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Renal Resistive Index as a Predictor of Adrenal Insufficiency and Mortality in Decompensated Cirrhosis Patients: A Prospective Cohort Study

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Abstract:

Introduction: Liver diseases are associated with adrenal insufficiency, predominantly in critically ill patients. In our first of kind study, we measured renal resistive index and predicted adrenal insufficiency as measured by serum cortisol level in decompensated cirrhosis patients.

Methodology: A prospective observational cohort study done from October 2014 to June 2016 included 100 decompensated cirrhosis patients admitted in Lady Hardinge Medical college, New Delhi. ACTH stimulation test was done with 250mcg/dl, basal cortisol, and cortisol after 60 mins of stimulation was recorded. Renal resistive index was calculated in all patients and charted in excel sheet for statistical analysis.

Results: 28% patient were found to have adrenal insufficiency. On univariate analysis, INR, serum total bilirubin, serum creatinine, low HDL, CTP score, MELD score, plasma renin activity level, renal resistive index correlated with patients of adrenal insufficiency. Multivariate analysis showed in patients with adrenal insufficiency, MELD score had odds ratio of 1.2 with AUC 0.714 (0.632-0.895), Bilirubin with odds ratio of 5.1±2.1 and AUC of 0.696 (0.659-0.892). PRA level was 4.4 ±0.6 in patient of adrenal insufficiency with odds ratio of 4.5 (3.2-6.1). Renal resistive index (RRI) was higher with 1.1±0.4, p value < 0.001, odds ratio 95% CI-9.2 (6.1-15.2), AUC 0.816 (0.714-0.845), high sensitivity of 85% and high specificity of 83% with cut off of 0.9. Patient with adrenal insufficiency had higher mortality.

Conclusion: Adrenal insufficiency (AI) forms important part of spectrum of chronic liver disease. Deterioration of synthetic functions of liver disease predicts presence of AI. Renal resistive index predicts accurately AI and can be used as marker in future.

Keywords*: Cirrhosis, Adrenal insufficiency, ACTH, Renal resistive index, Portal hypertension.*

I. INTRODUCTION

Liver diseases are common all over the world as well as in India; and the prevalence of liver diseases is likely to increase in future. (1)Chronic liver disease diagnosis isbased on deranged liver function of more than 6 months and/or evidence of portal hypertension or altered liver echotexture on ultrasonography. (2) Among the various functions of the liver one function is metabolism of hormones. Thus, liver diseases have been shown to be associated with various endocrine disturbances like adrenocortical insufficiency, both hypothyroidism and hyperthyroidism are seen, altered metabolism of sex hormone leads to feminization in men and infertility and amenorrhea in women, metabolic syndrome links liver disease with insulin resistance, hyperlipidemia, and central obesity. Liver is a synthetic storehouse for precursors of all adrenal hormones as well as cortisol binding globulin (CBG). Hence it is not surprising that adrenal dysfunction has been reported in various spectra of liver diseases. (3) Cortisol is synthesized in adrenal gland and circulates in free and bound form with CBG. (4) Liver diseases are associated withincreased circulating endotoxins and pro-inflammatory mediators with reduced levels of apoprotein-1/HDL, (5) which is quite similar to clinical state of sepsis and results in diseased adrenal state, leading to introduction of new term “hepatoadrenal syndrome”.Adrenal insufficiency is defined by basal cortisol less than 3 mcg /dl or peak cortisol response less than 18 mcg/dl (6,7) and relative adrenal insufficiency by increment of less than 9 mcg/dl after ACTH administration as per Critical illness Related Corticosteroid Insufficiency (CIRCI). (8)As portal hypertension leads to splanchnic vasoconstriction, renal arterial vasoconstriction assessment has been used to predict acute kidney injury (AKI) in cirrhosis patients, (9) renal resistive index could also postulate the adrenal insufficiency. We undertook this study to see the role of renal resistive index by simple doppler ultrasonography of abdomen in predicting adrenal insufficiency.We also studied basal cortisol and after ACTH stimulation in patients with Chronic Liver Disease.

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II. PATIENTS AND METHODS

A. Study Design

A prospective, observational cohort study was conducted in patients of cirrhosis attending outpatient department or admitted to the department of Internal Medicine between October 2014 to June 2016 at the Lady Hardinge Medical College, New Delhi. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by an independent ethics committee and institutional review board at each study site. Investigators were responsible for data collection, data collation, and analysis. All authors had full access to study data, participated in drafting the manuscript, approved its submission for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

B. Study Participants

Patients included were having cirrhosis with age between 18 to 60 years. Patients excluded were having primary adrenal insufficiency, patients on steroid for last 6 months, diagnosed case of tuberculosis, HIV and other immunosuppressed states,metastatic disease,fungal infection, hemochromatosis, sarcoidosis.

C. Study Procedure

After an informed consent all selected patients were asked and examined according to the questionnaire and Performa designed for study. All selected patients underwent following investigations, complete blood count with peripheral smear examination,Fasting blood glucose, Liver Function Tests with Serum Proteins, Kidney Function Tests, Serum Electrolytes, PT INR, Lipid profile, Hepatitis B, Hepatitis C, Urine examination: routine and microscopy, Ultrasound abdomen with doppler, renal doppler, The operator obtained the images using a phased array sector probe at 2–3 MHz, from the patient's right or left side, on any platform with the following modes: M-mode, 2D-mode, colour, pulsed, continuous, and tissue Doppler. Doppler ultrasound assessed arterial and venous blood flow velocity within the interlobar vessels of the kidney. From the arterial Doppler tracing, the RRI can be measured from the maximal velocity (V_{max}) and the minimal velocity (V_{min}) during the cardiac cycle: $V_{max} - V_{min}/V_{max}$. In addition, Doppler waveforms of intrarenal venous flow were divided into continuous, pulsatile, biphasic, and monophasic flow.Upper GIEndoscopy, CECT Abdomen done whenever indicated, serum cortisol estimation by chemiluminiscence. Patient blood was collected in fasting and serum was separated and stored, ACTH stimulation was done in all subjects with 250 mcg of ACTH given i.m, serum sample was collected again for cortisol measurement after 60 mins.Adrenal insufficiency is defined by basal cortisol less than 3 mcg /dl or peak cortisol response less than 18 mcg/dl or increment of less than 9 mcg/dl after ACTH administration as per Critical illness Related Corticosteroid Insufficiency (CIRCI) criteria.

Doppler flow of renal vessels

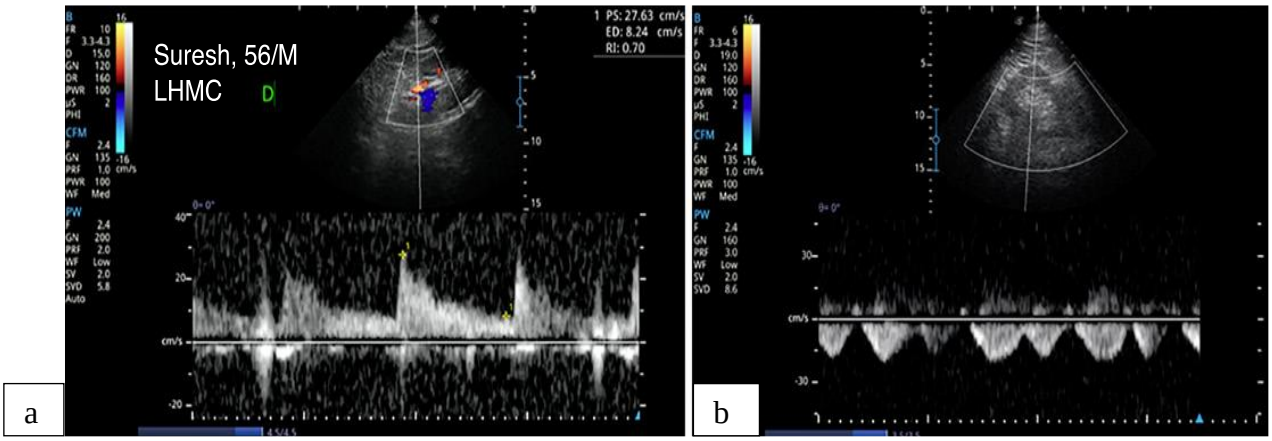

Figure 1: Depicts doppler volume position in the interlobar vessels, intrarenal artery flow. **b** Pulsatile venous pattern.

III. STATISTICAL ANALYSIS

Data was entered into Microsoft excel format and was analysed using the software packages SPSS version 20.0. Data was expressed as mean± S.D in case of normally distributed continuous variables and median (range) for continuous variables not normally distributed. Categorical variables were expressed as number (percentage). For comparison of categorical variables, chi-square and Fisher's exact tests were used. For comparison of continuous variables, t-test for normally distributed continuous variables and Mann-Whitney test for continuous variables not normally distributed were used. Beside this survival analysis, Kaplan Meir and lox regression, was carried out. P value <0.05 was considered as significant.

IV. RESULTS

Baseline characteristics showed mean age of 50±8.9 years with 76% being male and most common aetiology being alcohol liver disease (70%). Patient cohort had BMI of 27±4, BMI was not corrected with ascites. Baseline haemoglobin was 9.8±2.3g/dl, TLC was 7±4.5cells/mm^3, PLT 89±30 thousand/mm^3, baseline MELD was 22±7. Serum cortisol measure was 6.7±3.4 mcg/dl at baseline. Renal resistive index was 0.9±0.3, seen in cirrhosis patient which was higher than normal (<0.7).

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Variables	Cirrhosis (n-100)
Demography	
Age (years)	50±8.9
Gender	76% male
BMI (kg/m^2)	27±4
Biochemical	
Hb (g/dl)	9.8±2.3
TLC (cells/mm^3)	7±4.5
PLT (thousands/mm^3)	89±30
INR	2.07±0.45
T-bil (mg/dl)	5.76±1.32
AST (U/L)	63.24±24.2
ALT (U/L)	48±15
ALP (U/L)	111±39
S. Albumin (g/dl)	2.9±0.56
Urea (mg/dl)	52±17
S. Creatinine (mg/dl)	1.15±0.52
Sodium (mmol/l)	131±8.2
S. Cholesterol (mg/dl)	128±9.2
S. Triglyceride (mg/dl)	135±15
S. HDL (mg/dl)	38±18
HR (per min)	90±9
MAP (mm hg)	60±15
PRA	2.8±1.5
Basal Cortisol (mcg/dl)	6.7±3.4
Renal Resistive Index	0.71±0.3
Disease severity scores	
CTP	10.1±1.6
MELD	22±7

Table 1: Baseline characteristics of cirrhosis patients

Table 1: Baseline characteristics. CTP: child Turcotte Pugh; MELD: Model for End Stage liver disease; HR: Heart rate; MAP: Mean arterial pressure; HDL: High density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase.

Adrenal insufficiency was diagnosed in patient having basal cortisol <3mcg/dl or peak cortisol response <18mcg/dl or relative increase of less than 9mcg/dl from baseline. There were 28 patients who were diagnosed according to above mentioned criteria. On univariate analysis, INR, serum total bilirubin, serum creatinine, low HDL, CTP score, MELD score, plasma renin activity level, renal resistive index were found to be significant with p value <0.05.

Variables	Adrenal sufficient (n-72)	Adrenal insufficient (n-28)	P value
Age (yrs.)	56±7.4	57±12	0.75
BMI (Kg/m2)	27.9±2.4	27.5±2.2	0.58
Hb (g/dl)	9.5±1.7	8.8±1.5	0.18
TLC (cells/mm3)	6.6±2.6	8.1±2.7	0.08
PLT (thousand/mm3)	106±23	91±31	0.54
INR	1.3±0.25	2.0±0.44	< 0.001
Bilirubin (mg/dl)	3±1.6	5±2.1	0.001
AST (U/L)	65±20	76±24	0.50
ALT (U/L)	48±15	52±21	0.81
ALP (U/L)	153±65	125±48	0.11
Albumin (g/dl)	3.1±0.4	2.8±0.5	0.22
Urea (mg/dl)	28±14	38±18	0.09
Creatinine (mg/dl)	0.7±0.25	1.2±0.5	<0.001
Sodium (meq/L)	133±5	129±7	0.62
Potassium (meq/L)	4±0.5	4.1±0.6	0.34
HDL(mg/dl)	40±12	21±7.1	<0.02
CTP	8±0.8	10.4±1.3	<0.001

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MELD	14±4	20.6±5.3	<0.001
RRI	0.7±0.2	1.1±0.4	<0.001
PRA (ng/ml/hr)	1.8±0.3	4.4±0.6	0.001

Table 2: Univariate analysis of factors affecting the adrenal insufficiency in cirrhosis patients

Multivariate analysis was performed, in patients with adrenal insufficiency, MELD score had odds ratio of 1.2 with AUC 0.714 (0.632-0.895), sensitivity of 71% and specificity of 65.7% with cut off of 17. Bilirubin was 5±2.1 in patient of adrenal insufficiency with odds ratio of 5.1 95% CI (3.2- 12.8), AUC of 0.696 (0.659-0.892), sensitivity of 68% and specificity of 71%. PRA level was 4.4 ±0.6 in patient of adrenal insufficiency with odds ratio of 4.5 (3.2-6.1), sensitivity of 73% and specificity of 69%. Renal resistive index (RRI) was higher with 1.1±0.4, p value < 0.001, odds ratio 95% CI- 9.2 (6.1-15.2), AUC 0.816 (0.714-0.845), high sensitivity of 85% and high specificity of 83% with cut off of 0.9.

Variables	Odds ratio	AUC 95% CI	Sensitivity	Specificity
MELD	1.4 (1.2-1.6)	0.714 (0.632-0.895)	71%	65.7%
Bilirubin	5.1(3.2-12.8)	0.696 (0.659-0.892)	68%	71%
PRA	4.5 (3.2-6.1)	0.698 (0.679-0.812)	73%	69%
RRI	9.2 (6.1-15.2)	0.816 (0.714-0.845)	85%	83%

Table 3: Multivariate analysis of factors affecting the adrenal insufficiency in cirrhosis patients

Figure 2: Receiver operator characteristic (ROC) curve showed area under curve (AUC- 0.816 (0.714-0.845)) with significant p value of < 0.001. Shows patient with high renal resistive index (cut off-0.9) had more probability of adrenal insufficiency as compared to patient who had normal renal resistive index.

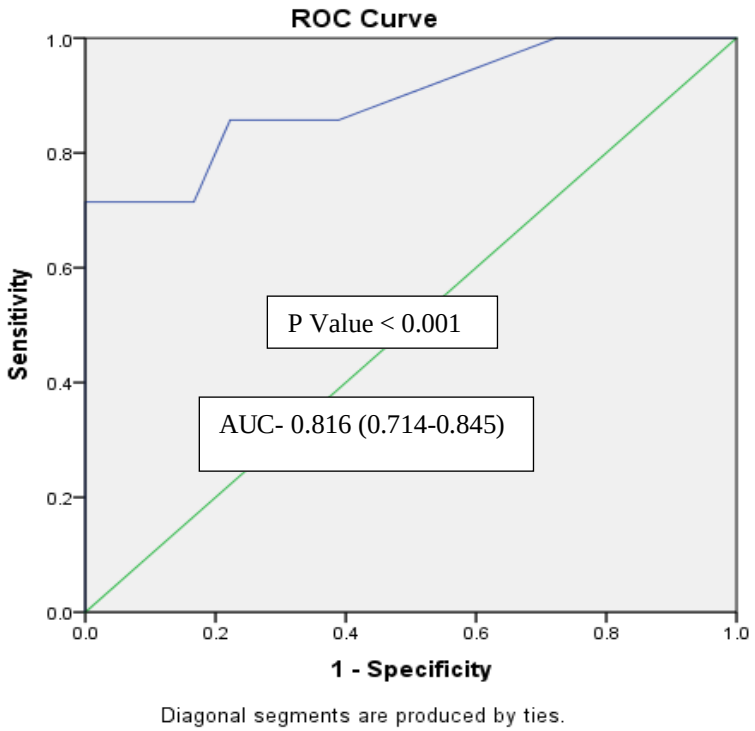

Fig. 2: Receiver operator characteristic (ROC) curve

Figure 3: Survival graph plotted in patients of adrenal insufficiency showed median survival of 35.7±6.5 days with 95% CI of (22.8-44.8), (graph showed in green line) patient who had normal adrenal function were having good survival of 74.4±3.4 days 95% CI (67.6-81.2), graph showing blue line, with significant p value of < 0.001.

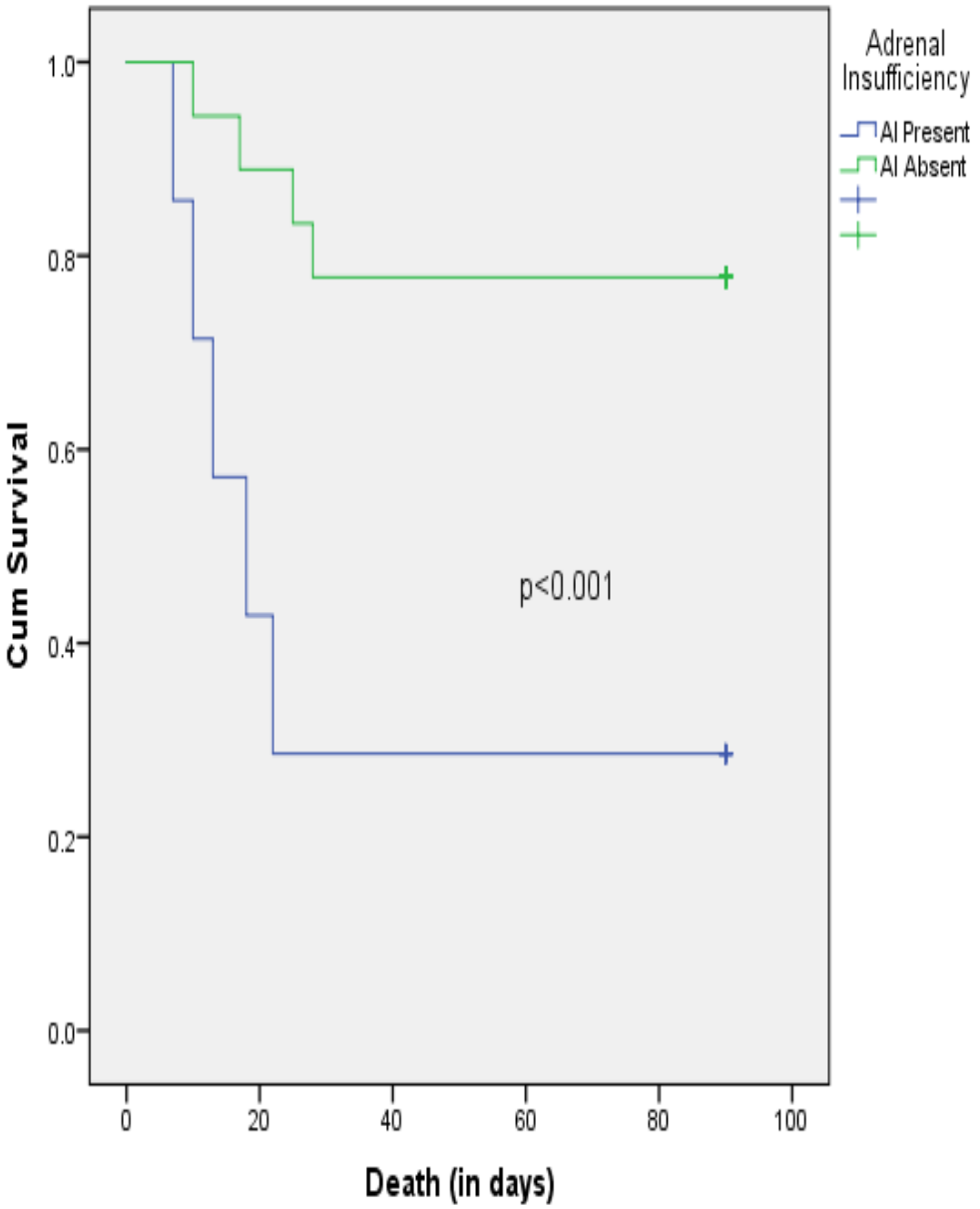

Fig. 3: Survival graph plotted in patients of adrenal insufficiency.

V. DISCUSSION

In our study, 200 patients were screened out of which 100 patients with chronic liver disease were enrolled who met inclusion and exclusion criteria from Internal medicine department in lady hardinge medical college and associated hospitals, New Delhi. They underwent a detailed history, examination, biochemical investigations, ACTH stimulation test, ultrasonography with portal venous Doppler and renal doppler, upper gastrointestinal endoscopy and hormonal evaluation. Adrenal insufficiency was diagnosed when basal cortisol was <3mcg/dl or peak cortisol of 18mcg/dl or increment of less than 9mcg/dl after ACTH stimulation test.

Study showed 28 out of 100 (28%) patients had been diagnosed as adrenal insufficiency based on serum cortisol level. Univariate analysis showed patient with adrenal insufficiency correlated with high INR, high serum total bilirubin, serum creatinine, CTP score, MELD score, high plasma renin activity level, high renal resistive index with significant p value of <0.05.

Recent study done by Wentworth et al (10) showed relative adrenal insufficiency in 37/95 patients (38.9%), using ACTH stimulation test with 250mcg/dl and measuring the increment in cortisol level, if increment less than 9mcg/dl then were classified as relative adrenal insufficiency. They also correlated with low HDL and cholesterol ester level in these patients.

Galbois et al (11) and Tan et al, (12)noted AI in 33% and 39% of subjects with stable cirrhosis using same method and criteria as in present study. However, percentage of AI

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decreased to 9 and 12% when free cortisol criteria were used by them.

In our study low HDL cholesterol 21±7.1 was associated with adrenal insufficiency as compared to 40±12 in adrenal sufficient patients.Studies by Marik et al (6)and Wentworth et al(10) also produced same result of adrenal insufficiency with low HDL levels. This can either be explained by direct decrease insubstrate supply or indirect effect of cytokines or alteration in adrenal function.

In our first of kind study we correlated renal resistive index with adrenal insufficiency and found that Renal resistive index (RRI) was higher with 1.1±0.4, p value < 0.001, odds ratio 95% CI- 9.2 (6.1-15.2), AUC 0.816 (0.714-0.845), high sensitivity of 85% and high specificity of 83% with cut off of 0.9. There have been other studies on renal resistive index as marker of predicting AKI HRS or marker of severity of liver disease but none has correlated with adrenal insufficiency.

Our study had some limitations. Firstly, we assessed AI by estimating total cortisol and liver diseases are known to decrease CBG levels and thus it might have led to over estimation of AI in this group. Secondly, AI couldn't be classified as primary or secondary as we did not measure plasma ACTH levels due to local constraints.

In conclusion, AI forms important part of spectrum of chronic liver disease. Deterioration of synthetic functions of liver disease predicts presence of AI, and these patients should be evaluated for adrenal dysfunction periodically. Adrenal function worsens with progression of liver disease. Steroid replacement in CLD patients at time of stress and critical illness may be beneficial. Also presence of AI may predict mortality of CLD patients.

- **Abbreviations**

AKI:	Acute kidney injury
BMI:	Body mass index
CTP:	Child Turcotte Pugh
MELD:	Model for end stage liver disease
HR:	Heart rate
CO:	Cardiac output
MAP:	Mean arterial pressure
RRI:	Renal Resistive index
ACTH:	Adreno corticotropic hormone
AI:	Adrenal insufficiency
HRS:	Hepatorenal syndrome

- **Conflict of interest:** None of authors have any relevant conflict of interest as it relates to this work.

- **Data Availability statement:**Manuscript draft and data collection: Satender Pal Singh. Data analysis: Satender Pal Singh, NitishaMondia. Study concept and design, and final manuscript approval: Satender Pal Singh. Patient monitoring: Lalit Kumar

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