Diagnostic and Prognostic Value of Serum Procalcitonin in Pneumonia - A Prospective Observational Study

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Abstract

Objectives: Community-acquired and nosocomial respiratory tract infections are public health problems of major concern and a leading cause of mortality. In the current prospective observational study, we intend to study the utility of procalcitonin (PCT) estimation in the diagnosis and prognosis of Community-acquired Pneumonia (CAP) and Ventilator-associated Pneumonia (VAP).

Materials and Methods: The study was conducted over a period of two years. 40 patients with diagnosis of CAP and 40 patients of VAP were included in the study. Serum Procalcitonin levels were estimated using BRAHMS PCT Kryptor Immunofluorescent Assay (Biomerieux, France). Other routine investigations including sputum culture and endotracheal secretions cultures were done. Chi-square analysis was done to assess its prognostic and diagnostic significance.

Results: PCT was positive (> 0.05ng/ml) in 68% patients with CAP and 80% patients with VAP. Higher absolute values of PCT were seen in patients with VAP compared to CAP. In VAP PCT was positive in more patients with bronchopneumonia than lobar pneumonia. Streptococcus pneumoniae was the most common bacterial etiology of CAP, and was associated with a positive PCT in 75% cases. Acinetobacter was the most common bacterial etiology of VAP, and was associated with a positive PCT in 80% cases. Mortality was more in PCT positive patients in both CAP and VAP. Maximum mortality in VAP was with PCT >10 ng/ml.

Conclusion: PCT is a useful adjuvant in the diagnosis of both CAP and VAP. Positive PCT levels indicate a bacterial etiology for pneumonia. A high PCT level is a poor prognostic indicator and is associated with a higher mortality.

Keywords: Biomarker, Pneumonia, Procalcitonin, Prohormone, Prognosis

Introduction

Nosocomial and community-acquired respiratory tract infections are public health problems of major concern and a leading cause of mortality. A rapid diagnosis of pneumonia and an accurate differentiation from viral respiratory illnesses, and non-infectious causes including pulmonary embolism, malignancy, and congestive heart failure, has important therapeutic and prognostic implications.

A novel approach to establish the presence of an infection and its treatment response is the use of biomarkers. The utility of serum markers of systemic infection, such as C-reactive protein (CRP), lipopolysaccharide-binding protein, or procalcitonin (PCT) has become a matter of interest in the last few years, for the differential diagnosis of various infectious conditions.

Numerous clinical studies have proposed procalcitonin as a specific marker of bacterial infection or inflammation. Procalcitonin is the prohormone of the hormone calcitonin. While, calcitonin is exclusively produced by C-cells of the thyroid gland in response to hormonal stimuli, PCT

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gets induced in many organs after bacterial insult and is subsequently released into the circulation. It has a long half-life and the assay is highly reproducible.

In the current study, we intend to study the utility of procalcitonin level in the diagnosis and prognosis of pneumonia.

**Material and Methods**

Eighty patients, aged more than 18 years, admitted with diagnosis of pneumonia were included in the prospective observational study over a period of two years (40 patients of community-acquired pneumonia and 40 patients of ventilator-associated pneumonia).

The diagnosis of CAP was considered in any patient who had newly acquired respiratory symptoms (cough, sputum production, and/or dyspnoea), especially if accompanied by fever, auscultatory findings of abnormal breath sounds and crackles, and at least one opacity on chest radiography. The diagnosis of VAP was based on three components: systemic signs of infection, new or worsening infiltrates seen on the chest roentgenogram, and bacteriologic evidence of pulmonary parenchymal infection. The same were not present or incubating at the time mechanical ventilation was started. Patients with malignancy and/or prior history of recent trauma or surgery were excluded.

A detailed history was elicited from the patients, and general physical examination and systemic examination of the patients was carried out. Data was collected in a pre-requisite proforma. Routine hemogram with haematocrit, routine urine analysis, renal function tests, random blood sugar, liver function tests, serum electrolytes, C-reactive protein (quantitative estimation by immune-turbidometric method in automated analyser), chest X-ray, sputum examination, blood culture, and serum procalcitonin (semi-quantitative - BRAHMS PCT Kryptor Immunofluorescent Assay), were done for all patients on the day of diagnosis. Statistical analysis was done using the Chi-square test.

**Results**

A total of 80 cases were enrolled in the study - 40 cases of CAP and 40 cases of VAP (Table 1). PCT was more frequently positive in VAP compared to CAP (80% vs 68%). PCT was positive in males more than females with CAP. PCT was equally positive in both males and females with VAP. PCT was equally positive in CAP with lobar pneumonia and bronchopneumonia (p = 0.91). In VAP, PCT was positive in more patients with bronchopneumonia than lobar pneumonia (p = 0.51). Only 17% of cases with CAP had a positive sputum culture. Cultures were equally positive in PCT positive and negative cases (p = 0.52). Culture positivity was more in VAP (55%) compared to CAP (17%). A large number of patients who had positive PCT in showed culture positivity suggesting a bacterial aetiology (p = 0.63).

Acinetobacter was the most common bacterial aetiology of VAP, and was associated with a positive PCT in 80% cases (Figure 1A). H1N1 virus was isolated in total 4 patients (2 CAP, 2 VAP). PCT was negative in all cases of H1N1 virus. Streptococcus pneumoniae was the most common bacterial aetiology of CAP, and was associated with a positive PCT in 75% cases (Figure 1B). Higher absolute values of PCT were seen in patients with VAP compared to CAP (Table 2).
CAP mortality was more in PCT positive patients (p = 0.74) (Figure 2A). VAP mortality was also more in PCT positive patients. Maximum mortality in VAP was with PCT >10 ng/ml (p = 0.52) (Figure 2B).

**Discussion**

We studied a total of 40 patients of CAP. 32% patients had PCT <0.05 ng/ml, i.e. negative. 10% had PCT between 0.05-0.5 ng/ml, 27% had PCT between 0.5-2 ng/ml, 10% between 2-10 ng/ml, and 13% had PCT >10 ng/ml. In a similar study done by Huang DT et al., patients with CAP were stratified according to procalcitonin levels into four tiers - I: <0.1; II: ≥0.1 to <0.25; III: ≥0.25 to <0.5; and IV: ≥0.5 ng/ml. 1651 patients formed the study cohort. 542 subjects (32.8%) were in tier I, 356 (21.6%) in tier II, 169 (10.2%) in tier III, and 584 (35.4%) in tier IV. Masia M et al. studied 185 patients of CAP. The mean PCT at admission was 0.49 ng/ml. In another study done by Holm A et al., 70% patients of a total of 48 had a positive PCT.
a mean PCT of 3.1 at admission.\(^8\) Boussekey N et al. did a study to determine the diagnostic and prognostic role of PCT in patients admitted for severe CAP.\(^9\) 20% of the patients had a serum PCT level <0.5 ng/ml, 30% between 0.5 ng/ml and 2 ng/ml, and 50% ≥2 ng/ml. Hedlund and Hansson studied 96 patients treated in the hospital for CAP. On admission, 60 patients (54%) had elevated PCT levels (>0.1 μg/l).\(^10\)

Radiographic analysis of CAP in our study showed that PCT was equally positive in patients with lobar pneumonia (44%) or bronchopneumonia (56%). Such an analysis was done in a study done by Lee JY et al.\(^11\) In this study, the serum PCT levels were significantly higher in the patients with lobar pneumonia than in those with bronchopneumonia (p=0.04). Serum PCT levels of above 0.5 ng/ml were noted more frequently in patients with lobar pneumonia than in patients with bronchopneumonia (p=0.04).

Culture positivity rate was poor in our study. Only 17% had a positive sputum culture. Cultures were equally positive in PCT positive and negative cases. Streptococcus pneumoniae was the most common bacterial aetiology, and was associated with a positive PCT in 75% cases. Other organism isolated were Haemophilus influenza (3), MSSA (1), MRSA (1), AFB (1), H1N1 (2), Candida (1). In the study done by Masia M et al., the causative pathogen was found in 54.6% cases. (56 classic bacterial pathogens, 43 atypical pathogens, 16 viral pathogens, and 16 mixed flora).\(^6\) Those with CAP caused by classic bacteria tended to have higher procalcitonin levels (>0.5 ng/ml), although differences did not reach statistical significance (p = 0.08).

Elevated procalcitonin level (>0.06 ng/ml) was common in pneumococcal infection (74%). In the study by Boussekey et al, serum PCT level was higher in microbiologically documented CAP (p=0.001), but was not predictive of any specific bacterial agent.\(^3\) In the Hedlund and Hanson study, an etiologic diagnosis was established in 38 patients, and in 36 patients a single etiologic agent was found. They found that eight of nine patients with pneumonia caused by atypical agents had PCT levels <0.5 μg/l compared with 6/27 patients with pneumonia caused by classic bacterial pathogens, mainly Streptococcus pneumoniae (p = 0.03).\(^10\) In a study by Kruger S et al., patients with typical bacterial CAP showed higher PCT levels compared with patients with atypical bacterial or viral CAP.\(^12\) In a study of bacterial aetiology among COPD patients admitted with severe pneumonia done by Daubin C et al., 44% patients had microbiologically-confirmed pneumonia. No bacteria were detected in patients with PCTmax level <0.1 μg/l. In contrast, bacteria were detected in more than half the patients estimated to have PCTmax >0.1 and <0.25 μg/l.\(^13\)

Thirty patients hospitalized with CAP were included in a prospective study by Jereb M et al.\(^14\) The median serum procalcitonin level in patients with typical pneumonia was 7.64 ng/ml (range 0.26-63.16) and in the group with atypical pneumonia 0.80 ng/ml (range 0.13-34.90). Nyamande K et al. assessed PCT in 266 patients.\(^15\) No organs were isolated in 97 subjects. The mean PCT levels for PTB, bacteria and PJP were 4.164 ng/ml; 19.479 ng/ml and 1.138 ng/ml, respectively (p = 0.0004). The PCT levels of patients with pneumococcal CAP were significantly higher than in patients with another bacterial CAP (p = 0.015).

In our study, 4 patients with CAP died (10%). PCT was positive in 3 patients. In the study by Huang DT et al., 6.4% died. 8% had negative PCT (<0.1 ng/ml); 28% had PCT ≥0.1 to <0.25; 15% had PCT ≥0.25 to <0.5; and 49%, had PCT ≥0.5 ng/ml.\(^3\) In the study by Mar Masia et al, the mean PCT in patients who died was 2.03 ng/ml.\(^6\) Boussekey N et al. showed that the initial PCT level was significantly higher in patients who died during the ICU stay (5.6 ng/ml vs. 1.5 ng/ml; p<0.0001).\(^5\) The same authors in another study in March 2006 studied 100 critically ill patients with CAP.\(^16\) Median PCT was 5.2 ng/ml on day 1 and 2.9 ng/ml on day 3. It increased from day 1 to day 3 in nonsurvivors but decreased in survivors. In the study by Kruger S et al., at 28 days follow-up, 70 patients died. Median PCT levels on admission of non-survivors were significantly higher compared with those in survivors (0.88 (0.32-3.38) versus 0.13 (0.08-0.38) ng/ml; p<0.0001). Moreover, the additional use of PCT using a threshold of 0.228 ng/ml was able to predict patients at very low risk of death.\(^12\)

In our study we also studied procalcitonin in ventilator-associated pneumonia. 40 cases of VAP were enrolled. PCT was positive in 80% cases. Ramirez P et al. performed sequential measurement of procalcitonin in patients mechanically-ventilated for >48 h with neither active infection for the duration or suspicion of VAP.\(^17\) Mean PCT in confirmed VAP cases was 0.46. Dufo F et al., in another study, enrolled 96 patients with a strong suspicion of VAP.\(^18\) Serum procalcitonin was significantly increased in the VAP group compared with the non-VAP group: 11.5 ng/ml versus 1.5 ng/ml. Radiographic analysis of VAP in our study showed that PCT was positive in more patients with bronchopneumonia (62%) than lobar pneumonia (38%). The result was, however, not statistically significant. Similar analysis was not done in any other study.

During our study 55% patients of VAP had a positive endotracheal-aspirate culture. Culture positivity was seen in more patients with a positive PCT. Acinetobacter was the most common bacterial aetiology of VAP, and was associated with a positive PCT in 80% cases. Other organisms isolated were Pseudomonas aeruginosa (6), Hemophilus influenzae (2), Enterococcus (2), MRSA (2), MSSA (1), Candida (1) and H1N1 (2). Polymicrobial growth was seen in 3 patients.

In our study, 19 patients (48%) with VAP died. Maximum mortality was seen with PCT >10 ng/ml (37%). Dufo et al also showed that serum procalcitonin was significantly increased in the nonsurvivors compared with the survivors.
for the VAP group: 16.5 ng/ml versus 2.9 ng/ml. In the study by Luyt CE et al., among the 63 patients enrolled in the study, 38 (60%) had unfavourable outcomes (14 deaths, 21 recurrences, and 3 documented extrapulmonary infections). On Day 1, serum procalcitonin of more than 1 ng/ml was the strongest indicator of unfavourable outcome with an odds ratio of 12.3. Seligman R et al. followed-up patients 28 days after the diagnosis, when they were considered survivors. PCT was determined on day 0 and day 4. Survival was directly related to decreasing PCT with odds ratio (OR) = 5.67. In another study, Brunkhorst FM et al. assessed 93 patients with documented pneumonia in a non-surgical intensive care. PCT levels were found to be a poor indicator for change in clinical status or death. Polzin et al. performed a study with 129 patients 25 with HAP, 26 CAP, 26 AECB, 27 tuberculosis, and 25 controls. In the HAP group, in four of five patients who subsequently died, procalcitonin concentrations of >0.5 ng/ml were found. While the PCT trends seen in our study were similar to several other studies, the results were not significant by Chi-square analysis (p <0.05). This could be attributed to the limitations of our study. In our study semi-quantitative estimation of PCT was done. Absolute values of PCT will improve accuracy in the work-up of patients. The rate of microbiologically documented CAP in our study population was low, limiting information about the diagnostic accuracy of PCT for etiological diagnoses. Testing for viruses and atypical pathogens was not routinely performed. Therefore, the use of the serum PCT level to differentiate bacterial from viral infections requires further confirmation. In addition, serial measurements were not obtained in this study. In order to determine the duration of high PCT levels in the serum further study is required. The PCT levels were measured at admission; the onset of disease prior to admission differed across the patients. Therefore, the PCT level at the time of admission may not represent the peak PCT level in the patients.

Conclusion

PCT was more frequently positive in VAP compared to CAP. Higher absolute values of PCT were seen in patients with VAP compared to CAP. PCT was equally positive in lobar pneumonia and bronchopneumonia in CAP. In VAP PCT was positive in more patients with bronchopneumonia than lobar pneumonia. Streptococcus pneumoniae was the most common bacterial aetiology of CAP, and was associated with a positive PCT in 75% cases. Acinetobacter was the most common bacterial aetiology of VAP, and was associated with a positive PCT in 80% cases. Mortality was more in PCT positive patients in both CAP and VAP. Maximum mortality in VAP was with PCT >10 ng/ml. A study with a larger sample size, absolute PCT values and serial measurements during the course of the hospital will be needed to consolidate our findings.

Conflict of Interest: None

References

1. Black AD. Non-infectious mimics of community-acquired pneumonia. *Pneumonia* 2016; 8(2): 1-5.
2. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. *British Journal of Pharmacology* 2010; 159(2): 253-264.
3. Niederman MS, Mandell LA, Anzueto A et al. Guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 2001; 163(7): 1730-54.
4. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165(7): 867-903.
5. Huang DT, Lisa A, Weissfeld et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 2008; 52(1): 48-58.
6. Masías M, Gutiérrez F, Shum C et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patient’s outcome research team pneumonia severity index. *Chest* 2005; 128(4): 2223-9.
7. Holm A, Pedersen SS, Nexoe J et al. Procalcitonin versus C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care. *Br J Gen Pract* 2007; 57(490): 555-60.
8. Müller B, Harbarth S, Stolz D et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis* 2007; 7(2): 10.
9. Bousskey N, Leroy O, Georges H et al. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. *Infection* 2005; 33(4): 257-63.
10. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with aetiology and prognosis. *Infection* 2000; 28(2): 68-73.
11. Lee JY, Hwang SJ, Shim JW et al. Clinical Significance of Serum Procalcitonin in Patients with Community-acquired Lobar Pneumonia. *Korean J Lab Med* 2010; 30(4): 406-13.
12. Krüger S, Ewig S, Marre R et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 2008; 31: 349-355.
13. Daubin C, Parienti JJ, Fradin S et al. Procalcitonin levels and bacterial aetiology among COPD patients admitted to the ICU with severe pneumonia: a prospective cohort study. *BMC Infect Dis* 2009; 9: 157.
14. Jereb M, Kotar T. Usefulness of procalcitonin to differentiate typical from atypical community-acquired pneumonia. *Wien Klin Wochenschr* 2006; 118(S-6): 170-4.
15. Nyamande K, Laloo UG. Serum procalcitonin distinguishes CAP due to bacteria, Mycobacterium tuberculosis and PJP. *Int J Tuberc Lung Dis* 2006; 10(5):
16. Bousskey N, Leroy O, Alfandari S et al. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. *Intensive Care Med* 2006; 32(3): 469-72.

17. Ramirez P, Garcia MA, Ferrer M et al. Sequential measurements of procalcitonin levels in diagnosing ventilator-associated pneumonia. *Eur Respir J* 2008; 31: 356-62.

18. Duflo F, Debon R, Monneret G et al. Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. *Anaesthesiology* 2002; 96(1): 74-9.

19. Luyt CE, Guerin V, Combes A et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 48-53.

20. Seligman R, Meisner M, Lisboa T et al. Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. *Crit Care* 2006; 10: R125.

21. Brunkhorst FM, Al-Nawas B, Krummenauer F et al. Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. *Clin Microbiol Infect* 2002; 8(2): 93-100.

22. Polzin A, Pletz M, Erbes R et al. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. *Eur Respir J* 2003; 21: 939-43.

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