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SERUM PROCALCITONIN AS A PREDICTING VALUE IN SEVERITY AND PROGNOSIS OF CAP IN SICKLE CELL-PATIENTS

By

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Abstract

The Pneumonia Severity Index (PSI) and CURB-65 predict outcomes in community acquired pneumonia but have limitations. The study evaluated if procalcitonin in community-acquired pneumonia provides prognostic information with the PSI and CURB-65 in sickle cell adult patients. Twenty sickle cell positive adult patients with a clinical and radiographic diagnosis of community acquired pneumonia were scored using PSI and CRUB-65, and measured procalcitonin levels.

They were 12 female 60% and 8 males 40% with mean of age 46.0±10.26 and were stratified with PSI, CRUB65 and sampled for procalcitonin level for PSI class I (3) patients 15%, class II (10) patients 50%, class III (3) patients 15%, class IV (one) patient 5% and class V (3) patients 15% with mean of 2.55±1.276 were CRUB65 0 (2) patients 10% 1 (11) patients 55% two (3) patients 15%, three (4) patients 20% with mean of 1.45±0.94 proclacitonin >0.25 (8) patients 40% and >0.50 were (12) patients 60% with mean of 1.098±1.346.

Key words: Procalcitonin level, sickle cell positive adult patient, Predicting value.

Introduction

To optimize and to reduce unnecessary hospital admission rates, professional organizations have developed prediction rules and propagated guidelines to stratify patients with Community-Acquired pneumonia (CAP) based on predicted risk for mortality (Niederman *et al,* 2001; Woodhead *et al,* 2005). Pneumonia Severity Index (PSI) is a well-validated scoring system that assesses the risk of death in a two-step algorithm and was developed to identify patient at low risk for mortality (Fine et al, 1997). However, it is complex and strongly dependent on age, limiting its general implementation in routine care. The less complex CURB65 (con-

fusion, urea >7 mmol·L^{-1}, respiratory frequency ≥30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value ≤60 mmHg) and age ≥65 yrs) score, focuses on five predictors (Lim et al, 2003). This score is easier to calculate, but has a slightly inferior prognostic accuracy. Both risk scores were validated for the prediction of mortality only, and their ability to predict other CAP-associated adverse outcomes is not validated. Both scores have limitations for clinical use, including practicability, risk of miscalibration, and only moderate sensitivity and specificity, which leads to hospitalization of patients where outpatient treatment would have been preferable (Schuetz *et al*, 2008). Thus, additional risk factors and prognostic biomarkers potentially enhance the prognostic performance of these established risk scores in CAP patients. Several inflammatory markers, such as leukocyte (WBC) counts and C-reactive protein (CRP) levels, are traditionally used in the evaluation of pulmonary infections. However, the value of these markers remains very limited. Recently, procalcitonin (PCT) has emerged as a promising alternative. Its level increases rapidly in the bacterial infections but remains low in viral diseases. High plasma concentrations of PCT are typically seen in sepsis, meningitis and pneumonia (Pencina *et al*, 1996; Neill *et al*, 1996; Schuetz *et al*, 2007; Mandell *et al*, 2007; Shuetz *et al*, 2010). PCT also seems to be a prognostic factor in sepsis and pneumonia (Briel *et al*, 2008; Bouadma *et al*, 2010). The prognostic value of procalcitonin measurement beyond existing prediction rules is unclear. Masia *et al*. (2005) observed that patients with high Pneumonia Severity Index scores had higher procalcitonin levels associated with mortality and complications, but Beovic *et al*. (2005) found no association between procalcitonin and Pneumonia Severity Index score. These single center studies were limited by small sample sizes and used older procalcitonin assays with low sensitivity (Nylen *et al*, 2003). It was hypothesized that an early procalcitonin measurement would aid risk assessment beyond that available from the Pneumonia Severity Index and CURB-65 in critical cases as sickle cell patients. Patients with sickle cell anemia are at greatly increased risk to pneumococcal infections, especially meningitis, but also to bacteremia. Some of these patients also have roentgenographic evidence of the acute pulmonary infiltrates, and in such cases there is little reason to doubt the diagnosis of pneu-

mococcal pneumonia. However, a much more common event, seen in38% to 45% of patients with sickle cell anemia, is an acute abacteremic febrile episode with a pulmonary infiltrate (Henderson, 1950; Reynolds, 1965; Barrett-Connor, 1971). Such episodes constitute the most common single reason for hospitalization of patients with SS hemoglobin. Although presumed to represent pneumonia, more than half of these cases lack bacterial confirmation, and the patients have prolonged fever despite administration of antibiotics (Tab. l). For this condition, it was unable to identify randomized control trial on efficiency and safety of antibiotic approach for people with sickle cell disease suffering for CAP, randomized control trials need to establish the options antibiotic.

The aim of this study was to understand and prove the relationship between the severities of serum PCT levels with community-acquired pneumonia in sickle cell patients.

Subjects, Materials and Methods

Cases of study Inclusion criteria: all sickle cell admitted to hospital with diagnosis in line with community-acquired pneumonia in hospitalized patients in adult respiratory department of our hospital from July 2011 to July 2012, diagnostic and therapeutic procedures in line with BTS and ATS community-acquired pneumonia treatment guidelines. Case exclusion criteria: (1) age <14 years; (2) merge different periods of pregnancy; (3) with underlying lung disease can fully explain and lack of imaging pulmonary infiltrates, such as bronchiectasis, pulmonary cyst with infection;(4) according to the American Thoracic Society/ Infection Society 2005 Guide to belong to the medical care associated pneumonia; (5) refuse blood PCT detection when admission.

Prognostic Scoring**:** The PSI was based on 20 factors that are evaluated at the time of clinical presentation and include three demographic characteristics (i.e. age, sex, and nursing home residence), five coexisting illnesses (i.e. active neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, and liver disease), five physical examination findings (i.e. pulse rate, respiratory rate, systolic blood pressure, temperature, and mental status), six laboratory measurements (i.e. BUN, glucose, hematocrit, and sodium levels; partial pressure of arterial oxygen; and arterial pH), and one radiographic finding (i.e. pleural effusion), patients were grouped into five risk classes CURB-65 is an acronym

based on a six-point score (range 0-5) that gives one point each for: confusion; urea >7mmol/l; respiratory rate ≥30/min; low blood pressure (systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg); and age 65 years or more. While CURB-65 is easy to calculate, it lacks formal assessment of vital signs and oxygen level, a major drawback in light of the importance of assessing oxygenation immediately on arrival in the emergency department (Capelastegui *et al*, 2006). Another drawback of any pneumonia Severity score was only measures severity at the time of hospital admission, and usually serial measurements of severity of illness are necessary to make decisions.

Blood procalcitonin measurement**:** 3 ml venous blood was taken into an additive-free test tube from patients before use of antibiotics within 6 h after admission. The serum was centrifuged at 1500 rpm, BRAHMS Diagnostica, Germany production testing equipment and reagents, using a double-antibody sandwich immunoassay chemiluminescence detection of serum PCT levels. Tube samples simultaneous determination of creatinine, urea nitrogen. All report results obtained within an hr.

Statistical analysis: Data were described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency less than 5. *p* values less than 0.05 was considered significant. All calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Twenty patients were sickle cell positive 12 female and 8 males with mean of age 46.00±10.26, and stratified with PSI , CRUB65 and sampled for procalcitonin level for PSI class I (3) patients 15%, class II (10) patients 50%, class III (3) patients 15%, class IV (1) patient 5% & class V (3) patients 15% with mean of 2.55±1.276 for CRUB65 (0) 2 patients 10% (1) eleven patients 55% two (3) patients 15%, three (4)

patients 20% with mean of 1.45± 0.94 proclacitonin >0.25 (8) patients 40% and >0.50 were (12) patients 60% with mean of 1.098±1.346

Increasing severity of CAP related to PSI & CRUB-65 was associated with a pronounced gradual increase of PCT. Mean PCT level were 0.256±0.02 (0.25-0.27) in PSI class I & CRUB-65 class 0, 0.464+-0.1o (0.28 -0.65) in PSI class II and CRUB-65 class 1, 0.743+-0.05 (0.69- 0.78) in PSI class III and CRUB-65 2, 3.1 (3.1-3.1) in PSI class IV and CRUB-65 3, 3.73+-1.23 (2.70-5.1) in PSI class V & CRUB-65 3. Mean for 20 patients 1.098±1.34 for PSI class mean 2.55±1.27 & CRUB-65 score 1.45 ±0.945. Correlation coefficient PSI to PCT was 0.924 and p= 0.000 and CRUB-65 to PCT 0.908 and p= 0.000 it's highly significant.

Table 1: Age, Sex, Pneumonia Score Index, Procalcitonin and CRUB 65 values.

No.	Age (year)	Sex	Sickle Cell	Psi	Pct	Crub 65
1	55	Female	+	I	0.27	0
2	62	Male	+	I	0.28	1
3	57	Female	+	I	0.25	0
4	49	Male	+	II	0.45	1
5	43	Female	+	II	0.50	1
6	48	Male	+	II	0.51	1
7	38	Female	+	II	0.28	1
8	36	Female	+	II	0.43	1
9	40	Female	+	II	0.55	1
10	42	Female	+	II	0.43	1
11	37	Female	+	II	0.34	1
12	63	Female	+	II	0.50	1
13	59	Male	+	II	0.65	1
14	61	Male	+	III	0.78	2
15	48	Male	+	III	0.76	2
16	37	Female	+	III	0.69	2
17	29	Male	+	IV	3.1	3
18	40	Male	+	V	2.70	3
19	39	Female	+	V	3.40	3
20	37	Female	+	V	5.1	3

Table 2: Procalcitonin mean and standard deviation in different levels of PCT

PSI	Mean	N	SD
1	0.267	3	0.02
2	0.464	10	0.10
3	0.743	3	0.05
4	3.100	1	1.23
5	3.733	3	1.35
Total	1.099	20	

Table 3: Percentage of male to female.

Sex	Frequency	Percent
Female	12	60.0
Male	8	40.0
Total	20	100.0

Table 4: Frequency, value and percentage of pneumonia score index.

	Frequency	Percent
1	3	15.0
2	10	50.0
3	3	15.0
4	1	5.0
5	3	15.0
Total	20	100.0

Table 5: Frequency, Value and Percentage of CRUB65.

	Frequency	Percent
0	2	10.0
1	11	55.0
2	3	15.0
3	4	20.0
Total	20	100.0

Table 6: Correlation of Procalcitonin to Pneumonia score index and CRUB65.

	No.	Minimum	Maximum	Mean	Std. Deviation
Age	20	29	63	46.0	10.260
PSI	20	1	5	2.55	1.276
PCT	20	0.25	5.10	1.0985	1.34679
CRUB 65	20	0	3	1.45	0.945
Valid N (listwise)	20				

Table 7: Correlations

Spearman's rho		PCT
PSI	Correlation Coefficient	0.924
	P value	0.000
	N	20
CRUB 65	Correlation Coefficient	0.908
	P value	0.000
	N	20

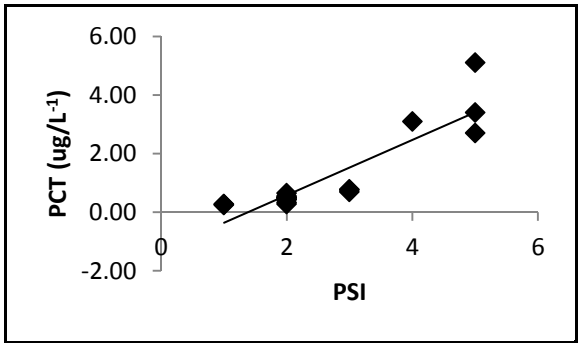

Fig. 1: Correlation between PSI and serum procalcitonin (PCT, ug/L^{-1}) among cases

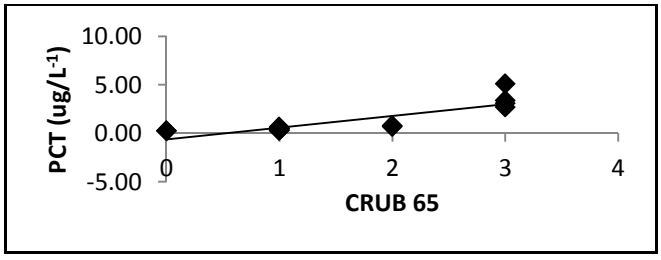

Fig. 2: Correlation between CRUB 65 and serum procalcitonin (PCT, ug/L^{-1}) among cases

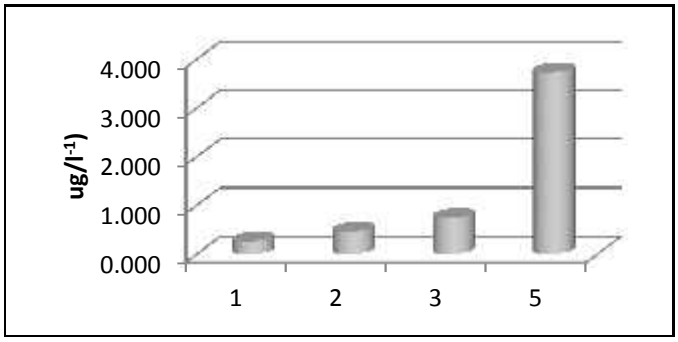

Fig. 3: Mean serum procalcitonin (PCT, ug/L^{-1}) according to PSI categories among cases

Discussion

The present study confirmed that the blood PCT can be used to judge the condition of the auxiliary pneumonia, 0.25μg· L-1 < PCT <0.5μg. L-1 prompted the limitations of an infection is present, PCT>0.5μg· L-1 prompted severe infection (Petch, 1970). PCT <0.228μg L can be used as the cut-off point of the of outpatient CAP patients with low mortality. Hospitalized CAP patients compared with

outpatient illness and high mortality, it is necessary to look for severe CAP, PCT cutoff value. In a large single-center Spanish cohort, an equivalence of the predictions made by the PSI, CURB-65, & CRB-65 score (Capelastegui *et al,* 2006). This study showed that the CURB-65 score had a slightly lower performance in predicting ICU admission and death, probably because it may have given too much weight to age impact. But, compared PSI, CURB-65, and CURB for predicting 30-day mortality in 3181 CAP patients showed that PSI gave higher sensitivity and negative predictive value for mortality than CURB & CURB-65 (Aujesky *et al,* 2005).

Fine *et al*. (1971) reported that all class I patients and many class II & III were candidates for outpatient therapy, which led to significant cost savings while class IV and V patients, associated with high mortality, were hospital managed. PSI score was limited, due to the impact of age on the score, and the possibility of underestimating the severity of illness in younger populations while overestimating the severity in an elderly population and patients with co morbidities (Ewig *et al,* 2004). Also, the PSI is a measure of mortality risk, not of pneumonia severity. Another score, which is a modified form of the British Thoracic Society rule, the CURB-65, has the benefit of being easy to calculate and simple to use. The CURB-65 score was developed in a study of 1068 prospectively studied patients with CAP from three countries, UK, New Zealand, and Netherlands A study from the German Community-Acquired pneumonia Competence Network (CAPNETZ) recently found that PCT levels on admission improve the prognostic performance of CRB-65 (confusion, respiratory rate $\geq$30 breaths$\cdot$min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leq$60 mmHg) and age $\geq$65yrs.) score (Kruger *et al,* 2004). However, a large USA-based CAP study found only a moderate additive value of PCT when compared to the PSI and CURB-65 scores (Huang *et al,* 2008)_which was the initiation of the present study agreed that serial PCT measurement may help to assess resolution of CAP (Menendez *et al,* 2009). Similarly, another Spanish study found that higher follow-up PCT concentrations were associated with development of complications and death. This study has limitations. Exclusion of patients with dementia, immunosuppression,

concomitant infections and active intravenous drug abuse limits its generalizability. So, this study confirmed the predictive value of PCT in combination with PSI or CURB-65 in regard to serious adverse events in adult CAP, and much less for mortality prediction which coincided with the current study. Needless to say readily measurable biomarkers that reflect the severity of CAP and outcome could be helpful as additional prognostic tools. The present study confirmed that PCT was a good predictor of pneumonia severity (Hedlund, 2000; Hausfater, 2002; Polzin *et al*, 2003). Patients with a higher CRB-65 score had significantly higher PCT levels. In contrast, CRP and WBC were not correlated to the severity of the disease. The present study has some limitations. The number of outpatients was limited, and the use of procalcitonin alone and in combination with CRB-65 should clearly be studied in this population. Also, the number of patients at high risk was also small, raising the concern whether the present observations can be expanded to other group. In another A acute bronchitis review study noted that a procalcitonin level less than 0.1 ng/mL may be able to safely discriminate between acute bronchitis and community acquired pneumonia but that more data were needed (Wenzel, 2006). But, clinical prediction rules have two important limitations: physicians may misapply or not remember them, and within a given risk category there can be a significant range in outcome. Thus, it was sought to determine whether procalcitonin could address these concerns, first as a standalone test and then as a layer on top of clinical risk assessment. The primary goal was to determine how procalcitonin might enhance existing community-acquired pneumonia prediction rules and decision-making in sickle cell patients. The authors recognized that physicians often do not explicitly calculate the PSI in daily clinical practice. However, the same factors that comprise Pneumonia Severity Index and other prediction rules also go into the bedside clinical judgment many physicians use to guide their decisions. The results thus suggest that procalcitonin may aid decision-making in high-risk patients as sickle cell, defined explicitly or implicitly with the Pneumonia Severity Index or a similar tool, but, didn't emphasize that procalcitonin level should be used in isolation to make clinical decisions and to replace physicians assessment.

The community-acquired pneumonia guidelines recommend that the clinically high-risk patients be hospitalized and that ICU admission be considered for patients in highest risk categories (Macfarlane, 2004; Mandell *et al*, 2007). Marrie and Huang (2007) found that many clinically high-risk patients might be safely treated at home. The data suggested that procalcitonin may aid in identifying Pneumonia Severity Index/CURB 65 high-risk patients who will rarely experience mortality and other complications. Thus, there could be considerable benefits, both in terms of conserved resources and antibiotic management, if one could better stratify high-risk patients. Prospective studies are needed to determine whether procalcitonin can improve management decisions and outcomes in high-risk patients as sickle cell patients**.**

Conclusion

Procalcitonin levels on admission predict severity of community-acquired pneumonia in sickle cell patients with a similar prognostic accuracy as PSI and CRUB65 and use of procalcitonin as an adjunct to existing rules may offer additional prognostic information in high risk patients as sickle cell positive patients. Future studies must address whether adding PCT to risk scores can increase their safe implementation in clinical practice. This was the scope for patients with sickle cell.

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