

**A STUDY ON PROGNOSTIC VALUE OF SERUM CORTISOL IN DETERMINING THE OUTCOME IN THE CRITICALLY ILL PATIENTS**Chandrashekar M<sup>1</sup>, Shivaraj B. M<sup>2</sup>, V. P. Krishna<sup>3</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT: INTRODUCTION:** Critically ill patients are at risk for the development of adrenal insufficiency of critical illness (AICI). This may present as hypotension, unresponsiveness to catecholamine infusions, and/or ventilator dependence. The study aims at the prognostic value of serum cortisol in determining the outcome in the critically ill patients. **METHODOLOGY:** The study was conducted at the General Medicine and Intensive Care units of SMS Medical college Hospital, Jaipur. It was a Hospital based Case control study done over one year period. Patients were enrolled in to two groups after matching factors like age, sex etc. Those fulfilling definition of critical illness and APACHE II score >20 were enrolled as cases (Group A) and those with non-critical illness were included in control group (Group B). Venous blood samples for serum cortisol were drawn under aseptic conditions at morning 8AM. Serum cortisol level was determined by Chemo Luminescent Immuno Assay. Cortisol levels were then compared between group A and group B patients. Later correlation between serum cortisol and outcome in these groups was analyzed. **RESULTS:** 80 patients admitted in Medical ICU and wards, who satisfied the inclusion criteria were enrolled in the study and were grouped in to group A (40 Critically - ill ) and Group B (40 non Critically - ill ) and were followed till discharge or death. Group A, mean cortisol level was 33.68µg/dl, and in group B mean cortisol level was 15.94µg/dl and the difference was statistically significant p=0.001. There was a positive correlation between APACHE II score and cortisol level and was statistically significant. **CONCLUSION:** Cortisol level is increased in critically ill and can be used as a prognostic marker of mortality in critically ill. Correlation between APACHE II score and cortisol in our study proposes cortisol level as an alternative to complicated APACHE II score in predicting outcome in critically ill patients. Cortisol level was significantly increased in critically ill patients as compared to non-critically ill patients. Cortisol level was increased more in non-survivors than survivors.

**KEYWORDS:** Serum Cortisol, APACHE II, Critically Ill.

**INTRODUCTION:** Cortisol is a stress hormone, secreted by Zona-fasciculata which is a part of adrenal cortex, under the influence of ACTH. ACTH is released from anterior pituitary, the master gland, in pulsed manner whose peak reaches in the early morning at 6 AM, under the influence of CRH which is released from hypothalamus. Critically ill patients are at risk for the development of adrenal insufficiency of critical illness (AICI). This may present as hypotension, unresponsiveness to catecholamine infusions, and/or ventilator dependence. Cortisol level in critically ill has always been a controversy as different studies have shown variable results. Prevalence of adrenal insufficiency has been estimated to be about 30% and this value rises to 50 to 60% in septic shock (Maxime et al).<sup>1,2,3,4,5,6</sup>

**AIMS AND OBJECTIVE:** To study the prognostic value of serum cortisol in determining the outcome in the critically ill patients.

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### **MATERIAL AND METHODS:**

**Study Area:** The present study was conducted in the general medicine and Intensive Care units of SMS. Medical college Hospital, Jaipur. It was a Hospital based Case control study.

**Study Period:** This study was carried out over a period of one year (May 2012 to Apr. 2013).

**Sample Size:** Sample size was calculated at 80% study power and 0.05  $\alpha$ -error, assuming incidence of adrenal insufficiency among critically ill and non-critically ill patients to be 25% and 1% respectively. The sample size obtained was 38 in each group which was rounded off to 40 patients.

**Sample Technique:** Cases and controls were chosen randomly after matching and fulfilling inclusion and exclusion criteria.

### **Inclusion Criteria:**

#### **Group A (Critically ill patients):**

- 1) Patients admitted in Medicine department, with critical illness as defined by Van den et al.<sup>7</sup> Patients who had not received steroids previously.
- 2) Age > 18 yrs.
- 3) APACHE II score > 20.<sup>8</sup>

#### **Group B (Non-critically ill patients):**

- 1) Patients admitted in Medicine wards that were not critically ill.
- 2) Age > 18 years.

### **Exclusion Criteria:**

- 1) Those who were not willing to give informed consent.
- 2) Those who had received steroid previously.
- 3) Patients with serum albumin level < 2.5 mg/dl.
- 4) Patients previously on drugs like Phenytoin, Ketoconazole, Phenobarbitone, and Rifampin.
- 5) Pregnancy.

**METHODOLOGY:** Patients/relatives were explained about the study and given complete information regarding the procedures undertaken and written consent was taken in their local language. Patients were enrolled in to two groups after matching confounding factors like age, sex etc. Those fulfilling definition of critical illness and APACHE II score > 20 were enrolled as cases (Group A) and those with non-critical illness were included in control group (Group B).

A thorough history and past history of using steroids or corticosteroids was taken and necessary information filled in proforma. Venous blood samples for serum cortisol were drawn under aseptic conditions at morning 8AM.

Samples were transported in ice box to Advanced Immunology lab. Serum cortisol level was determined by Chemo Luminescent Immuno Assay (CLIA) (Immulite 2000). Cortisol levels were then compared between group A and group B patients. Control group was categorized in to three groups based on cortisol levels: < 15  $\mu$ g/dl (low cortisol), 15-34  $\mu$ g/dl (Normal serum cortisol), > 34  $\mu$ g/dl (Abnormally raised cortisol). (Cooper et al)<sup>9,10</sup> Later correlation between serum cortisol and outcome in these three groups was analyzed.

**Outcome Analysis:** Data obtained from predesigned proforma was entered in to MS Excel sheets and thus master charts were prepared so as to find out statistical significance by unpaired t test or Chi-

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square test as per the character of data. Linear regression coefficient was used to find out the correlation between APACHE II score and Cortisol levels.

**Defining Critical Illness:** "Critical illness is any condition requiring support of failing vital organ systems without which survival would not be possible".<sup>11</sup>

**OBSERVATION AND RESULTS:** From May 2012 to Apr. 2013. 80 patients admitted in Medical ICU and wards, who satisfied the inclusion criteria were enrolled in the study and were grouped in to group A (40 Critically - ill ) and Group B (40 non Critically - ill ) and were followed till discharge or death.

**Patients Demographics:** The following were the base line demographics in the two groups who were enrolled in study.

AGE	Group A (CRITICALLY-ILL)		Group B NON CRITICALLY ILL	
	A	Percentage	N	Percentage
0-20	3	7.5	2	5
21-40	10	25	11	27.5
41-60	15	32.5	14	35
61-80	10	25	10	25
>80	2	5	3	7.5
Mean	49.88	16-86 Yrs. (Range)	51.4	17-82Yrs (range)

**Table 1: Baseline Demographic data of patients according to age**

Age distribution of patients in the two groups is shown in table 1. Mean age of patients in critically ill group and non-critically ill group were 49.88 and 51.4 respectively. Most common age group among both was between 41 to 60 years.

Out of 40 patients included in the group A Pulmonary and neurologic illness were most common causes (25%) of critical illness. Followed by sepsis (20%), CAD (3%) and Malignancy (3%) were among least common etiology.

	Group A	Group B
Mean cortisol in ( $\mu\text{g}/\text{dl}$ )	33.68	15.94
SD	15.94	5.93
SEM	2.77	0.9391
Median	28.59	14.6
Range	13.2-75	5.02-30.77
Un paired t test: $t=6.047$ , $P=0.001$		

**Table 2: Comparison of Serum cortisol in critically- ill and non -critically ill**

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From the above table it can be clearly seen that in group A, mean cortisol level was 33.68 $\mu$ g/dl, and in group B mean cortisol level was 15.94 $\mu$ g/dl. And the difference was statistically significant  $p=0.001$ .

APACHE II score	Cortisol level in $\mu$ g/dl					
	<15		15-34		>34	
	N	%	N	%	N	%
20-25	2	8.6	15	65.2	6	26.08
26-30	2	16.6	5	41.66	5	41.66
31-35	0	0	1	20	4	80
Pearson correlation coefficient: $R=0.55$ , $R^2$ is 0.3						
<b>Table 3: Correlation of APACHE II scores with cortisol levels in critically ill</b>						

The above table depicts the correlation between APACHE II score and Cortisol level, which clearly shows that there, is a positive correlation between APACHE II score and cortisol level and was moderately statistically significant according to Pearson correlation coefficient.

Out come	Number (n)	%
Survivors	15	37.5
Non-Survivors	25	62.5
<b>Total</b>	<b>40</b>	<b>100</b>

**Table 4: Outcome of critical illness**

**Mortality:** 62%.

The above table depicts the outcome of critical illness. Among 40 critically ill groups 25 (62.5%) patients expired due to their illness.

APACHE II SCORE	PREDICTED MORTALITY%*	OBSERVED MORTALITY%
20-24	40	40.9
25-29	55	100
30-34	75	77.7

**Table 5: APACHE II Score and Mortality**

In table 5 it can be seen that predicted mortality among APACHE II score group 20-25, 26-30, 31-35 were 40, 55 and 75% respectively. However the actual mortality rate among the study population was 40.9%, 100% and 77.7% respectively.

\* As predicted by APACHE II calculator of Medscape. And CCU survival guide.

**DISCUSSION: Cortisol As a Prognostic Marker of Outcome:** APACHE II score is routinely used for prediction of mortality in critically ill patients. Yang Y et. al<sup>11</sup> in their study found that serum cortisol was comparable to APACHE II score in predicting mortality among critically ill patients. In our study we found that cortisol level was a reliable tool for prediction of mortality and it has moderately significant positive correlation with APACHE II score as derived by Pearson correlation coefficient

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with R value of 0.55. Thus Serum cortisol level can be used to predict mortality, as an alternative to APACHE II score which is cumbersome to calculate because large number of data is required to calculate it.

### Limitations of Our Study:

- 1) Serum free cortisol was not evaluated which is considered as the best indicator of cortisol level in critically ill. However we managed to negate this effect by excluding patients with hypoalbuminemia.
- 2) ACTH stimulation test is important in diagnosis of adrenal Insufficiency. Which tells about functional state of HPA axis? However we could not perform this test due to economic constrains.

**SUMMARY AND CONCLUSION:** The present study was a hospital based case control study conducted from May 2012 to Apr. 2013 from Medicine wards and Medical ICU. 80 patients were enrolled in the study and grouped in to two, Group A (critically ill) Group B (Non-critically ill) 40 patients in each group. Serum cortisol levels were estimated and a comparison was done in both the groups. The age range in group A was 16-86 years and mean age was 49.88yrs. In group B age range was 17-82 years and mean age was 51.4 years. Male outnumbered females in both group A and group B. Most common cause of critical illness in our study was pulmonary infections (25%) and neurologic illness (25%). While in non-critically ill most common cause of hospital admission was Dengue (35%) followed by Malaria(17%). Cortisol level was significantly increased in critically ill group ( $33.68 \pm 15.9$ ) compared to non-critically ill ( $15.94 \pm 5.93$ ). It was also noted that mortality was high in patients with increased cortisol level as compared to those with normal cortisol level ( $15-34 \mu\text{g}/\text{dl}$ ). Hence it can be derived that cortisol level is increased in critically ill and can be used as a prognostic marker of mortality in critically ill. Correlation between APACHE II score and cortisol in our study proposes cortisol level as an alternative to complicated APACHE II score in predicting outcome in critically ill patients.

Cortisol level was significantly increased in critically ill patients as compared to non-critically ill patients. Cortisol level was increased more in non-survivors than survivors. Which implies that this stress response can be used as a prognostic tool of mortality in critically ill patients?

### REFERENCES:

1. Maxime, Oliver Lensur Adrenal insufficiency in septic shock. Clin. chest Med 30(2009) 17-27.
2. Collip JB, Anderson EM, Thompson DL. The adrenocorticotrophic hormone of the anterior pituitary lobe. Lancet 1933; 2: 347-8.
3. Gallo-payet N, Guilion G. Regulation of adrenocortical function by vasopressin. Horm Metab Res 1998; 30(6-7): 360-7.
4. Oelskar W. Hyponatremia and inappropriate secretion of vasopressin (Antidiuretic hormone) in patients with hypopituitarism. N Eng. J Med 1989; 321(8): 492-6.
5. Papenek PE, Raff H. Chronic physiologic increases in cortisol inhibit the vasopressin response to hypertonicity in conscious dogs. Am J Physiol 1994; 267(5pt2): R1342-9.
6. Maxime v, Siami S, Annae D. Metabolism modulators in sepsis: the abnormal pituitary response. Crit. care Med 2007; 35(9S): S596-601.

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7. Tatemoto k, Hosoya M, Habata,et al. isolation and chatacterization of a novel endogenous peptide ligand for the human APJ receptor ligand for human APJ receptor. Biochem Biophys Res commun 1998; 251(2): 471-6.
8. Amir H. Hamrahian, M. D., Tawakalitu S. Oseni, M. D., and Baha M. Arafah, M.D. Measurements of Serum Free Cortisol in Critically Ill Patients. N ENG J MED 350; 16.
9. Jenn-Yu Wu, Szu-Chun Hsu, Shih-Chi Ku, Chao-Chi Ho, Chong-Jen Yu and Pan-Chyr Yang. Adrenal insufficiency in prolonged critical illness. Critical Care 2008, 12.
10. Mark S. Cooper, M. D., and Paul M. Stewart, M.D. Corticosteroid Insufficiency in Acutely Ill patients. N Engl. J Med 2003; 348: 727-34.
11. Muzaffar Maqbool, Zafar Amin Shah, Fayaz Ahmad Wani, Abdul Wahid, Shaheena Parveen, and Arjumand Nazir. Prevalence of occult adrenal insufficiency and the prognostic value of a short corticotropin stimulation test in patients with septic shock Indian J. Crit. Care Med. 2009 Apr-Jun; 13(2): 85-91.

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