



# Procalcitonin Level is Correlated with Community Pneumonia Severity

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## ABSTRACT

Procalcitonin (PCT) is a peptide consisting of 116 amino acids released by thyroid C cells in very low concentrations (<0.05 ng/mL). Microbial infection will increase the expression of CALC - 1 gene causing release of PCT from cells. A cross-sectional research was done on 60 patients with community pneumonia (July 2011 to June 2013) in Department of Internal Medicine, H.Adam Malik Hospital, Medan, consist of 33 men, 27 women, age 52.47±13.31 years. The objective is to determine the correlation between procalcitonin levels and severity of community pneumonia. The results were the percentage of PCT class I 18.3%, class II 8.3%, class III 16.7%, and class IV 56.7%; 41.7% have PSI scores ≤90, which are 25% have PSI score 91-130 and 33.3% have PSI score >130. There is a statistically significant correlation between PCT levels and severity of community pneumonia (p =0.0001 somers'd test)

**Keywords:** Pneumonia community, procalcitonin, prognosis, PSI score.

## ABSTRAK

Prokalsitonin adalah prohormon kalsitonin, berupa peptida 116 asam amino yang dilepaskan oleh sel C tiroid dalam keadaan normal dan konsentrasinya sangat rendah (<0,05 ng/mL). Infeksi mikroba akan meningkatkan ekspresi gen CALC-I yang menyebabkan lepasnya PCT dari sel. Penelitian observasional dengan metode *cross-sectional* dilaksanakan pada 60 pasien pneumonia komunitas rawat inap (Juli 2011 s/d Juni 2013) di Departemen Ilmu Penyakit Dalam RS H. Adam Malik Medan, terdiri dari 33 pria dan 27 wanita dengan usia rata-rata 52,47±13,31 tahun. Tujuan penelitian untuk mengetahui hubungan kadar prokalsitonin terhadap derajat dan beratnya pneumonia komunitas. Hasil penelitian menunjukkan bahwa persentase pasien dengan kadar PCT derajat I 18,3%, derajat II 8,3%, derajat III 16,7%, dan derajat IV 56,7%; pada 41,7% pasien dijumpai skor PSI (*Pneumonia Severity Index*) ≤90, 25% pasien dengan skor PSI 91-130 dan 33,3% pasien dengan skor PSI >130. Terdapat hubungan signifikan antara derajat skor PSI dan peningkatan kadar PCT (uji korelasi Somers'd p=0,0001). **Doharjo Manullang, EN Keliat, Alwinsky Abidin. Kadar Prokalsitonin Berhubungan dengan Beratnya Pneumonia Komunitas**

**Kata kunci:** Pneumonia komunitas, prognosis, prokalsitonin, skor PSI (*Pneumonia Severity Index*)

## INTRODUCTION

Pneumonia has high morbidity and mortality throughout the world. In Indonesia, deaths from pneumonia and respiratory tract infections are 34/100.000 population (in men) and 28/100.000 population (in women).<sup>1</sup> Among 235 patients in Hasan Sadikin hospital, 75.3 % suffered from community pneumonia (PC).<sup>2</sup> In developed countries like United States, PC affected 1.3 million people per year<sup>3-5</sup> and recorded as the biggest cause of severe sepsis and deaths due to infection.<sup>4,5</sup> The high incidence is associated by high cost of health care, especially in severe PC.<sup>4,5</sup> Masia, *et al*, reported that, of 240 patients researched, pneumonia is caused by bacteria (39 people), atypical (36 people), viruses (15 people), the

combination of bacteria, atypical, and viruses (14 people).<sup>6</sup>

Procalcitonin (PCT) is known as biomarkers for sepsis and infection, fulfilling several criteria, i.e.: 1. Has high sensitivity and specificity, 2. Can be measured (measureable), 3. Available at health facilities such as hospitals (affordable), 4. Responsive and reproducible, 5. Has a half-life of 24 hours and can be checked repeatedly (timely fashion ).<sup>7,8</sup> Procalcitonin level is more accurate than CRP or leukocyte count in distinguishing PC from other medical conditions.<sup>9</sup> PCT value (cut-off ≥0.25 ng/mL) was used as a consideration for antibiotics treatment, resulting in 50% reduction of antibiotics use in lower respiratory tract

infections. It also decrease hospitalisation from 12 days to 5 days, decrease of antibiotic use duration by 65% without changing the clinical outcome.<sup>10,11</sup>

As a prognostic tool, PCT levels <0.1 ng/mL had a risk of death due to low PC regardless of the degree of PSI scores.<sup>4</sup> PCT was correlated to pneumonia severity scores.<sup>6</sup> In pneumonia patients with a low PSI (PSI, class I - II), PCT is able to predict bacterial pneumonia; PCT levels will be increased in bacterial pneumonia rather than in non-bacterial with a cut-off ≥0.15 ng/mL. In patients with high PSI (class III - IV), PCT is prognostic; PCT ≥0.5 ng/mL is correlated with higher complications and mortality.<sup>4,5,8</sup> PC patients with higher PSI scores

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also have higher levels of procalcitonin; PCT values increased according to the severity score of PSI and correlated to the increased mortality and complications.<sup>6</sup> A research involving 1671 PC patients reported that PCT levels can predict the severity and the clinical impact with the same accuracy as CURB-65 scores.<sup>12</sup> This research aims to determine the correlation between procalcitonin levels and the severity of community pneumonia in our subjects.

### METHOD

This research is an observational cross-sectional study. The target population is pneumonia community patients and diagnosed based on clinical symptoms and radiological examination results. The samples are pneumonia patients fulfilling the inclusion and exclusion criteria and signed a written informed consent. Samples was obtained with consecutive sampling method on community pneumonia patients hospitalized at Haji Adam Malik Hospital in Medan, diagnosed clinically and radiologically. The inclusion criteria are community pneumonia patients - men or women aged  $\geq 18$  years - diagnosed clinically and radiologically. The exclusion criteria are patients from other hospitals, discharged within 10 days, suffering from pneumonia in the last 30 days, using mechanical ventilation and patients with pulmonary cystic fibrosis or active pulmonary tuberculosis. The name, age, sex, weight, and height of all the research subjects are recorded. Laboratory tests performed were the tests of blood gas analysis (pH, PaO<sub>2</sub>), urea, sodium, blood glucose, hematocrit, procalcitonin. Then, the thoracic photos (radiologic examination) was performed. The analysis used to analyze the correlation between procalcitonin levels and the severity of pneumonia community is somers'd test done with SPSS software version 15.0;  $p < 0.05$  are considered significant.

### Pneumonia Severity Index

The severity of pneumonia community was measured with pneumonia severity index according to ATS (*American Thoracic Society*) 1997 guidelines (Table 1). Patients with PCI score  $\leq 90$  were classified as mild pneumonia, PCI score 91-130 were classified as moderate pneumonia, and those with PCI score  $> 130$  were classified as severe pneumonia.<sup>13</sup>

### Procalcitonin Levels

Procalcitonin levels were measured using *electrochemiluminescence immunoassay* (ECLIA) method with Elecsys BRAHMS PCT reagent kit and with Cobas 6000. Blood samples were taken from the vena mediana cubiti after antiseptic measure using 70% alcohol and allowed to dry. A 6 mL of blood sample was taken using disposable syringe 10 mL then divided into 2 parts. The first syringe contains 3 mL blood with EDTA anticoagulants for a complete blood test. The second syringe contains 3 mL blood without anticoagulant; serum was taken for PCT examination. Blood sampling was done anytime in a lying

position; if the patient fell into sepsis, the blood sample was taken within 24 hours. A complete blood examination was performed with a cell Dye 3700 device and peripheral blood morphology was identified by Giemsa staining. Erythrocyte sedimentation rate (ESR) was measured with Westergreen method.

Procalcitonin was measured with Sandwich principle.

■ Incubation 1: antigen in the sample (30  $\mu\text{L}$ ), a biotinylated monoclonal PCT-specific antibody and a monoclonal-specific antibody labeled with ruthenium complex and reacting to form a sandwich complex.

Table 2. Characteristics of subjects

Variable	N (%)
<b>Gender</b>	
Male	33 (55%)
Female	27 (45%)
Age (year) ( $\pm$ SD)	52.47 $\pm$ 13.31
<b>Vital Signs (<math>\pm</math> SD)</b>	
Systolic blood pressure (mmHg)	130.07 $\pm$ 28.97
Diastolic blood pressure (mmHg)	80.08 $\pm$ 13.91
HR (per minute)	89.40 $\pm$ 13.43
RR (per minute)	26.80 $\pm$ 5.58
Temperatur (Celcius)	37.20 $\pm$ 1.07
<b>Laboratory</b>	
Hb (g/dL) ( $\pm$ SD)	10.35 $\pm$ 2.67
Leucocyte (/mm <sup>3</sup> ) ( $\pm$ SD)	12.853 $\pm$ 6.875
Ureum (mg/dL) ( $\pm$ SD)	64.81 $\pm$ 58.03
Creatinine (mg/dL) ( $\pm$ SD)	2.55 $\pm$ 4.21
Procalcitonin (PCT) (ng/mL) (%)	
I (<0.1)	(18.3%)
II (0.1 $\leq$ PCT <0.25)	5 (8.3%)
III (0.25 $\leq$ PCT <0.5)	10 (16.7%)
IV (PCT $\geq$ 0.5)	34 (56.7%)
<b>PSI Score n (%)</b>	
$\leq 90$	25 (41.7%)
91-130	15 (25%)
$> 130$	20 (33.3%)

Table 3. Procalcitonin Levels in Correlation to PSI scores

PCT (ng/mL)	PSI Score		
	Mild ( $\leq 90$ )	Moderate (91-130)	Severe ( $> 130$ )
PCT < 0.1	9	2	0
0.1 $\leq$ PCT < 0.25	4	1	0
0.25 $\leq$ PCT < 0.5	4	5	1
PCT $\geq$ 0.5	8	7	19

Somers'd Correlation  $p = 0.0001$

Table 4. Correlation of PSI scores and mean PCT level

PCT (ng/mL)	PSI Score		
	Mild ( $\leq 90$ )	Moderate (91-130)	Severe ( $> 130$ )
PCT < 0.1	0.045	0.045	-
0.1 $\leq$ PCT < 0.25	0.15	0.14	-
0.25 $\leq$ PCT < 0.5	0.38	0.36	0.29
PCT $\geq$ 0.5	1.28	6.67	9.1
<b>Total</b>	<b>1.85</b>	<b>7.12</b>	<b>9.39</b>



■ Incubation 2: after the addition of a microparticle coated with streptavidin, the complex will bind; become to a solid phase through the interaction of biotin and streptavidin.

■ The reaction mixture is aspirated into the cell mask where the microparticles are captured magnetically onto the electrode surface. The unbonding substance is then transferred with Procell®. The application of voltage to the electrode will induce chemiluminescent emissions as measured by the photomultiplier.

■ The results are determined by the calibration curve which is the specific instrument by 2 point calibration and a master curve provided through the reagent barcode.

■ Based on the level of procalcitonin, research subjects will be divided into 4 classes:

- Class I: PCT <0.1 ng/mL
- Class II : 0.1 ≤ PCT <0.25 ng/mL
- Class III : 0.25 ≤ PCT <0.5 ng/mL
- Class IV : PCT ≥ 0.5 ng/mL

**RESULT**

Overall, 60 community pneumonia patients were involved in this research, consist of 33 (55%) male and 27 (45%) women with an age of 52.47 ± 13.31. The characteristics of patients can be seen in **table 2**.

The correlation of PCT (Procalcitonin) levels with PSI scores (Pneumonia Severity Index) was significant (Somers'd test 0.0001 <0.005); higher PCT levels was correlated with higher PSI scores (**Table 4, Figure 1**).

The average levels of PCT in mild PSI was approximately 1.85 ng/mL, in moderate PSI was 7.12 ng/mL and in severe PSI was 9.39 ng/mL. More severe pneumonia (based on PSI score) was associated with the higher the levels of PCT (**Table 5**).

In this research, 8 subjects (13.3%) suffering from community pneumonia sepsis have PCT average of 10.5 ng/mL, while 52 subjects (86.7%) suffering from community pneumonia without sepsis have PCT average of 2.96 ng/mL (p = 0.002); the more severe community pneumonia, the higher the PCT levels.

**DISCUSSION**

Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues revolve around the initial assessment of severity.<sup>14</sup> Assessment of disease severity is one of the initial steps in determining the management plan after diagnosis. The key of safe and efficient PC management is the ability to predict prognosis.<sup>4</sup>

Several biomarkers and cytokines have been proposed as potential predictors of pneumonia. Among them the predictive capability of CRP and PCT has been most widely studied and validated. Numerous studies have been conducted on the potential role of PCT as a prognostic biomarker.<sup>4,6,15-7</sup> They found that PCT levels increase with increasing severity of sepsis and organ dysfunction. Several other studies have shown that PCT levels help predict the severity of pneumonia and may predict survival based on the magnitude of the result. It has been suggested that PCT should be regarded as a prognostic rather than a diagnostic factor in patients with CAP.<sup>6,18,19</sup> Christ-Crain et al. found gradual increase of PCT levels with increasing severity of CAP, classified according to PSI score (P < 0.001).<sup>20</sup> The prognostic value of PCT has also been demonstrated in patients with VAP. Abula et al. found that the increased PCT levels in VAP patients were associated with poor control of infection and subsequent deterioration.<sup>21</sup>

Procalcitonin (PCT), the prohormone of calcitonin, mirrors the severity of infection and has emerged as the most studied and promising blood biomarker for the risk stratification of patients. PCT is a calcitonin precursor peptide and is produced during inflammation mainly by parenchymal cells. This result can be explained by, PCT increases markedly during severe infection as many tissues express PCT throughout the body in response to sepsis. These tissues include C cells of the thyroid, pulmonary, and pancreatic tissues.<sup>22</sup>

The present study was done to assess the role of procalcitonin as an indicator for severity of CAP. For this purpose, many clinical scoring systems' benefits have been widely tested such as PSI scores with AUC: 0.74 to 0.83. Its usage has been recommended by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA).<sup>23</sup> A research involving 185 CAP patients showed strong correlation between PCT level and CAP severity; more severe CAP (as assessed by PSI score) is associated with higher PCT levels.<sup>6</sup> This research showed the same result; PCT levels were more increased in severe CAP; and the increase is in line with the increase of CAP severity. This may be evident in this study which 8 sepsis PC patients have higher mean

Figure 1. The correlation between PCT and PSI scores

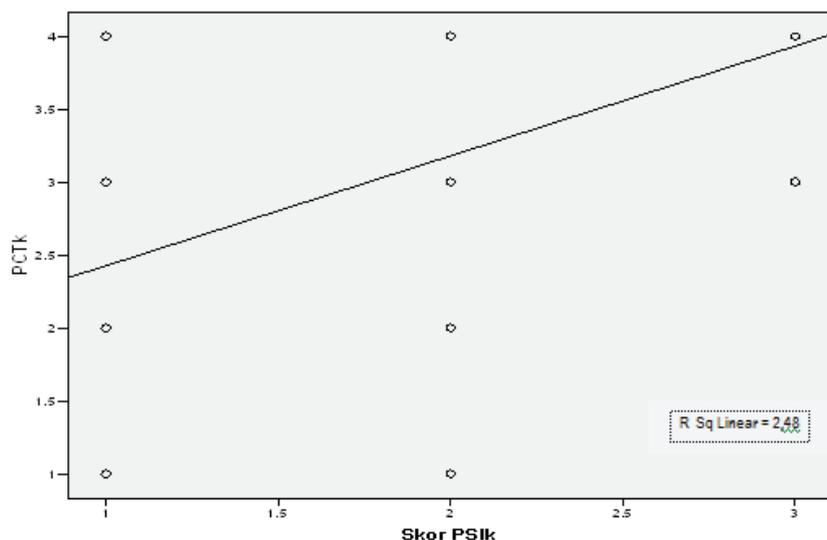


Table 5. Average PCT levels in sepsis and nonsepsis PC patients

Diagnosis	Procalcitonin		
	n	Mean	SD
Sepsis PC	8	10.15	16.58
Nonsepsis PC	52	2.96	7.52

Mann-Whitney : p=0.002

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PCT (10.15 ng/mL) compared to 52 nonsepsis PC patients with PCT 2.96 ng/mL.<sup>6</sup>

The demographic data of the studied subjects included in this study are illustrated in table 2. This study was carried out on 60 patients (33 male and 27 female). The mean age was  $52.47 \pm 13.31$  years. In our study, PCT levels (ng/mL) in patients with severe CAP were approximately 9.39 ng/mL, while in mild and moderate CAP were 1.85 ng/mL and 7.12

ng/mL. This in agreement with the results of Ahmad, *et al*, and Masia M, *et al*.<sup>6,22</sup>

This research has several limitations; subjects of this research were the emergency room (ER) patients; therefore, this result does not extend to the outpatient PC. Also the cross-sectional method can not follow the clinical course and determine the clinical effect; therefore, mortality can not be correlated to both the PSI score and the PCT.

### CONCLUSION

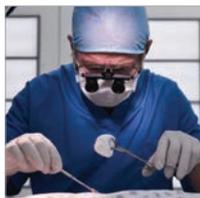
The results of this study suggest that procalcitonin contribution to the evaluation of patients with CAP varies according to severity of pneumonia. PSI scores and PCT is statistically correlated: more severe community pneumonia is significantly correlated with higher procalcitonin levels.

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### Appendix 1. Pneumonia severity index for community-acquired pneumonia<sup>14</sup>

PNEUMONIA SEVERITY INDEX FOR COMMUNITY-ACQUIRED PNEUMONIA



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RISK FACTOR	POINT
<b>Demographics</b>	
Men	Age (years): ____
Woman	Age (years) – 10: ____
Nursing home resident	+10
<b>Comorbidities</b>	
Neoplasm	+30
Liver disease	+20
Heart failure	+10
Stroke	+10
Renal failure	+10
<b>Physical examination findings</b>	
Altered mental status	+20
Respiratory rate $\geq$ 30 breaths per minute	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 95°F (35°C) or $\geq$ 104°F (40°C)	+15
Pulse rate $\geq$ 125 beats per minute	+10
<b>Laboratory and radiographic findings</b>	
Arterial pH < 7.35	+30
Blood urea nitrogen > 30 mg per dL	+20
Sodium < 130 mmol per L	+20
Glucose $\geq$ 250 mg per dL	+10
Hematocrit < 30 percent	+10
Partial pressure of arterial oxygen < 60 mm Hg	+10
Pleural effusion	+10
<b>Total points:</b>	

Point total	Risk class	Deaths/total (%)		Recommendation†
		Adults with CAP*	Nursing home patients with CAP†	
< 51	I	3/1,472 (0.2)	None	Outpatient therapy should be considered, especially for patients in classes I and II
51 to 70	II	7/1,374 (0.5)	None	
71 to 90	III	41/1,603 (2.6)	1/21 (4.8)	
91 to 130	IV	149/1,605 (9.3)	6/50 (12.0)	Patient should be hospitalized
>130	V	109/438 (24.9)	28/85 (32.9)	