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Adrenal insufficiency in decompensated cirrhotic patients without infection: prevalence, predictors and impact on mortality

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Abstract

Background Relative adrenal insufficiency (RAI) is common in compensated and decompensated chronic liver disease in the presence of sepsis. This study was performed to find out the prevalence of RAI in decompensated cirrhotic patients presenting with hepatic encephalopathy and variceal bleeding without any evidence of infection.

Methods The study prospectively included 75 cirrhotic patients with signs of decompensation. The short Synacthen test (SST) was performed on all patients after ruling out infection. Patients with positive blood, urine, sputum, ascitic and pleural fluid cultures or evidence of infection on chest X-ray and those with elevated procalcitonin levels (>0.05 ng/ml) were excluded. RAI in critical illness was defined by a delta cortisol level (difference between basal and post-stimulation cortisol) of ≤9 µg/dl after SST.

Results The mean age of the study population was 54 ± 11 years. Upper gastrointestinal bleed and hepatic encephalopathy were seen in 56.6% and 41.5%, respectively, and both were seen in 1.9%. Of the 75 patients, 55 (73%) were in Child–Turcotte–Pugh (CTP) class C and the mean model for end-stage liver disease (MELD) score was 21 ± 7. Forty-five patients (60%) met our criteria for RAI. Those with RAI had lower serum albumin (2.4 ± 0.5 g/dl vs 2.7 ± 0.5 g/dl, p = 0.03) and higher MELD scores (22 ± 7 vs 19 ± 6, p = 0.03). Prevalence of RAI in CTP class C was 65% (36 out of 55 patients) compared to 45% (9 out of 20 patients) in Child–Pugh stage A and B. Similarly, 82% (23 out of 28 patients) with MELD scores >25 had RAI compared to 54% with MELD scores <20. None of biochemical parameters were predictive of RAI on logistic regression analysis. Three-month mortality rate was not significantly different in patients with or without adrenal insufficiency (44% vs 28%, p = 0.11).

Conclusion The present study showed RAI to be common in noninfected decompensated cirrhotic patients, but did not predict 3-month mortality. There were no other predictive factors in those with RAI. Hence, in patients with cirrhosis without infection, the clinical utility of routine adrenal function testing needs further elucidation.

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Introduction

During critical illness, an increase in blood cortisol level due to hypothalamo-pituitary adrenal axis activation serves as an important compensatory mechanism.[1] However, relative adrenal insufficiency (RAI) can occur in these patients because of blunted pituitary response to circulating cytokines. It is postulated that RAI could be associated with haemodynamic instability, increased vasopressor requirement and higher mortality rates in critically ill patients.[2,3]

It has been known for a long time that liver cirrhosis is associated with adrenal insufficiency.[4,5] This entity has been termed 'hepatoadrenal syndrome'.[6] Recent literature has shown that the prevalence rates of RAI range from 51 to 77% in patients with liver cirrhosis who are critically ill.[7] Moreover,

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Variables	Relative adrenal insufficiency (n = 45)	Normal adrenal function (n = 30)	p-value
Basal cortisol (μg/dl)	10.8 ± 4.6	12.7 ± 8.5	0.23
Post ACTH cortisol – 60 min (μg/dl)	16.5 ± 4.6	26.5 ± 9.1	<0.001
Delta cortisol (μg/dl)	5.6 ± 2.6	13.8 ± 4.8	<0.001

ACTH: adrenocorticotropic hormone

Table 1 Serum cortisol – basal and 60-min post-Synacthen test

evidence points to RAI being associated with a poor outcome in such patients.[8] A prevalence of 7–49% of RAI is reported even in noncritically ill patients with cirrhosis, which has largely been attributed to associated sepsis.[9–12] However, limited data exist on whether RAI can be induced by decompensated cirrhosis itself in the absence of infection. Hence the present study was undertaken to estimate the prevalence of RAI in decompensated cirrhosis in the absence of infection, study the possible risk factors and study RAI impact on outcome.

Methods

Patients

This prospective study was conducted in the liver disease intensive care unit (ICU) of a tertiary care teaching hospital.

The inclusion criteria were as follows: 1) patients with decompensated cirrhosis admitted to liver disease ICU; 2) aged 18–75 years; 3) diagnosis of cirrhosis based on clinical, laboratory, ultrasonography, endoscopic findings or histology if available; 4) no overt evidence of infection; and, 5) haemodynamically stable with a mean arterial pressure (MAP) >70 mm Hg and not on vasopressors. Exclusion criteria were as follows: 1) patients who had obvious evidence of infection (such as on chest X-ray, urine examination or had a positive bacterial culture result in blood or body fluids, spontaneous bacterial peritonitis, presence of cellulitis or overt sepsis/systemic inflammatory response syndrome) at the time of entry into the study; 2) patients who were haemodynamically unstable; 3) patients with an acute increase in liver enzymes [aspartate amino transferase (AST)/alanine amino transferase (ALT) >250 IU/ml] or those diagnosed as acute-on-chronic liver failure; and, 4) elevated procalcitonin >0.5 ng/ml at the time of admission.

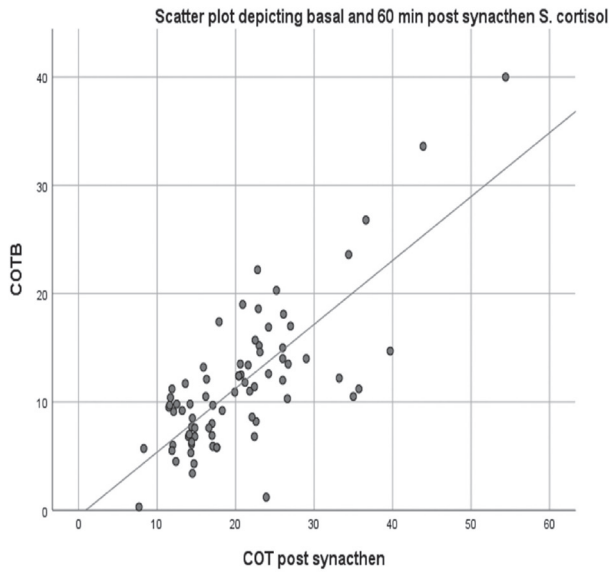

Figure 1 Scatter plot depicting basal and 60-min post-Synacthen cortisol levels in study subjects (n = 75). COT: cortisol stimulated; COTB: cortisol basal; S: serum

Assessments

Apart from routine haematological parameters (complete blood counts including platelet count), liver function tests (serum bilirubin, AST/ALT, serum total protein, serum albumin, serum globulin and international normalised ratio), blood glucose, serum lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and very-low-density lipoprotein), serum sodium and potassium, blood urea nitrogen and serum creatinine were obtained. Routine blood cultures and relevant body fluid cultures as indicated were sent at the time of admission, results of which were obtained by third day of admission.

A short Synacthen test (SST) was performed on the third day of hospitalisation in those who had a negative infection screen based on culture report and procalcitonin levels. Synthetic adrenocorticotropic hormone (ACTH; Synacthen, 250 mic; Novartis Pharma, Switzerland) was given intravenously at 10 am, after an overnight fast. Blood samples for serum cortisol levels were obtained immediately before and 60 min after injection. Blood samples were collected in the fasting state and serum was separated and stored at -80˚C. Measurements of serum cortisol were performed with the use of a standard chemi luminiscent immuno assay.

RAI in critical illness was defined by three criteria: 1) post-stimulation cortisol level >550 nmol/l (20 μg/dl) excludes adrenal insufficiency; 2) random total plasma cortisol level of <276 nmol/l (<10 μg/dl); and, 3) a delta cortisol level (difference between basal and post-stimulation cortisol) of ≤250 nmol/l (≤9 μg/dl) after SST. Follow-up information was available until discharge from the hospital and was later obtained by telephonic communications, for a maximum period of 3 months after initial enrolment.

Statistical analysis

The categorical variables were expressed as rates, ratios and percentages, whereas continuous data was expressed as mean ± standard deviation. Prevalence of adrenal

Table 2 Baseline characteristics of different study groups

Baseline variables	Total patients (n = 75)	Relative adrenal insufficiency (n = 45)	Normal adrenal function (n = 30)	p-value
Age (years)	54 ± 11	53 ± 11	54 ± 11	0.88
Male, n (%)	67 (89)	40 (89)	27 (90)	
Mean arterial pressure (mm Hg)	92 ± 14	92 ± 13	92 ± 15	0.93
Serum creatinine (mg/dl)	1.4 ± 0.8	1.5 ± 0.9	1.3 ± 0.6	0.45
Serum sodium (mEq/l)	129 ± 7	128 ± 8	131 ± 6	0.07
Serum albumin (g/dl)	2.6 ± 0.5	2.4 ± 0.5	2.7 ± 0.5	0.03
INR	2.1 ± 0.7	2.1 ± 0.6	1.9 ± 0.7	0.12
Total cholesterol (mg/dl)	104 ± 40	99 ± 34	112 ± 46	0.14
MELD score	21 ± 7	22 ± 7	19 ± 6	0.03

INR: international normalised ratio; MELD: model for end-stage liver disease

insufficiency was calculated. Apart from overall and subgroup prevalence expressed as percentages, Chi-square test and Mann Whitney-U test were used to test significance of association between adrenal insufficiency and qualitative variables. Student t-test was used to test significance of quantitative variables, such as MAP and MELD score. Univariate and multivariate analyses were performed to identify the role of RAI as a predictor of 3-month mortality.

Ethical clearance

The study was approved by the Institutional review board and ethics committee of our institution. Written informed consent was obtained from all participants or their legally authorised representative.

Results

Out of 318 cirrhotic patients who underwent initial screening, 75 patients were enrolled into the study. A total of 243 patients were excluded: 196 had evidence of infection or sepsis, 28 were haemodynamically unstable or on vasopressor support, 16 had acute flares (AST/ALT >250 IU/ml) or had acute-on-chronic liver failure, and three patients were on current or had recent history of corticosteroid therapy.

The mean age of the study group was 54 ± 11 years. Aetiology of cirrhosis was alcohol in 62 cases, hepatitis C virus in one, hepatitis B virus in four and eight were cryptogenic. Upper gastrointestinal bleed and hepatic encephalopathy were seen in 56.6% and 41.5%, respectively, and both seen in 1.9%. A total of 55 patients were in Child–Turcotte–Pugh (CTP) class C and average MELD score was 21 ± 7.

RAI was present in 45 out of 75 (60%) patients. A total of 80% (36 out of 45) of those with adrenal insufficiency and 63% (19 out of 30) with normal adrenal function belonged to CTP class C. Prevalence of RAI in CTP class C was 65% (36 out of 55 patients) compared to 45% (9 out of 20 patients) in Child–Pugh class A and B. Similarly, 82% (23 out of 28 patients) with MELD score >25 had RAI compared to 54% with MELD <20. The mean basal cortisol level was 11.6 ± 6.5 µg/dl, 60-min post-Synacthen was 20.6 ± 8.3 µg/dl (Table 1). The mean delta cortisol level was 8.9 ± 5.4 µg/dl (Figure 1). On multivariate analysis, those with RAI had lower serum albumin (2.4 ± 0.5 g/dl vs 2.7 ± 0.5 g/dl, p = 0.03) and higher MELD scores (22 ± 7 vs 19 ± 6, p = 0.03) (Table 2).

Three-month mortality in the whole group was 37% (28 out of 75). The mortality rate was not significantly different in patients with or without adrenal insufficiency (44% vs 28%, p = 0.11) (Table 3). On multivariate analysis, serum creatinine (1.2 ± 0.5 mg/dl vs 1.7 ± 1.1 mg/dl, p = 0.015) and MELD scores were significantly higher in those who died (19 ± 7 vs 24 ± 6, p = 0.003).

Table 3 Risk factors at presentation for mortality at 3 months

Variables	Survivors (n = 47)	Died (n = 28)	p-value
Age (years)	54 ± 10	52 ± 11	0.454
Serum creatinine (mg/dl)	1.2 ± 0.5	1.7 ± 1.1	0.015
Serum sodium (mEq/l)	130 ± 5	128 ± 9	0.219
Serum albumin (g/dl)	2.6 ± 0.5	2.4 ± 0.5	0.146
MELD score	19 ± 7	24 ± 6	0.003
Delta cortisol (µg/dl)	7.8 ± 5.6	9.5 ± 5.3	0.190

MELD: model for end-stage liver disease

Discussion

In our study, we found a high prevalence of RAI (60%) in decompensated cirrhosis patients even in the absence of infection and haemodynamic instability. They had lower albumin and higher MELD scores suggesting that more severe liver disease was associated with higher prevalence of RAI. Mortality at 3 months was associated higher serum creatinine and higher MELD scores but not with RAI.

RAI has been identified previously in 10–82% of decompensated cirrhotic patients and in 9–83% of compensated cirrhosis.[13] Fede et al.[12] reported a prevalence of 38% of adrenal insufficiency in a decompensated cirrhotic cohort without infection. The higher prevalence of adrenal insufficiency in our patient group could be due to the presence of more advanced liver disease as evidenced by higher CTP class and MELD scores.

Subjects with RAI had lower serum albumin levels than those who had normal adrenal function. Both these factors along with higher a MELD score indicate more severe liver disease and a poorer prognosis in such patients.[14,15] This has previously been shown in studies with decompensated cirrhotic patients.[16,17] Although RAI patients were noted to have hyponatraemia and low cholesterol in earlier studies, our study failed to show any such relationship.[7]

Mortality at 3 months in our cohort was 37%, which is similar to that reported in previous studies.[18–21] There was no correlation between presence of adrenal insufficiency at baseline and mortality at 3 months. This is also in keeping with previous literature, which did not show that RAI could be detrimental to survival.[7] A rise in creatinine and a higher MELD score were noted to be independent risk factors for survival.[7,8]

Recent studies have shown clear benefit with hydrocortisone and fludrocortisone treatment in patients with septic shock but have not found a reduction in 30-day mortality.[20,22–26] However, no studies have shown any benefit in treating those without haemodynamic instability. We did not aim to study the treatment of RAI but our results would support the view that treatment may not be required for RAI in patients with cirrhosis without septic shock.

The main limitation of our study is that we measured total cortisol and not free cortisol in response to ACTH, which could have contributed to overestimation of RAI in our patients with low albumin. This has been highlighted in previous studies that have tried to reduce this error by excluding patients with albumin <2.5 g/dl.[7] It is accepted that free cortisol estimation gives a more accurate picture of adrenal cortical function in hypoalbuminaemia patients and measurement of cortisol-binding globulin (CBG) and calculating free cortisol index is superior to total cortisol in such patients.[27] The baseline cortisol levels in both groups were comparable in our study, despite having lower albumin in the RAI group, but CBG was not measured.

In summary, RAI is common in cirrhotic patients even in the absence of sepsis and is more prevalent in those with advanced liver disease. However, our data suggest that this may not impact the short-term mortality. Hence there is no clear clinical indication for routine screening of adrenal function in the absence of sepsis.

References

1 Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med* 2003; 31: 141–5.
2 Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348: 727–34.
3 Marik PE, Pastores SM, Annane D et al.; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36: 1937–49.
4 Trifan A, Chiriac S, Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. *World J Gastroenterol* 2013; 19: 445–6.
5 Tsai MH, Peng YS, Chen YC et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006; 43: 673–81.
6 Marik PE, Gayowski T, Starzl TE; Hepatic Cortisol Research and Adrenal Pathophysiology Study Group. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care* 2005; 33: 1254–9.
7 Singh RR, Walia R, Sachdeva N et al. Relative adrenal insufficiency in cirrhotic patients with ascites (hepatoadrenal syndrome). *Dig Liver Dis* 2018; 50: 1232–7.
8 Acevedo J, Fernandez J, Prado V et al. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology* 2013; 58: 1757–65.
9 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.
10 McDonald JA, Handelsman DJ, Dilworth P et al. Hypothalamic-pituitary adrenal function in end-stage non-alcoholic liver disease. *J Gastroenterol Hepatol* 1993; 8: 247–53.
11 Zietz B, Lock G, Plach B et al. Dysfunction of the hypothalamic-pituitary-glandular axes and relation to Child-Pugh classification in male patients with alcoholic and virus-related cirrhosis. *Eur J Gastroenterol Hepatol* 2003; 15: 495–501.
12 Fede G, Spadaro L, Tomaselli T et al. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology* 2012; 55: 1282–91.

13 Karagiannis AK, Nakouti T, Pipili C et al. Adrenal insufficiency in patients with decompensated cirrhosis. *World J Hepatol* 2015; 7: 1112–24.
14 Biggins SW, Rodriguez HJ, Bacchetti P et al. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005; 41: 32–9.
15 Kim WR, Biggins SW, Kremers WK et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; 359: 1018–26.
16 Moini M, Hoseini-Asl MK, Taghavi SA et al. Hyponatremia a valuable predictor of early mortality in patients with cirrhosis listed for liver transplantation. *Clin Transplant* 2011; 25: 638–45.
17 John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. *World J Gastroenterol* 2015; 21: 3197–205.
18 Zietz B, Lock G, Plach B et al. Dysfunction of the hypothalamic pituitary-glandular axes and relation to Child-Pugh classification in male patients with alcoholic and virus-related cirrhosis. *Eur J Gastroenterol Hepatol* 2003; 15: 495–501.
19 Jang JY, Kim TY, Sohn JH et al. Relative adrenal insufficiency in chronic liver disease: its prevalence and effects on long-term mortality. *Aliment Pharmacol Ther* 2014; 40: 819–26.
20 Marik PE, Pastores SM, Annane D et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36: 1937–49.
21 Kharb S, Garg MK, Puri P et al. Assessment of adrenal function in liver diseases. *Indian J Endocrinol Metab* 2013; 17: 465–71.
22 Sprung CL, Annane D, Keh D et al.; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358: 111–24.
23 Annane D, Pastores SM, Arlt W et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med* 2017; 43: 1781–92.
24 Annane D, Pastores SM, Rochwerg B et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017; 43: 1751–63.
25 Venkatesh B, Finfer S, Cohen J et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378: 797–808.
26 Annane D, Renault A, Brun-Buisson C et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378: 809–18.
27 Le Roux CW, Chapman GA, Kong WM et al. Free cortisol index is better than serum total cortisol in determining hypothalamic–pituitary–adrenal status in patients undergoing surgery. *J Clin Endocrinol Metab* 2003; 88: 2045–8.