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THE COMPARISON OF SERUM CORTISOL LEVEL, CURB-65, AND PSI SCORES BEFORE AND AFTER TREATMENT IN COMMUNITY-ACQUIRED PNEUMONIA

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Abstract

Background: Pneumonia severity index (PSI) dan CURB-65 were deemed as themes established and commonly used scoring systems in community-acquired pneumonia (CAP). Serum cortisol concentration has been reported to be associated with severity of CAP. This study was aimed to compare the serum cortisol level, CURB-65, and PSI scores on hospital admission to day 7 of treatment in CAP.
Methods: This was an observational analytic cohort study. The study was conducted at Haji Adam Malik Medan public hospital. Analysis were done using paired-t test if the data were normally distributed, and Wilcoxon test if otherwise.
Results: There were significant differences values on initial and day 7 of cortisol levels (23.12±8.57 µg/dL vs 13.74±2.64 µg/dL; $p < 0.001$), CURB-65 scores (3.25±0.67 vs 1.47±0.67; $p < 0.001$), and PSI scores (3.73±0.93 vs 2.2±0.76; $p < 0.001$).
Conclusion: There were significant differences of serum cortisol levels, CURB-65, and PSI scores on admission compared to day 7 treatment.

Introduction

Pneumonia is defined as an inflammatory condition of the lung caused by microorganisms (bacteria, virus, fungus, parasite) other than *Mycobacterium tuberculosis* (PDPI, 2003).Pneumonia causes enormous human and economic burden. Based on Indonesian Basic Health Researches, the period prevalence and prevalence of pneumonia in 2013 were 1.8% and 4.5%, respectively (Kemenkes, 2013).

Community-acquired pneumonia (CAP) is a type of pneumonia that is acquired outside the hospital. It is accounting for a considerable number of hospital admissions, with an increasing incidence and an increasing rate of serious complications (Steel *et al*, 2013).

Various scoring systems could be used to predict the severity of CAP. Among those tools, pneumonia severity index (PSI) dan CURB-65 were deemed as the most established and commonly used scoring systemsfor predicting the risk and mortality of CAP in clinical practice (Shehata*et al*, 2017; Chandravanshi*et al*, 2015).

Serum cortisol concentration has been shown to be associated with severity and mortality of CAP. Cortisol was reported to be able to predict persistent clinical instability, making it a potential parameter to improve the identification of patients with high risk for a complicated disease course (Kolditz*et al*, 2010; Kolditz*et al*, 2012).

Recently, studies have shown that cortisol, PSI, and CURB-65 are able to assess CAP severity. However, to our knowledge, no previous studies has been undertaken to compare those parameters before and after treatment. IDSA/ATS recommended that patients with CAP should be treated for a minimum of 5 days (Mandell*et al*, 2007). ERS/ESCMID recommended a treatment duration that no longer than 8 days (Pinzone*et al*, 2014). The aim of this trial was to compare the serum cortisol level, CURB-65, and PSI scores on hospital admission to day 7 of treatment in CAP. Furthermore, we also evaluate the correlation of initial cortisol level with CURB-65 and PSI scores.

Methods

Design and Subject

This study was approved by the Ethic Committees of University of North Sumatera and Haji Adam Malik Medan Public Hospital. This was an observational analytic study with prospective design and was held since 1 June to 30 June 2018.

The inclusion criteria was patients with primary diagnosis of community-acquired pneumonia and aged ≥ 18 years old. Patients were excluded if they consumeany anti-inflammatory medicine, die before the end of follow up period (7 days), or refuse to participate in the study. Subjects were recruited using consecutive sampling technique.

Statistics

The comparison of serum cortisol concentration, CURB-65 score, and PSI on admission and day 7hospitalisation was done using paired t test if the data was normally distributed, and Wilcoxon test if otherwise. The same also applied for the comparison of initial serum cortisol with CURB-65 score and with PSI score.

Results

Among 50 CAP patients, ten (20%) were died within 7 days of care, leaving 40 (80%) others to continue in this study. The subjects' demographic characteristics were displayed in Table 1.

Table 1. Demographic Characteristics

Characteristics	Frequency	Percentage (%)
Gender		
Male	23	57,5
Female	17	42,5
Age (years)		
< 65	19	47,5
≥ 65	21	52,5
Marital status		
Married	36	90
Not married	4	10
Education		
Primary	8	20
Secondary	28	70
Tertiary	4	10
Occupation		
Entrepreneur	8	20
Housewife/ unemployed/ retired	22	55
Farmer	6	15
Officials	3	7,5
Lecturer	1	2,5
Nursing house resident	0	0

More than half of the subjects were male (57.5%), ≥ 65 years old (52.5%), and not working/ housewife/ retired (55%). Predominant of the subjects were married (90%), and had high school as the last education (70%). None of the subjects (0%) was nursing home resident.

Table 2 showed the clinical characteristics of the subjects. CAP in this study was most commonly caused by Streptococcus pneumoniae (32.5%), and the most common co-morbid disease was congestive heart failure (20%).

Table 2. Clinical Characteristics

Characteristics	Frequency	Percentage (%)
Microorganism		
Strep. pneumoniae	13	32,5
Staph. haemolyticus	10	25
K. pnemoniae	9	22,5
Acinobacter sp.	3	7,5
K. oxytoca + E. hermannii	3	7,5
Staph. pneumoniae	1	2,5
Staph. hominis	1	2,5
Comorbidities		
Malignancy	1	2,5
Liver disease	1	2,5
Congestive heart failure	8	20
Cardiovascular disease	3	7,5
Renal disease	3	7,5

The comparison of initial and day 7 admission studied parameters were shown in Table 3. The mean of initial cortisol level was 23.12±8.57 µg/dL and 7 days after admission was 13.74±2.64 µg/dL. The difference was 9.38 µg/dL and was statically compared using Wilcoxon test, resulting $p < 0.001$.

Table 3. Comparison of Mean Cortisol Level, CURB-65, and PSI Scores on Before and Day 7 Treatment

Variable	Initial	Day 7	p value
Serum cortisol (μg/dL)	23,12±8,57	13,74±2,64	<0,001
CURB-65	3,25±0,67	1,47±0,67	<0,001
PSI	3,73±0,93	2,2±0,76	<0,001

The mean initial CURB-65 score was 3.25±0.67 and 7 days after 1.47±0.67. Statistic test was done using paired t test showed p <0.001.Initial PSI was 3.73±0.93 and 7 days post treatment was 2.2±0.76. The difference was analysed paired t test, $p < 0.001$.

Table 4. Mean Cortisol Level in Each Group of CURB-65 and PSI

Variable	Score	Mean Cortisol (μg/dL)	P value
CURB-65	2	20.67±9.37	0.047
	3	21.00±7.13	
	4	25.86±7.81	
	5	42.05±3.61	

	1	17.60	
	2	17.83±6.41	
PSI	3	18.04±6.30	0.002
	4	22.31±6.78	
	5	35.03±6.39	

Table 4 showing the mean cortisol level on each group of CURB-65 and PSI. Statistic showed p values 0.047 and 0.002, for CURB-65 and PSI respectively.

Discussion

Cortisol, the predominant corticosteroid secreted by the adrenal cortex, is an important endogenous regulator of inflammation. During a severe acute illness such as severe pneumonia, a complex interaction between the circulating proinflammatory cytokines and the endocrine system occurs (Salluh*et al*, 2008). Plasma cytokines, including interleukin (IL)-1, IL-6 and tumor necrosis factor-a, stimulate the production of corticotropin-releasing hormone and adrenocorticotropic hormone (ACTH) (Gotoh*et al*, 2008). Cytokines also signal to vagal afferent fibers and activate the hypothalamic-pituitary axis (Salluh*et al*, 2008).

There was a significant difference of serum cortisol level at the admission and on day 7 treatment. Remmelts*et al* (2012) done a study focusing on the changes of serum cortisol on pneumonia patients, and reported that the changes cortisol level during admission can be a useful biomarker for prognosis. However, there were some differences between their and our studies. The study involved a group of subjects who were given dexamethasone as the comparison, and reported that cortisol levels on day 30 did not have apparent difference between the dexamethasone and the control group.

In this study, the significant changes of cortisol value on day 7 might be related to the ongoing resolution process. Cortisol as an inflammatory related hormone might reacted during the treatment, as inflammation process declined due to antibiotic treatment.

This study also found significant changes of cortisol level among CURB-65 and PSI classes. Serum cortisol is a marker of stress and shows the degree of the activation of the HPA axis thereby reflecting the severity of illness, with a gradual increase of cortisol levels at a greater degree of illness (Mueller *et al*, 2014). Meanwhile, Pneumonia Severity Index (PSI) and CURB-65 are clinical scoring tools that have been widely validated and shown to have strong value to stratify the severity and predict the mortality of CAP (Zhang *et al*, 2016).

Either CURB-65 or PSI are both consisted of vital signs and laboratory measurements, in which both assess mental state, blood pressure, respiratory rate, and blood urea nitrogen. PSI has additional measurements, i.e. body temperature, heart beats, arterial pH, sodium, blood glucose, hematocrit, partial arterial oxygen pressure, and pleural effusion. Therefore, CURB-65 and PSI scores mostly depend on vital signs and laboratory results.

During infection, vital signs and laboratory results tend to change. The hydration status of patients should be considered when evaluating the results of blood investigations, because water deficiency develops rapidly and insidiously in patients with pneumonia. In the dehydrated condition, reabsorption of urea by the kidneys is increased, making the elevation of blood urea nitrogen levels is frequently observed (Ugajin*et al*, 2012).

Similar results were found in the study conducted by Quinten *et al* (2016). They observed the trends in vital signs and routine biomarkers in patients with sepsis during resuscitation in the emergency department. Vital signs, blood pressure; heart rate; mean arterial pressure; respiratory rate; oxygen saturation; and temperature, showed significant improvements. The laboratory examination involved 24 biomarkers, which included glucose, sodium, thrombocytes, urea, and cortisol, showed significant changes in those five parameters.

The changes could be caused by medication given to the subjects, despite antibiotic. As an example, the use of antipyretic medicine led to a declining trend in body temperature. Cortisol could be affected by the decrease of body stress, as the results of treatment response (Quinten *et al*, 2016).

Zasowski*et al* (2014) studied the relationship between time to clinical response and outcomes among hospitalized patients with CAP who received ceftriaxone and azithromycin. Clinical response was evaluated by clinical stability (temperature ≤ 37.8°C; heart rate ≤ 100 beats per min; systolic blood pressure ≥ 90 mm Hg; respiratory rate ≤ 24 breaths per min; oxygen saturation ≥ 90%; arterial PaO2 ≥ 60mmHg; normal mental status; no receipt of supplemental oxygen by face mask or mechanical ventilation; and able to take oral medications) with improvement in at least one symptom of pneumonia (cough, shortness of breath, chest pain, or sputum production) and with no symptom worsening that was sustained for at least 24 hours. They reported that among 250 patients, 62.8% had given clinical response on day 3. On day 4, the it reached 72.9%, and on day 5 it was 77.9%.

As we can see, the criteria used in clinical response were similar to CURB-65 and PSI scoring system. According to other studies on CAP, Zasowski*et al* (2014) reported that clinical response has reached 77.9% at day 5, and Jaoude*et al* (2014) also reported that clinical stability was reached in 4 days. It seemed reasonable that this study was along with those others which CURB-65 and PSI scores were improved on day 7, as we used a longer follow-up period.

However, there was a substantial point that came to our attention when using CURB-65 as well as PSI to assess after treatment condition. There are several components of the scoring system that will never or will be difficult to change even after the treatment, as example: age component in CURB-65, and gender; history of nursing home residency; comorbidities; cerebrovascular diseases; and chronic renal disease in PSI. Therefore, we suggest that CURB-65 might be better than PSI in evaluating after treatment condition.

The comparison of CURB-65 and PSI to cortisol level also shown to be significant. Christ-Crain *et al* (2007) reported that total and free cortisol levels tend to arise as the increasing PSI score. Gotoh*et al* (2008) also suggested that serum cortisol and ACTH would increase as CAP worsens. Kruger *et al* (2008) study showed that cortisol level increase was parallel to the infection severity and prognosis of septic patients. Chandravanshi*et al* (2015) reported a significant correlation between pneumonia severity, which was assessed using CURB-65, and cortisol level.

The significant results obtained in this study and the similarities with previous studies, might be explained by the roles of those three variables. Cortisol was known to act in inflammatory condition and was in line to the severity of infection. So do CURB-65 and PSI, which reflect the severity of pneumonia (Chandravanshi*et al*, 2015).

This study had several limitations. We only assessed total cortisol level, without evaluating free cortisol level. We also did not do specific investigation for other comorbidities. Moreover, there were difference in time of cortisol examination and this study was only done in one centre. Nonetheless, this study had its own strength. The study was conducted in a prospective cohort design. Further studies are needed to confirm the results of this study.

Conclusion

There were significant difference of serum cortisol, CURB-65 score, and PSI between initial and day 7 admission. This study has several limitations, in which we did not evaluate free cortisol level, perform further examination for other comorbidities. There was also difference in time of cortisol examination. Nonetheless, this study has its own strength as it is a prospective cohort study.

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