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Clinical characteristics and prevalence of adrenal insufficiency in hemodynamically stable patients with cirrhosis

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Abstract

It is well known that adrenal insufficiency is common in septic shock or hemodynamically unstable patients. But, there is as yet no sufficient clinically significant data about the exact prevalence or differences in the cause of cirrhosis with adrenal insufficiency. To investigate adrenal insufficiency prevalence in hemodynamically stable patients with cirrhosis and determine differences based on cirrhosis severity or etiology.

From July 2011 to December 2012, 69 hemodynamically stable patients with cirrhosis without infection admitted at Hallym University Medical Center were enrolled. Adrenal insufficiency was defined as a peak cortisol level $< 18\,\mu g/dL$, 30 or 60 minutes after 250 μg Synacthen injection.

The study included 55 male patients (79.7%), and the mean age was 57.9 ± 12.9 years. Cirrhosis etiology was alcohol consumption, HBV, HCV, both viral and alcohol related, and cryptogenic in 49, 15, 7, 11, 9 patients, respectively. Adrenal insufficiency occurred in 24 patients (34.8%). No differences were found in age, sex, mean arterial pressure, heart rate, HDL, cirrhosis etiology, degree of alcohol consumption, encephalopathy, variceal bleeding history, or hepatocellular carcinoma between patients with or without adrenal insufficiency. Serum albumin level was lower ($P < .05$), and INR was higher ($P < .05$) in patients with than in those without adrenal insufficiency. However, multivariate analysis revealed no independent adrenal insufficiency predictor. Significant negative correlations were found between Child–Pugh score and peak cortisol levels ($\gamma = -0.365$, $P = .008$).

Adrenal insufficiency was frequent even in hemodynamically stable patients with cirrhosis and tended to be associated with only liver disease severity, being unrelated to cirrhosis etiology.

Abbreviations: ACTH = adrenocorticotropic hormone, AI = adrenal insufficiency, Apo = apolipoprotein, HBV = hepatitis B virus, HCV = hepatitis C virus, HDL = high-density lipoprotein, HPA = hypothalamic–oituitary–adrenal, IL-6 = interleukin-6, INR = International Normalized Ratio, LDL = low-density lipoprotein, SST = short corticotrophin stimulation test, TNF-α = tumor necrosis factor.

Keywords: adrenal insufficiency, adrenocortical hormones, hemodynamic stability, liver cirrhosis

1. Introduction

Cortisol is a hormone secreted by the adrenal cortex and is essential for the maintenance of stability of major organs. Increased cortisol results in increased vascular tone and cardiac output.[1] These effects are necessary for the body to counteract inflammation in situations, such as septic shock, where the inflammatory response is activated rapidly.[2]

Adrenal insufficiency (AI) has been well known to be common in septic shock and has a significant impact on the prognosis of patients with AI.[3] Liver failure shares many clinical similarities to septic shock. Both conditions are characterized by the presence of hyperdynamic circulatory failure, with a low mean arterial pressure, decreased systemic vascular resistance, and increased cardiac output.[4,5] Elevated cytokine levels, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, can be observed in both conditions, and liver failure also leads to decreased monocyte function and immunoparalysis, a finding first noted in patients with septic shock.[6–8] Therefore, many studies of AI in liver failure have been reported based on the similarity between liver failure and sepsis. They reported that AI prevalence in liver failure was 52% to 63%.[2,9,10] In these patients, treatment with low doses of hydrocortisone is associated with a marked increase in shock reversal and hospital survival.[10]

In contrast, AI also existing in hemodynamically stable patients with cirrhosis has been recently raised. According to 2 studies by Fede et al[11] and Galbois et al,[12] the presence of AI was demonstrated even in hemodynamically stable patients with cirrhosis. However, no sufficient clinically significant data exist

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regarding the exact prevalence or differences in the cause of cirrhosis with AI. Orozco et al[13] recently reported that AI is frequent in patients with stable cirrhosis and that it is related to the liver disease severity. Moreover, many studies have been reported for the clinical importance of AI in liver failure or cirrhotic patients with septic shock, but few studies have been reported regarding stable cirrhosis, except for the prevalence or risk factors of AI.

Nowadays, liver cirrhosis is considered to be among the major groups of high-risk diseases with a predisposition to AI.[14] Some data suggest that AI may be a feature of cirrhosis *per se*, with a pathogenesis subtly different from that occurring in septic shock from other causes. Mechanisms of AI in cirrhotic patients are not entirely known, but they may include impaired synthesis in total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, as well as increased levels of proinflammatory cytokines and circulating endotoxin (e.g., lipopolysaccharide).[15]

The short corticotrophin stimulation test (SST), which uses 250 μg of synthetic adrenocorticotropic hormone, is considered as the standard test to diagnose AI in critically ill patients, best described as critical illness-related corticosteroid insufficiency.[16]

The purpose of this study was to investigate AI prevalence in hemodynamically stable patients with cirrhosis and to evaluate whether a difference is found on the basis of liver disease severity or cirrhosis etiology.

2. Patients and methods

This prospective study was performed at Hallym University Medical Center Kangnam Sacred Heart Hospital (Seoul, Korea). This study was approved by the Institutional Review Board, and written informed consent was obtained by all participants. From July 2011 to December 2012, patients with cirrhosis without infection or hemodynamic instability admitted to the hospital were enrolled. Diagnosis of cirrhosis was based on histology or on clinical, laboratory, and ultrasonographic data. Patients with any sign of infection or sepsis, defined by a body temperature <36°C or >38°C; heart rate,>90/min; respiratory rate,>20/min; leukocyte count, <4000/mm^3 or >12,000/mm^3, etc., or hemodynamic instability, defined by a mean arterial pressure <60 mm Hg or vasopressor dependency on the day of the tests, were excluded. Patients with a history of hypothalamic–pituitary or adrenal disease, current or recent (within the preceding 3 months) history of corticosteroid therapy or other drugs (oral contraceptive, rifampicin or anticonvulsants such as phenytoin, phenobarbital, primidone) that could influence the hypothalamic–pituitary–adrenal (HPA) axis, younger than 18 years, and pregnancy were also excluded.

The liver disease severity was graded by the Child–Pugh score. Adrenal function was assessed by performing the SST. Synthetic adrenocorticotropic hormone 250 μg (Synacthen, Novartis Pharma AG, Basel, Switzerland) was administered intravenously between 07:00 and 8:00 A.M. Blood samples were obtained immediately before, 30 minutes and 60 minutes after injection. Serum cortisol levels were measured using radioimmunoassay. Hematology, routine biochemistry, and coagulation profiles were obtained on the day of the SST.

2.1. Definition of AI

Basal cortisol was defined as morning cortisol concentration (between 07:00 and 08:00 A.M.), before Synacthen injection. The peak cortisol was defined as the highest cortisol concentration whether at 30 or 60 minutes after Synacthen injection. Delta cortisol was defined as the difference between the peak and basal cortisol levels. AI was defined as a peak cortisol level <18 μg/dL (497 nmol/L). Another definition of AI include basal cortisol level <15 μg/dL (414 nmol/L) or delta cortisol <9 μg/dL (248 nmol/L).[17]

2.2. Statistical analysis

Descriptive statistics are expressed as mean ± SD and frequency (percentage). Student's *t*-test or the Mann–Whitney *U* test was used to compare the means of continuous variables and normal distribution data. Comparisons between groups were performed using the chi-square test for categorical variables. Multivariate analysis was performed by applying a multiple logistic stepwise regression procedure to obtain independent associated factors with the presence of AI. All statistical tests were two-tailed, and the significance level was set at $P = .05$ or less. All statistical analyses were performed using R software, version 2.14 (The R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients' characteristics

This study enrolled 69 patients with cirrhosis, with 55 male patients (79.7%), and the mean age was 57.9 ± 12.9 years. Cirrhosis etiology was alcohol, HBV, HCV, both viral and alcohol-related, and cryptogenic in 49, 15, 7, 11, and 9 patients, respectively. The diuretic therapy included furosemide and spironolactone, which were prescribed as spironolactone 50 mg only, spironolactone 100 mg only, spironolactone 50 mg plus furosemide 20 mg, spironolactone 100 mg plus furosemide 40 mg in 4, 2, 13, and 13 patients, respectively. The other 37 patients did not take diuretics.

The clinical characteristics and laboratory finding of included patients are shown in Tables 1 and 2. No significant difference was observed regarding age, sex, mean arterial pressures, heart rates, high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1(Apo A1), and apolipoprotein B (Apo B) between patients with or without AI. No differences were found in cirrhosis etiology and degree of alcohol consumption, presence of encephalopathy, history of variceal bleeding, or presence of hepatocellular carcinoma between patients with or without AI.

A trend was observed that more Child–Pugh class A patients were in the non-AI group (12.5% and 35.6% in AI and non-AI, respectively) and more Child–Pugh class Band C patients were in the AI group ($P = .054$; 62.5, 25.0% in AI and 48.9, 15.6% in non-AI, respectively). In addition, a significantly high Child–Pugh score was found in the AI group compared with the non-AI group ($P = .016$; 8.8 ± 1.9 and 7.6 ± 1.6, respectively; Table 1). Laboratory data showed that serum albumin level was lower ($P<0.05$) and INR was higher ($P < .05$) in patients with than in those without AI. Multivariate analysis showed no independent predictor of AI (data not shown). Regarding to alcohol, AI was more prevalent in alcoholic cirrhosis compared to nonalcoholic cirrhosis without statistical significance. ($P = .282$; 21.7% and 35.6% in nonalcoholic and alcoholic patients in AI group, respectively.).

3.2. Short corticotropin stimulation test

The mean total cortisol values 30 and 60 minutes after Synacthen injection were 20.2 ± 9.7and 21.7 ± 8.3 μg/dL in all patients

Table 1

Demographic and clinical characteristics of the enrolled patients.

	All patients (n = 69)	Adrenal insufficiency (n = 24)	Without adrenal insufficiency (n = 45)	*P*-value
Age, years	57.9 ± 12.9	56.6 ± 13.3	58.6 ± 12.8	.537
Sex (M/F)	55 / 14	20 / 4	35 / 10	.591
MAP, mm Hg	86.4 ± 15.0	85.8 ± 9.06	86.7 ± 17.5	.819
Heart rate, bpm	77.8 ± 11.8	78.9 ± 10.1	77.2 ± 12.7	.559
Cirrhosis etiology (%)				.090
Alcohol	49 (71.0)	19 (79.1)	30 (66.7)	
Viral	22 (31.9)	7 (29.2)	15 (33.3)	
Both	11 (15.9)	3 (12.5)	8 (17.8)	
Others	9 (13.0)	1 (4.2)	8 (17.8)	
Alcohol consumption (%)				.698
<210 g/week	6 (12.2)	2 (8.3)	4 (8.9)	
>210 g/week	43 (87.8)	18(75.0)	25 (55.6)	
Child–Pugh classification (%)				.054
Class A	19 (27.5)	3 (12.5)	16 (35.6)	
Class B	37 (53.6)	15 (62.5)	22 (48.9)	
Class C	13 (18.8)	6 (25.0)	7 (15.6)	
Child–Pugh score	8.0 ± 1.9	8.8 ± 1.9	7.6 ± 1.8	.016
Hepatic encephalopathy (%)	9 (13.0)	3 (12.5)	6 (13.3)	.923
Ascites (%)	55 (79.7)	20 (83.3)	35 (77.8)	.591
Variceal bleeding Hx. (%)	15 (21.7)	7 (29.2)	8 (17.8)	.281

Hx = History, MAP = mean arterial pressure.

The clinical characteristics and laboratory finding of included patients are shown. No differences were observed in the cirrhosis etiology between patients with or without AI. However, more Child–Pugh class A patients are in the non-AI group, and more Child–Pugh class B and C patients are in the AI group. In addition, significantly high Child–Pugh score in the AI group was reported compared with the non-AI group.

Table 2

Laboratory findings of enrolled patients according to the presence of adrenal insufficiency.

	All patients (n = 69)	Adrenal insufficiency (n = 24)	Without adrenal insufficiency (n = 45)	*P*-value
Hb, g/dL	10.9 ± 1.8	10.5 ± 1.8	11.1 ± 1.8	.214
Albumin, g/dL	3.2 ± 0.5	3.0 ± 0.6	3.3 ± 0.5	.007
INR, PT	1.4 ± 0.3	1.5 ± 0.4	1.3 ± 0.3	.034
T. bilirubin, mg/dL	2.9 ± 3.8	3.4 ± 3.2	2.6 ± 4.1	.394
Creatinine, mg/dL	0.9 ± 0.4	0.8 ± 0.2	0.9 ± 0.4	.214
Sodium, mEq/L	136 ± 5.3	135 ± 6.1	136 ± 4.8	.573
T. cholesterol, mg/dL	116 ± 45	107.4 ± 50	121 ± 42	.238
HDL, mg/dL	32.0 ± 10.6	30.8 ± 10.7	32.5 ± 10.6	.570
LDL, mg/dL	72.7 ± 37.7	67.1 ± 43.9	75.3 ± 34.8	.434
Apo A1, mg/dL	65.8 ± 32.4	59.7 ± 34.1	69.3 ± 31.3	.294
Apo B, mg/dL	68.1 ± 35.7	64.8 ± 39.5	69.9 ± 33.9	.614

Apo A1 = apolipoprotein A1, Apo B = apolipoprotein B, Hb = hemoglobin, HDL = high density-lipoprotein, LDL = low density-lipoprotein, PT = prothrombin time, T = total.

Laboratory data show that serum albumin level is lower, and INR is higher in patients with AI than those without AI, with statistical significance. No significant difference was observed regarding HDL, LDL, Apo A1, and Apo B between patients with and without AI.

group. However, the values were significantly lower in AI compared with non-AI group (mean 13.3 vs 23.8 and 14.8 vs 25.4 μg/dL, $P < .01$).

AI defined by peak total cortisol was present in 24 patients (34.8%). Peak serum cortisol level also showed significant correlation with absolute neutrophil counts (γ=0.325, $P < .01$, aspartate aminotransferase (γ=0.422, $P < .01$), bilirubin (γ=0.463, $P < .01$), total protein (γ=−0.283, $P < .05$), baseline cortisol (γ=0.707, $P < .01$), delta cortisol (γ=0.516, $P < .01$).

The median basal total cortisol value was 12.6 ± 5.9 μg/dL, which was significantly low in the AI group compared with the non-AI group (8.4 ± 2.4 vs 14.8 ± 6.1 μg/dL, Table 3). Significant negative correlations were observed between the Child–Pugh score and peak cortisol levels (γ=−0.365, P=.008, Fig. 1A) and

Table 3

Basal cortisol, peak cortisol levels, and delta cortisol levels with short corticotropin stimulation test.

	All patients (n = 69)	Adrenal insufficiency (n = 24)	Without adrenal insufficiency (n = 45)	*P*-value
Basal cortisol, μg/dL	12.6 ± 5.9	8.4 ± 2.4	14.8 ± 6.1	<.001
Peak cortisol, μg/dL	22.4 ± 9.8	15.1 ± 2.0	26.2 ± 10.1	<.001
Delta cortisol, μg/dL	9.9 ± 6.9	6.6 ± 2.3	11.6 ± 7.9	.004

The median basal total cortisol value is significantly low in the AI group compared with the non-AI group. Significant negative correlations were found between Child–Pugh score and peak/basal cortisol levels. However, no statistical significance was found between Child–Pugh score and delta cortisol levels.

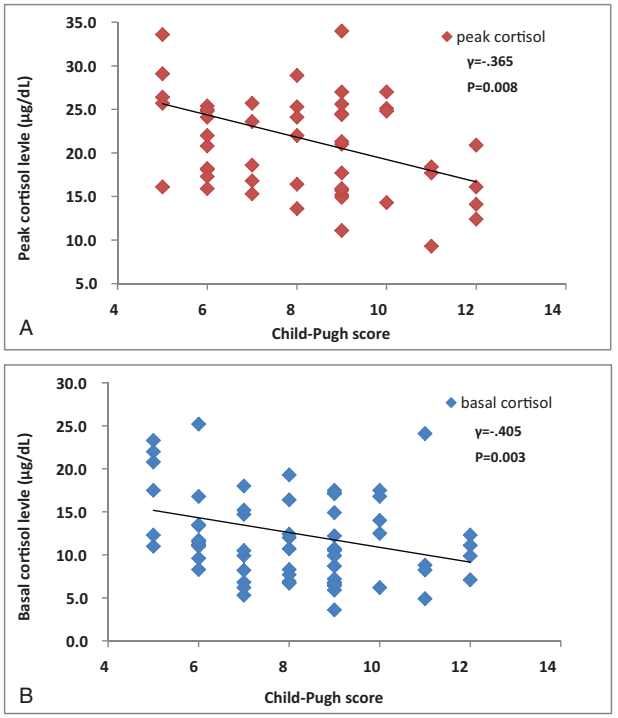

Figure 1. Correlation between Child–Pugh score and cortisol levels. Significant negative correlations were observed between Child–Pugh score and both cortisol levels: peak cortisol (A) and basal cortisol (B).

between the Child–Pugh score and basal cortisol levels (γ=−0.405, P=.003, Fig. 1B).

The median delta cortisol value was 9.9 ± 6.9 μg/dL, which was also significantly low in the AI group compared with the normal adrenal function group (6.6 ± 2.3 vs 11.6 ± 7.9 μg/dL, Table 2). However, no significant differences were found between the Child–Pugh score and delta cortisol levels (γ=-0.064, P=.652).

There were no significant correlations between the etiology of cirrhosis and prevalence of AI (γ=−0.217, P=.090, Table 4). Data are shown in Table 4.

4. Discussion

This study showed that AI, which was evaluated by SST, is common in patients with cirrhosis even without infection or hemodynamic instability (34.8%). Presence of AI in these patients tended to be related to liver disease severity based on the Child–Pugh score. The etiology of cirrhosis or alcohol consumption was not also associated with the presence of AI. Similarly, a small study in Korea included 46 patients (29 liver cirrhosis/17 chronic hepatitis), defining AI as <9 μg/dL cortisol increasing from baseline after corticotrophin injection. They showed that AI prevalence in cirrhosis was 24%, and no AI in patients were found with chronic hepatitis.[18]

Table 4

The prevalence of AI with etiology of cirrhosis.

	Alcohol	Viral	Both	Others	*P*-value
AI	19	7	3	1	.073
Non-AI	30	15	8	8	.090

AI = adrenal insufficiency, Both = both alcohol and viral.
There were no significant correlations between prevalence of AI and etiology of cirrhosis.

The AI prevalence has been reported as 9% to 38% in stable cirrhosis.[11,12] However, AI definition in every study has diverse diagnostic methods. Fede et al[11] revealed that AI existed in 38% of patients with cirrhosis without infection or hemodynamic instability by using 1 μg low dose adrenocorticotropic hormone (ACTH) stimulation. The other study performed a 250 μg ACTH stimulation test to examine AI in 98 stable patients with cirrhosis, and an inadequate response was detected among 9% of the patients by saliva cortisol and among 33% by serum total cortisol.[12] In another study, Tan et al[19] revealed that adrenal dysfunction defined by stimulated free cortisol<33 nmol/L was significantly associated with higher mortality. These showed that the significant difference of AI prevalence was based on assay methods and sites. Low dose stimulation test and measurement from saliva cortisol are not yet standardized methods for diagnosing AI. In addition, basal and delta cortisol levels are suggested as important factors for diagnosing AI.[11] Another study showed that a negative correlation between delta cortisol level and illness severity, particularly absolute increment of cortisol <9 μg/dL, was an independent predictor for hospital mortality.[9,20] In our study, basal and delta cortisol levels were significantly lower in patients with AI. In addition, negative correlations between the Child–Pugh score and basal cortisol levels were significant, which corresponds with the findings of the previous study.

The pathomechanism of AI in stable cirrhosis is unclear. Although both HDL and ApoA1 play a primary role in providing substrates for steroidogenesis to adrenal cells, this deficiency may contribute to the pathogenesis of AI in these patients.[21,22] However, 2 studies from Fede et al[11] and Galbois et al[12] showed conflicting results in the HDL concentration between patients with and those without AI. Similarly, HDL and Apo A1 were not significantly related to AI in our study. We also evaluated total cholesterol, LDL, triglyceride, and Apo B, but no significant association was found. Thus, further studies are required to explain the mechanism of AI in stable patients with cirrhosis.

The prognostic relevance of AI in noncritically ill patients with liver disease has not been defined.[21] A study by Annane et al[3] reported that clear associations were observed between survival rate and presence of AI in sepsis. Several studies also reported that AI was associated with increased mortality in patients with cirrhosis and sepsis.[9,20] Another study showed that low total delta cortisol levels have been associated with higher incidence of severe sepsis, type 1 hepatorenal syndrome, and higher short-term mortality in a cohort of noncritically ill patients with cirrhosis,.[23] In contrast, in the study of Thevenot et al,[24] a higher stimulated free cortisol level was associated with lower survival in patients with stable cirrhosis.

Moreover, AI could be a subclinical condition triggered by acute events, such as acute illness as infections, ultimately leading to a worse prognosis.[11] Several studies showed that corticosteroid administration increased survival in patients with cirrhosis with septic shock.[10,25] However, results whether corticosteroid administration could improve clinical outcome in those patients have been inconsistent.[26] Therefore, further studies are needed for influence of AI on clinical outcome in stable patients with cirrhosis.

According to Trifan et al, there are some studies reporting beneficial results while a recent randomized control study has shown no benefit, which means the effects of steroid therapy in cirrhotic patients with AI remain controversial.[17] Further prospective randomized clinical studies are needed to assess

the effect of corticosteroid therapy in critically ill cirrhotic patients with AI.

The limitation of this study is the relatively small number of patients enrolled. That would be the reason that although the Child–Pugh score, albumin, and basal and delta cortisol values were associated with AI in univariate analysis, no independent predictor for AI was observed in multivariate analysis (data not shown). We expect to obtain more significant results in further studies with a large number of patients. Another limitation is that we did not measure the free cortisol levels. Normally, 70% of circulating cortisol is bound to corticosteroid-binding globulin, 20% is bound to albumin, and the remaining 10% is free, and only the unbound cortisol is biologically active.[27] Hypoalbuminemia in cirrhosis could overestimate the prevalence of AI when determined by serum total cortisol level compared with salivary cortisol measurement. Measurement of salivary cortisol, which is a surrogate marker of free cortisol is a useful approach in cirrhotic patients.[19]

In summary, our study shows that AI was frequent even in stable cirrhosis. AI was not related to the etiology of cirrhosis or alcohol consumption and revealed to be only associated with liver disease severity.

5. Conclusion

AI is common in patients with cirrhosis even without infection or hemodynamic instability, and is not related to cirrhosis etiology. AI tended to be only associated with liver disease severity although no independent predictor for AI was observed in multivariate analysis. This study suggested that further studies are needed for the influence of AI on the clinical outcome in stable patients with cirrhosis.

Author contributions

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