



## PREVALENCE OF ADRENAL INSUFFICIENCY IN LIVER CIRRHOSIS & CORRELATION WITH CHILD PUGH SEVERITY

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**ABSTRACT** Adrenocortical dysfunction in patients with liver cirrhosis has been described for over half a century, patients had an inappropriately low response of adrenal glands to stimulation, and treatment with corticosteroids decreased mortality. To evaluate the correlation between adrenal insufficiency and the complications of chronic liver disease. The study was conducted including the patients with chronic liver diseases admitted in Liver Care Unit, Department of Medical Gastroenterology, Osmania General Hospital, Hyderabad. Among the 100 patients, 73 (73%) were males and 27(27%) were females. 20 healthy control subjects were included in this study for comparison. Among the 20 controls, 12(60%) were males and 8(40%) were females.

**KEYWORDS :** Adrenal Insufficiency; Liver Cirrhosis; Child Pugh Severity; Total cholesterol

### INTRODUCTION

Adrenocortical dysfunction in patients with liver cirrhosis has been described for over half a century(1), but was ignored until a decade ago when several studies reported that some septic patients had an inappropriately low response of adrenal glands to stimulation, and treatment with corticosteroids decreased mortality. Relative adrenal insufficiency (RAI) is the term given to inadequate production of cortisol with respect to the severity of illness [2,3].

Liver cirrhosis is a major cause of mortality worldwide, often with septic shock as the terminal event. It is a well-established fact that cirrhotic patients have increased susceptibility to bacterial infections. Both cirrhosis and septic shock share many hemodynamic abnormalities such as hyperdynamic circulatory failure, decreased peripheral vascular resistance, decreased mean arterial pressure, increased cardiac output, hyporesponsiveness to vasopressors, increased levels of proinflammatory cytokines [interleukin-1, IL-6, tumor necrosis factor and, consequently, several studies reported that adrenal insufficiency (AI) is common in critically ill cirrhotic patients (4)

The term hepato-adrenal syndrome is used to define AI in patients with advanced liver disease with sepsis and/or other complications, suggesting that adrenocortical insufficiency may be a feature of liver disease per se, with a different pathogenesis from that occurring in septic shock. Furthermore, AI may occur in compensated and decompensated cirrhosis without sepsis or in early and late post-liver transplantation (LT)[17,18]. Nowadays, liver cirrhosis is considered to be among the major groups of high-risk diseases with a predisposition to AI(5).

### AIM OF THE STUDY

To assess the prevalence of adrenal insufficiency in patients with chronic liver disease. To evaluate the correlation between adrenal insufficiency and the disease severity scores and the complications of chronic liver disease.

### MATERIAL & METHODS

The study population included consecutive patients with chronic liver diseases who were admitted in our institution.

The period of study is from January 2016 to January 2018. Patients were included to this study after offering their willingness to undergo necessary investigations. Informed written consent was obtained from the study participants before enrolment. Type of study is Cross-sectional, observational and comparative study.

### INCLUSION CRITERIA

Stable cirrhosis, Cirrhosis patients with GI bleed, Cirrhosis patients with hepatic encephalopathy, Cirrhosis patients with hepato-renal syndrome.

### EXCLUSION CRITERIA

Patients on steroids or with history of steroids intake during last 6 months, Patients with hepatocellular carcinoma, Patients with portal venous thrombosis.

### METHODOLOGY

All the patients were subjected to detailed history taking, clinical examination, blood investigations, ascitic fluid analysis, ultra sonogram and UGI endoscopy. The diagnosis of chronic liver disease is made on the basis of evidence of deranged liver function for more than 6 months duration with evidence of portal hypertension and cirrhosis in ultrasonography and upper gastrointestinal endoscopy(6)

### LABORATORY INVESTIGATIONS

Blood investigations: haemoglobin, WBC count, platelet count, prothrombin time, INR, Serum bilirubin, Total protein, albumin, alanine aminotransferase, aspartate aminotransferase, HBSAg, Anti HCV, urea, creatinine, total cholesterol. Fasting serum cortisol was done for all patients. Child Pugh score and MELD score were calculated using the various parameters.

### COMPLICATIONS

Portal hypertension, variceal bleed, ascites, renal failure, coagulopathy, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato renal syndrome, Hepatopulmonary syndrome, portopulmonary syndrome, Hepatocellular carcinoma are the most common complications.

### RESULTS

A total of 100 patients were included in the study. Among the 100 patients, 73 (73%) were males and 27(27%) were females. 20 healthy control subjects were included in this study for comparison. Among the 20 controls, 12(60%) were males and 8 (40%) were females.

**Table 1: Gender Distribution of Study Population**

| Gender  | Group    |          | Total |
|---------|----------|----------|-------|
|         | Control  | Cases    |       |
| Males   | 12 (60%) | 73 (73%) | 85    |
| Females | 8 (40%)  | 27 (27%) | 35    |
| Total   | 20       | 100      | 120   |

The preponderance of males in this study may be attributed to the etiology of the liver diseases. The most common being ethanol induced chronic liver disease.

**Table 2: Prevalence of Adrenal Insufficiency in the study Population**

| Serum Cortisol | Frequency | Percentage | Valid percentage | Cumulative percent |
|----------------|-----------|------------|------------------|--------------------|
| <5             | 29        | 29%        | 29%              | 29%                |
| >5             | 71        | 71%        | 71%              | 71%                |

|       |     |      |      |      |
|-------|-----|------|------|------|
| Total | 100 | 100% | 100% | 100% |
|-------|-----|------|------|------|

In our study, out of 100 patients, 29 patients (29%) demonstrated adrenal insufficiency with a highly significant.

**Table 3: Correlation between Adrenal Insufficiency and Etiology of the Liver Disease**

| Etiology  | Serum Cortisol |      |           |      | Total |
|-----------|----------------|------|-----------|------|-------|
|           | <5             |      | >5        |      |       |
|           | Frequency      | %    | Frequency | %    |       |
| Ethanol   | 21             | 72.5 | 31        | 43.7 | 52    |
| HBV       | 3              | 10.3 | 28        | 39.4 | 31    |
| Metabolic | 3              | 10.3 | 10        | 14.1 | 13    |
| HCV       | 2              | 6.9  | 2         | 2.8  | 4     |
| Total     | 29             |      | 71        |      | 100   |

21 patients (72.5%) with Ethanol related chronic liver disease had adrenal insufficiency. Only 3 patients (10.3%) with HBV related chronic liver disease and (6.9%) in the HCV related chronic liver disease had adrenal insufficiency. Patients (10.3%) with chronic liver disease due to metabolic cause showed adrenal insufficiency.

**Table 4: Correlation between Serum Cortisol and Child Turcotte Pugh Score**

| CTP Score | Serum Cortisol |      |           |      | Total |
|-----------|----------------|------|-----------|------|-------|
|           | <5             |      | >5        |      |       |
|           | Frequency      | %    | Frequency | %    |       |
| A         | 0              | 0    | 30        | 42.3 | 30    |
| B         | 10             | 34.5 | 25        | 35.2 | 35    |
| C         | 19             | 65.5 | 16        | 22.5 | 35    |
| Total     | 29             |      | 71        |      | 100   |

Among 100 study patients, 30 patients belong to CTP-A, 35 in CTP-B and 35 patients in CTP-C. Among the 30 patients in CTP-A, none of the patients had adrenal insufficiency. Out of 35 patients in CTP-B, 10 (28.6%) patients had adrenal insufficiency. Among 35 patients with CTP-C, 19 (54.3%) patients had adrenal insufficiency.

**Table 5: Correlation between Adrenal Insufficiency and UGI Bleed**

| UGI BLEED | Serum Cortisol |      |           |      | Total | p-value |
|-----------|----------------|------|-----------|------|-------|---------|
|           | <5             |      | >5        |      |       |         |
|           | Frequency      | %    | Frequency | %    |       |         |
| Present   | 14             | 48.3 | 17        | 23.9 | 31    | 0.017   |
| Absent    | 15             | 51.7 | 54        | 76.1 | 69    |         |
| Total     | 29             |      | 71        |      | 100   |         |

Out of 100 study patients, 31 (31%) patients had UGI bleed. Among these 31 patients, 14 patients (45.2%) had adrenal insufficiency. The correlation between adrenal insufficiency and UGI bleed was found to be statistically significant.

**Table 6 Correlation Between Adrenal Insufficiency and Hepatic Encephalopathy**

| HEPATIC ENCEPHALOPATY | Serum Cortisol |      |           |      | Total |
|-----------------------|----------------|------|-----------|------|-------|
|                       | <5             |      | >5        |      |       |
|                       | Frequency      | %    | Frequency | %    |       |
| Present               | 15             | 51.7 | 24        | 33.8 | 39    |
| Absent                | 14             | 48.3 | 47        | 66.2 | 61    |
| Total                 | 29             |      | 71        |      | 100   |

Out of 100 study patients, 39 (39%) patients had hepatic encephalopathy. Among 39 patients, 15 patients (38.5%) had adrenal insufficiency. The correlation between adrenal insufficiency and hepatic encephalopathy.

**Table 7: Correlation between Serum Cortisol and Total Cholesterol**

| Total Cholesterol | Serum Cortisol |      |           |      | Total |
|-------------------|----------------|------|-----------|------|-------|
|                   | <5             |      | >5        |      |       |
|                   | Frequency      | %    | Frequency | %    |       |
| <150              | 19             | 65.5 | 0         | 0    | 19    |
| 150 - 250         | 7              | 24.1 | 10        | 14.1 | 17    |
| >250              | 3              | 10.4 | 61        | 85.9 | 64    |
| Total             | 29             |      | 71        |      | 100   |

|           |    |      |    |      |     |
|-----------|----|------|----|------|-----|
| <150      | 19 | 65.5 | 0  | 0    | 19  |
| 150 - 250 | 7  | 24.1 | 10 | 14.1 | 17  |
| >250      | 3  | 10.4 | 61 | 85.9 | 64  |
| Total     | 29 |      | 71 |      | 100 |

In our study, 19 patients (19%) had total cholesterol <150 mg/dl, 17 patients (17%) had total cholesterol between 150-250 mg/dl and 64 patients (64%) had total cholesterol >250 mg/dl. Among the 19 patients with total cholesterol <150 mg/dl, all 19 patients (65.5%) had adrenal insufficiency which is highly significant.

**Table: 8 Comparison of Total Cholesterol between Cases and Controls**

| TOTAL CHOLESTREOL | Control   |     | Cases     |    | Total     |     |
|-------------------|-----------|-----|-----------|----|-----------|-----|
|                   | Frequency | %   | Frequency | %  | Frequency | %   |
| <150              | 0         | 0   | 19        | 19 | 19        | 100 |
| 150 - 250         | 20        | 100 | 17        | 17 | 37        | 100 |
| >250              | 0         | 0   | 64        | 64 | 64        | 100 |
| Total             | 20        |     | 100       |    | 120       |     |

On comparing total cholesterol between cases and controls, 19 (19%) patients had total cholesterol <150 mg/dl, 37 (37%) patients had cholesterol levels between 150-250mg/dl and 64 (64%) patients had cholesterol levels >250 mg/dl.

Out of 17 patients with total cholesterol between 150 - 200 mg/dl, 7 patients (24.1%) had adrenal insufficiency.

Among the 64 patients with total cholesterol >250 mg/dl, only 3 patients (10.3%) had adrenal insufficiency. The correlation between adrenal insufficiency and total cholesterol was highly significant.

**DISCUSSION**

Initial reports on AI in liver cirrhosis were followed by multiple studies and recently, by excellent systematic reviews. There are significant discrepancies between studies on the prevalence of AI in patients with liver cirrhosis<sup>(7)</sup>.

Thus, the prevalence of AI varies between critically ill cirrhotic patients (10%- 87%), those with stable cirrhosis (7%-83%), and patients with liver transplant (61%-92%).

Kharbe et al have shown that prevalence of AI varies in different stages of liver disease, with about 34.6% in acute liver disease, (40%) % in CLD and (40%) % in post liver transplant patients<sup>(8)</sup>.

**Adrenal Insufficiency And Ctp Score**

Mohamed et al showed statistically significant relationship between serum cortisol and the CTP score. Fernandez et al also reported that AI was more frequent in patients with advanced cirrhosis. (CTP C 76% Vs CTPB 25%)<sup>(9)</sup>.

Our study also demonstrates similar results with AI being reported in 10(28.6%) of patients with CTP B and 19(54.3%) of patients with CTP C and none of the patients in CTPA.

**Adrenal Insufficiency& Upper Gastro Intestinal Bleed**

Our study evaluated the correlation between AI and variceal bleeding and found that AI was significantly higher in bleeders than in non-bleeders. Among the total bleeders, 14 patients (45.2%) had been found to have adrenal insufficiency<sup>(10)</sup>.

Similar results were also shown by Triantos et al who reported higher prevalence of AI in bleeders (60%) than in non-bleeders. Wamrahian et al had reported that coagulopathy, which is commoner in patients with cirrhosis, can lead to adrenal haemorrhage and AI. Graupera et al reports high chances of failure to control bleed in patients with Adrenal Insufficiency<sup>(11)</sup>.

**Adrenal Insufficiency And Hepatic Encephalopathy**

We evaluated the correlation between Adrenal Insufficiency and hepatic encephalopathy. Totally 39 (39%) patients had hepatic encephalopathy among the study population. Among the 39 patients with hepatic encephalopathy, 15 (38.5%) patients had associated adrenal insufficiency.

Arafa et al had reported that serum cortisol concentration in cirrhotic patients with hepatic encephalopathy was significantly decreased

compared to those in patients without hepatic encephalopathy(12). Similar results were reported in most of the previous studies. Marik et al found that reduced levels of total cholesterol were associated with Adrenal Insufficiency<sup>(13)</sup>.

### Prediction Of Adrenal Insufficiency

Our study analysed the various predictors of Adrenal Insufficiency (AI) in patients with chronic liver disease. Among severe parameters, most important predictors of AI in chronic liver disease are: CTP score, Variceal bleed, Low total cholesterol.

Several studies have reported the predictors of AI in chronic liver disease. Eldamarawy et al reported that the presence of ascites, high temperature, high CRP, neutrophilia, high AST, ALT, high total bilirubin, prolonged INR and liver albumin were all factors associated with Adrenal Insufficiency<sup>(14)</sup>.

Kharb et al reports that AI was predicted by INR, CTP scores and lower basal total cortisol, albumin, total cholesterol.

### CONCLUSIONS

1. Adrenal Insufficiency occurs frequently in patients with liver cirrhosis both during critical illness and in stable disease.
2. Adrenal insufficiency occurs more frequently in patients with more severe liver disease and correlated with disease severity score (CTP).
3. Significant correlation was found with variceal bleeding, CTP score and total cholesterol.
4. Significant correlation was not observed with hepatic encephalopathy.

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