among groups

Delta cortisol	Group 2	Group 3	Group 4	P-value
< 9 (AI)	18 (45%)	29(72.5%)	31(77.5%)	< 0.01
> 9	22 (55%)	11(27.5%)	9 (22.5%)	

**Table 3:** the relation between adrenal insufficiency and Child-Pugh score

Delta cortisol	5-6 (Child A)	7-9 (Child B)	10-15 (Child C)	P-value
< 9 (AI)	18 (45%)	14(66%)	40 (68%)	< 0.01
> 9	22	7	19	

## Discussion

Adrenal insufficiency (AI) in cirrhosis is an issue that has recently gained momentum<sup>(3)</sup>. Adrenal insufficiency is frequent in stable and in decompensated cirrhosis without sepsis, such as variceal bleeding (30%-48%) and ascites (26%-64%)<sup>(10)</sup>. Moreover, Adrenal insufficiency is overestimated in cirrhosis using serum total cortisol, rather than free cortisol, because of low levels of cortisol-binding protein and decreased synthetic function of the liver<sup>(11)</sup>. Recently, liver cirrhosis is considered as one of the major groups of high-risk diseases with a predisposition to AI<sup>(3)</sup>. Adrenocortical insufficiency may be a sign of liver disease *per se*, with a different pathogenesis from that occurring in septic shock<sup>(4)</sup>. Our study was an cross sectional analytic study conducted on 160 patients of in and outpatient clinic of internal medicine who were divided into four groups and only three of them under went (SD-SST) synacthen test as the first group was considered as a control group, the results showed that group 2 who represents the child A patients had AI prevalence rate (45%), group 3 who represents stable cirrhotic patients (had only ascites with hemodynamic stability) had AI incidence of (72.5%) and group 4 who

represents unstable cirrhotic patients (ascetic patients with SBP) had a prevalence rate of (77.5%) and as we see the results reflects the response of adrenal glands once the person catches any hepatic pathology irrespective of its etiology in the form of adrenal insufficiency specially after infection or sepsis as clearly appeared in groups 3 and 4 in case of ascetic patients and ascetic patient with SBP. Our study included 106 males and 54 females in a percentage of 66.2 and 33.8 respectively indicating the increased risk of liver insult in males due to more contact with bilharzia infestation and HCV infection as farmers represented most of male's occupation. The range of age was between forties and sixties in a percentage of 56.88% and the least was 1.25% in age below twenties. Regarding the residence rural areas had the upper hand in a percentage of 57.5% while the urban was 42.5% also reflecting that rural people are more liable for having hepatic infections. Most of the studies in this entity (AI) agreed with our study with some differences in diagnostic tests and criteria to define AI as mentioned before but always the final results nearly are the same. Risso et al<sup>(9)</sup> studied 85 cirrhosis with ascites without sepsis using SD-SST reported AI in 39% of patients, while in our study AI was

72.5% in 40 cirrhotic patients. Acevedo et al<sup>(10)</sup> has another study using SD-SST, studied the prevalence of AI in 198 patients with liver cirrhosis which was 64%, which was 65% in our study within 120 patients which reflects the epidemicity of liver cell failure in our country specially the infectious type in the form of HCV infection. Fernandez et al<sup>(2)</sup> noticed high incidence of AI 68% using SD-SST including 25 cirrhotic patients with sepsis which was nearly equal our results 77.5% using SD-SST including 40 patients and this may be due to the similarity in the nature of sepsis or the etiological cause. Besides, in the same study, the AI prevalence rate was correlated with the severity of liver disease (76% Child-Pugh C vs 25% Child-Pugh B) as our study revealed (68% Child-Pugh C vs 66% Child-Pugh B). Arabi et al<sup>(8)</sup> is an important randomized double blinded study that was conducted on 2010 including 75 patients, this study also applied the same test SD-SST revealing AI in a 76% prevalence rate in cirrhotic patients with sepsis nearing to our results which was 77.5% in 40 cirrhotic patients with SBP, but Arabi et al continuing the study by assigning the patients for hydrocortisone till hemodynamic stability occur then tapering of steroids is done. Tsai et al<sup>(11)</sup> has another study that also used SD-SST to assess adrenal function in a prospective study which included 101 critically ill patients with cirrhosis and sepsis, they found that 51% of their patients met the criteria for AI which was related to the disease severity (Child-Pugh score), like our study that found AI was related to the disease severity in a percentage of 68% in group 4. In a prospective observational study on 20 patients with variceal bleeding and 60 with stable cirrhosis, Triantos et al<sup>(12)</sup> reported an AI rate of 30% following SD-

SST; with the use of LD-SST, AI prevalence was significantly higher in bleeders (60%) than in stable cirrhotic (48%). This study reflects two major facts, first; with stress condition, AI is increased markedly as we see specially the risk of infection increases with bleeding. Second; as we discussed before the test used for diagnosis of AI has its impact on its results as shown before, and again our study which used SD-SST only as a test for diagnosis of AI has different results with different number of candidates as 40 patients were included per each group as a stable cirrhosis and cirrhosis with sepsis (SBP) showing 72.5% and 77.5% respectively proving that infection and sepsis had their severe impact on the results. Also, Tan et al<sup>(5)</sup> evaluated adrenal function in 43 clinically stable patients; all patients underwent SD-SST, and AI was 47% using delta cortisol < 250nmol/l which is nearly to our results regarding number of patients (40) and result of study (72.5%) indicating similarity of nature of the hepatic insult and patient's condition. Galbois et al<sup>(13)</sup> evaluated adrenal function in 88 patients hospitalized for complications of cirrhosis without bleeding and shock. Salivary and serum total cortisol were assessed with SD-SST in all patients. This study was slightly different as it used both salivary and serum total cortisol for assessing adrenal function showing two different results which were 33% when serum total cortisol versus 9.1% using salivary cortisol. In our study we avoid using salivary cortisol as diagnostic test for adrenal insufficiency although its accuracy because of confounders to cortisol level like mouth ulcers, dental caries, small tongue lacerations or poor oral hygiene. Also, Fede et al<sup>(14)</sup> has another study reported an AI prevalence rate 38% in 101 patients with

stable cirrhosis correlated with the severity of liver disease according to Child-Pugh or MELD score. What's more, in a prospective study, Molennar et al<sup>(15)</sup>, using SD-SST, assessed the value of free vs total cortisol levels while evaluating AI in 49 septic and 63 non-septic patients and found that total cortisol correlated with free cortisol during critical illness. More ever, in sepsis, hypoalbuminemia did not affect total and free cortisol<sup>(16-18)</sup> the main limitation of the study is the sample size. A wide prospective study is required for more exploration of this point.

## Conclusion

Sepsis plays a very major role in adrenal insufficiency. Many tests can be used to assess adrenal function and varies markedly between their uses and indications. SD-SST is one of major tests used for adrenal assessment and showed good tool for comparison between studied groups.

**Conflict of interest:** None

## References

1. Trifan A, Chiriac S. and Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. *World J Gastroenterol.* 2013 Jan 28; 19(4): 445-456
2. Fernández J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology.* 2006; 44:1288-95.
3. Rakici H. 2017. Adrenal Insufficiency in Cirrhosis Patients: Evaluation of 108 Case Series. *Euroasian J Hepato-Gastroenterol,* 2017; 7(2): 150-153
4. Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med.* 2009; 360:2328-39.
5. Tan T, Chang L, Woodward A, et al. Characterizing adrenal function using directly measured plasma free cortisol in stable severe liver disease. *J Hepatology.* 2010; 53:841-48.
6. Albillos A, de la Hera A, González M, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology.* 2003; 37:208-17.
7. Marik PE, Gayowski T and Starzl TE, Hepatic Cortisol Research and Adrenal Pathophysiology Study Group. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med.* 2005; 33:1254-59.
8. Arabi YM, Aljumah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ.* 2010; 182:1971-77.
9. Risso A, Alessandria C, Elia C, et al. Adrenal dysfunction in non-septic cirrhotic patients with ascites: Impact on survival. *Dig Liv Dis.* 2011;43 Suppl 2: S74-75.
10. Acevedo J, Fernandez J, Castro M, et al. Prognostic value of relative adrenal insufficiency in decompensated cirrhosis. *J Hepatol.* 2010; 52 Suppl 1: S65.
11. Tsai MH, Peng YS, Chen YC, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology.* 2006; 43:673-681.
12. Triantos CK, Marzigie M, Fede G, et al. Critical illness-related corticosteroid insufficiency in patients with cirrhosis and variceal bleeding. *Clin Gastroenterol Hepatol.* 2011; 9:595-601.
13. Galbois A, Rudler M, Massard J, et al. Assessment of adrenal function

- in cirrhotic patients: salivary cortisol should be preferred. *J Hepatol.* 2010; 52:839–845.
14. Fede G, Spadaro L, Tomaselli T, et al. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology.* 2012; 55:1282–1291.
  15. Molenaar N, Johan Groeneveld AB, Dijkstra HM, et al. adrenal insufficiency of corticosteroid secretion using free versus total cortisol levels in critical illness. *Intensive Care Med.* 2011; 37:1986–19
  16. Moini M, Yazdani Sarvestani M, Shams M, Nomovi M. Evaluation of Adrenal Function in Non-hospitalized Patients with Cirrhosis. *Can J Gastroenterol Hepatol.* 2017; 2017: 2354253. doi: 10.1155/2017/2354253. Epub 2017 Jul 24. PMID:28812008
  17. Kim G, Huh JH, Lee KJ, Kim MY, Shim KY, Baik SK. Relative Adrenal Insufficiency in Patients with Cirrhosis: A Systematic Review and Meta-Analysis. *Dig Dis Sci.* 2017 Apr;62 (4):1067-1079. 10.1007/s10620-017-4471-8. Epub 2017 Feb 7. Review. PMID: 28176190
  18. Singh RR, Walia R, Sachdeva N, Bhalla A, Singh A, Singh V. Relative adrenal insufficiency in cirrhotic patients with ascites (hepatoadrenal syndrome). *Dig Liver Dis.* 2018 Nov; 50 (11): 1232-1237.