ORIGINAL ARTICLE

SERUM CORTISOL LEVEL AS A PREDICTOR OF SEVERITY AND OUTCOME IN COMMUNITY ACQUIRED PNEUMONIA

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ABSTRACT: Community Acquired Pneumonia imposes a considerable burden on health care facilities in developing countries like ours where resources are already scarce, therefore the need for simple and easy methods of stratification of the cases with regard to severity is undeniable. Recent studies have shown that cortisol level is a reliable predictor of outcome and risk stratification in patients with Community Acquired Pneumonia, therefore cortisol level estimation is advisable which will help guide the management, and reduce the burden on the individual and health care facilities. The most established scoring systems are the PSI-score and the CURB or CRB-65 scores, which perform comparably for mortality prediction and identification of low risk patients suitable for an outpatient management strategy.¹ additionally, biomarkers have been found to improve risk stratification and management decisions in CAP.² The aim of our study is to determine the serum cortisol level as a predictor of severity and outcome in Community Acquired Pneumonia. **MATERIAL AND METHODS:** The study was conducted in the Department of Medicine, Pt. Jawaharlal Nehru Memorial Medical College and Dr. B.R.A.M. Hospital, Raipur (C. G.) among 50 patients admitted in medicine ward who were diagnosed as a case of pneumonia on admission. The study was conducted between April 2013-September 2014. **RESULTS:** Out of the 17 patients with a CURB-65 score of 0-1, the mortality is 0, 2 out of the 17 patients with CURB-65 score of 2 died within 30 days of admission and 6 out of the 16 patients with a CURB-65 score of 3-5 died within 30 days of admission which was statistically significant ($p < 0.01$, OR= 9.75). Out of the 37 patients with a Cortisol level ≤ 27.23 , there was negative outcome on 5.4% of the patients. Out of the 13 patients with Cortisol level > 27.23 , 46.15% had a negative outcome and this findings was statistically significant with p value of < 0.01 and OR=8.53. **CONCLUSION:** The findings in our study indicates that severity of pneumonia is related to serum cortisol level which has a strong prediction as to the course of the disease and outcome of the patients. Strong association between elevated cortisol levels and severity of illness and the risk of death have been demonstrated. There is a positive correlation between CURB-65 score and serum cortisol level. **KEYWORDS:** Serum Cortisol Level, Community Acquired Pneumonia.

INTRODUCTION: Pneumonia was described 2,500 years ago by Hippocrates, the father of medicine. Dr. William Osler, the founder of modern medicine, who studied pneumonia throughout his career, called pneumonia the "Captain of the men of death" because of the great toll it exacted on humanity. In the 1930s, before the advent of antibiotics, pneumonia was the third-leading cause of death in the United States. Notably, it remains a leading cause of death. In 2006, it was the eighth-leading cause of death, accounting for about 55,000 deaths (CDC, 2010).

The human and economic burden of pneumonia is enormous.

In fact, World Health Organization data indicate that respiratory infections, a term which in this context is synonymous with pneumonia, account for more deaths among children worldwide than any

ORIGINAL ARTICLE

other cause and for more disability-adjusted life years lost around the world than any other category of disease, including cancer and cardiovascular disease.³

Indian Context: There are no large studies from India on the incidence of CAP, but mortality data on the total number of deaths caused by “lower respiratory tract infections” are available (WHO, 2012).

The number of deaths due to lower respiratory tract infections was 35.1/100,000 population in the year 2008 compared to 35.8/100,000 population for TB, while it was 194.9/100,000 for infectious and parasitic diseases. Thus, around 20% of the mortality due to infectious diseases in India is caused by lower respiratory tract infections.

The reported mortality of CAP from India is similar to that reported elsewhere in the world.

WHO mortality figures for lower respiratory tract infections in India (WHO, 2012)	
Age Group (years)	No. of Deaths per lakh Population in 2008
15–59	6.2
>60	622.2
Overall	35.1

A disease severity based approach with initial risk stratification is required to guide management and treatment decisions in CAP. International guidelines recommend prognostic scores to support clinical decision on management as outpatient, inpatient or admission to ICU. The most established scoring systems are the PSI-score and the CURB or CRB-65 scores, which perform comparably for mortality prediction and identification of low risk patients suitable for an outpatient management strategy.¹ amongst them, the CRB-65 score is the easiest way to calculate and widely used in Europe.⁴ Additionally, biomarkers have been found to improve risk stratification and management decisions in CAP.²

However, accurate mortality prediction does not automatically lead to accurate identification of patients developing critical disease in need for intensive care treatment. Both the CRB-65 and PSI scores lack accuracy for the prediction of high risk situations resulting in ICU admission.⁵ other scoring systems have been proposed to identify patients requiring admission to ICU like the modified American Thoracic Society (ATS)-rule.⁴ and more recently the new ATS/Infectious Diseases Society of America (IDSA)-recommended score.⁶

However, both scores still fail to identify a significant proportion of patients with early deterioration and have poor positive predictive values for ICU-admission. Thus, identifying patients with a high benefit from initial intensive management strategies in CAP remains an important task to be done.⁴ recently, serum cortisol concentration was shown to be associated with severity and mortality in CAP in three small trials by Kolditz M et al, Christ Crain M et al and Gotoh S et al.

Additionally, high cortisol levels reflect a higher degree of stress.⁷ the effects of cortisol are directed toward the acute provision of energy, protection against excessive inflammation, and improvement in hemodynamic status.⁸ Therefore, appropriate activation of the hypothalamic-pituitary adrenal axis during illness is essential for survival, and parallels the degree of stress.

The activation of the hypothalamic-pituitary-adrenal axis in critically ill patients is characterized by an increase in free cortisol levels,⁹ and a strong association between elevated cortisol levels and severity of illness and the risk of death have been demonstrated.¹⁰

ORIGINAL ARTICLE

AIMS AND OBJECTIVES:

- To determine CURB-65 score of all the patients.
- To determine the serum cortisol level of all the patients.
- To evaluate the relationship between CURB-65 score and outcome (30 days mortality) of the patients.
- To compare CURB-65 score and Serum Cortisol level regarding outcome of the patients.
- To determine the serum cortisol level as a predictor of severity and outcome in Community Acquired Pneumonia.

MATERIAL AND METHODS: This cross sectional study comprising 50 cases was conducted in the Department of Medicine, Pt. Jawaharlal Nehru Memorial Medical College and Dr. B.R.A.M. Hospital, Raipur (C.G.) between April 2013 –September 2014. The study was approved by the Institutional ethical committee.

Inclusion Criteria: Age above 16 yrs. with the following signs or symptoms:

1. Cough, sputum production, dyspnoea.
2. Core body temperature exceeding 38 degree Celsius/100.4 degree Fahrenheit.
3. Auscultatory findings of abnormal breath sounds and rales.
4. Leukocyte count greater than 10×10^9 or less than 4×10^9 cells/L.
5. Infiltrates on chest radiograph.

Exclusion Criteria:

1. Active pulmonary tuberculosis.
2. Immunocompromised patients.
3. Hospital acquired pneumonia.

METHODS:

1. A total of 50 patients were taken fulfilling the inclusion criteria for the study.
2. Patient's informed consent was taken.
3. Detailed clinical history was recorded using a pre-structured questionnaire which included age, sex, presenting complaints, past, personal and family history.
4. All patients then underwent complete clinical examination including pulse, blood pressure, general examination and systemic examination.
5. Severity of Pneumonia was graded according to CURB-65 scoring system.
6. Cortisol level of all patients diagnosed as CAP on admission was estimated using Elisa kit. Enzyme immunoassay kit (EIA) was used to measure serum cortisol level.
7. The cut-off value of cortisol level was taken as 27.23 microgram/decilitre (the upper limit of normal value), where value higher than the cut-off were considered to predict poor prognosis.

Statistics: Statistical analysis was done using Pearson Chi square test and Odds ratio. Statistical significance was taken as a value of $p < 0.05$. The Chi-square tests for association between two categorical variables - for example, gender (males and females) and smoking habit (smoker and non-smoker).

ORIGINAL ARTICLE

Requirements:

- Random sample.
- Observations must be independent of each other (for example, no matched pairs).
- Cell count must be 5 or above for each cell in a 2 x 2 contingency table.

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

Formula for CHI SQUARE TEST (where O is observed value and E is expected value)

$$\text{Odds ratio} = \frac{PG_1 / (1 - PG_1)}{PG_2 / (1 - PG_2)}$$

Formula for obtaining odds ratio. (Where “PG1” represents the odds of the event of interest for Group 1, and “PG2” represents the odds of the event of interest for Group 2).

Fig. 1: Correlation of Cortisol Level in relation to CURB-65 with Outcome

	<u>Cortisol <27.23</u>	Cortisol>27.23
Mean CURB-65 score	1.59±0.79	3.38±0.65

Table 1. Mean CURB-65 score in relation to cortisol level.

ORIGINAL ARTICLE

	Cortisol level	
Curb-65 score	≤ 27.23	> 27.23
0-1	16(32%)	0(0%)
2	17(34%)	1(2%)
3-5	4(8%)	12(24%)
Total	37(74%)	13(26%)
Chi square statistic =29.498, $p < 0.01$		

Table 2. Correlation of CURB-65 and Cortisol Level

Curb-65 Score	Cases	Mortality
0_1	16	0 (0%)
2	18	2 (11.76)
3_5	16	6 (37.5)
Chi Square statistic =6.1638		
P = 0.04 , Odds ratio =9.75		
95% CI =1.22 -37		

Table 3. Correlation of CURB-65 score with Mortality (Outcome)

RESULTS: In our study out of 50 patients, 26 patients (52%) were male while 24 patients (48%) were female. Maximum of the subjects were between 40-64 years of age and comprised 22(44%) of sample size, subjects above or equal to 65 years comprised 9(18%) and the age group between 15-39 comprises 19(36%) of the study group.

The mean CURB-65 of the study population whose cortisol level was < 27.23 was 1.59 ± 0.79 and the mean CURB-65 score of the study population whose cortisol level > 27.23 was 3.38 ± 0.65 . So, we observed from the above findings that the mean CURB-65 score of the patients whose cortisol level were more than 27.23 are much higher.

There were 12 patients who had a history of chronic smoking out of which 2 patients had a negative outcome which was 16.67% of the total smoker, but this finding was statistically insignificant. Comorbidities were present in 8 patients of which 1 patients had history of CVA, 3 patients had history of HTN, 3 patients had history of DM 2 and 1 patient had both HTN and DM 2.

Out of these patients with comorbidities there was no negative outcome, so the presence of comorbidities had no significant impact in our study.

In our study group, there were 17 patients with low risk group and all of these patients had a cortisol level ≤ 27.23 and no patient had cortisol level above 27.23. Among patients with moderate risk

ORIGINAL ARTICLE

group there were 16 patients with a cortisol level of ≤ 27.23 and 1 patient with a cortisol level of >27.23 and among patients with high risk group, 4 patients had a cortisol level of ≤ 27.23 and 12 patients had cortisol level above the cutoff value. This findings were statistically significant ($p < 0.01$) meaning there was a positive correlation between CURB-65 score and cortisol level.

CURB-65 score is further grouped into 0-1 (Low risk), 2 (Moderate risk) and 3-5 (high risk) groups.

In our study, the mean CURB-65 score of the population under study was 2.06 with standard deviation of ± 1.09 . We also found that the mean CURB-65 score were much higher in patients with cortisol level above 27.23.

Out of the 17 patients with a CURB-65 score of 0-1, the mortality is 0, 2 out of the 17 patients with CURB-65 score of 2 died within 30 days of admission and 6 out of the 16 patients with a CURB-65 score of 3-5 died within 30 days of admission which was statistically significant ($p < 0.01$, OR= 9.75).

In our study we found association between Cortisol level with CURB-65 scoring system.

Within a CURB-65 score of 0-1(low risk), there were 16 patients with cortisol level within normal limits whereas there were no patient with a low CURB-65 score with cortisol level above the normal cutoff range .

Within a CURB-65 score of 2(moderate risk), there were 17 patients with cortisol level within normal limits whereas only 1 patient had a low CURB-65 score but had a cortisol above the normal cutoff range .

Within a CURB-65 score of 3-5(high risk), there were 4 patients with cortisol level within normal limits whereas there were 12 patients with a cortisol level above the cutoff value.

This finding help us to conclude that with higher CURB-65 score greater are the chances of getting cortisol level above normal. This was also statistically relevant with $p < 0.01$.

Out of the 37 patients with a Cortisol level ≤ 27.23 , there was negative outcome on 5.4% of the patients. Out of the 13 patients with Cortisol level > 27.23 , 46.15% had a negative outcome and this findings was statistically significant with p value of < 0.01 and OR=8.53.

DISCUSSION: The main findings in our study shows that higher CURB-65 score and cortisol level above 27.23 is related with poorer outcome. Physiologically, acute stress like severe illness leads to an activation of the hypothalamic-pituitary-adrenal axis which protects the organism against excessive inflammatory responses. However, before cortisol measurement can be recommended for clinical routine use as biomarker in CAP, a prospective interventional trial is necessary to prove its accuracy and cost-effectiveness in comparison to evaluated clinical scores and competitive biomarkers for predicting patients benefiting from intensified treatment and monitoring strategies.

Previous studies have shown an increase of cortisol levels that parallels the severity of infection and prognosis of patients with severe sepsis and septic shock². In our study we correlate the severity as measured by CURB-65 scoring system with cortisol level with a significant correlation between them and the outcome in CAP and cortisol level independent of the CURB-65 score had a good prognostic correlation with the severity and outcome.

In our study we did not find the correlation between severity and outcome of pneumonia with comorbidities and smoking which had been demonstrated in previous studies.⁶

The Limitation of our study is that not all critically ill patients received early ICU admission and as blood samples were taken at time of first contact, controlling for the time point of blood sampling

ORIGINAL ARTICLE

could not be done. Cortisol exhibits diurnal concentration changes; however, during infectious diseases the circadian pattern is often lost⁸ and previous adrenal status was not known.

SUMMARY AND CONCLUSION:

Following is the Summary and Conclusion:

- In our study out of 50 patients, 26 patients (52%) were male while 24 patients (48%) were female.
- Maximum of the subjects were between 40-64 years of age and comprised 22(44%) of sample size, subjects above or equal to 65 years comprised 9 (18%) and the age group between 15-39 comprises 19 (36%) of the study group.
- There were 12 patients who had a history of chronic smoking out of which 2 patients had a negative outcome which was 16.67% of the total smoker, but this finding was statistically insignificant.
- Comorbidities were present in 8 patients of which 1 patients had history of CVA, 3 patients had history of HTN, 3 patients had history of DM 2 and 1 patient had both HTN and DM 2. Out of these patients with comorbidities there was no negative outcome, so the presence of comorbidities had no significant impact in our study.
- In our study group, there were 17 patients with low risk group and all of these patients had a cortisol level <27.23 and no patient had cortisol level above 27.23. Among patients with moderate risk group there were 16 patients with a cortisol level of <27.23 and 1 patient with a cortisol level of >27.23 and among patients with high risk group, 4 patients had a cortisol level of <27.23 and 12 patients had cortisol level above the cut-off value. This findings were statistically significant ($p<0.01$) meaning there was a positive correlation between CURB-65 score and cortisol level.
- In our study, the mean CURB-65 score of the population under study was 2.06 with standard deviation of +1.09. We also found that the mean CURB-65 score were much higher in patients with cortisol level above 27.23.
- Out of the 17 patients with a CURB-65 score of 0-1, the mortality is 0, 2 out of the 17 patients with CURB-65 score of 2 died within 30 days of admission and 6 out of the 16 patients with a CURB-65 score of 3-5 died within 30 days of admission which was statistically significant ($p<0.01$, OR= 9.75).
- Out of the 37 patients with a Cortisol level <27.23, there was negative outcome on 5.4% of the patients. Out of the 13 patients with Cortisol level >27.23, 46.15% had a negative outcome and this findings was statistically significant with p value of <0.01 and OR=8.53.

To conclude, the findings in our study indicates that severity of pneumonia is related to serum cortisol level which has a strong prediction as to the course of the disease and outcome of the patients. Cortisol as a single reading on admission is a reliable and easy method in planning the management and can serve as an important tools for risk stratification.

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ORIGINAL ARTICLE

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