10.5005/jp-journals-10045-0030

ORIGINAL ARTICLE

Study of Clinical Profile of Community-acquired Pneumonia with Special Reference to C-reactive Protein and Procalcitonin Levels

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ABSTRACT

Introduction: Pneumonia is defined as an infection of the pulmonary parenchyma. Despite being the cause of significant complications and deaths, pneumonia is often wrongly diagnosed, mistreated, and underestimated. The incidence rates are highest in old-aged patients. In the current prospective observational study, we intend to study the utility of procalcitonin (PCT) level and serum C-reactive protein (CRP) level for diagnosing pneumonia.

Design: Prospective observational studies.

Materials and methods: The study was conducted in RajaRajeswari Medical College and Hospital, Bengaluru, during the period extending from June to May 2014. Eighty patients, aged more than 18 years, with diagnosis of pneumonia were included in the study. Serum PCT levels were calculated using BRAHMS PCT Kryptor immunofluorescent assay (Biomerieux, France). Other routine investigations, including CRP, sputum culture, and endotracheal secretions cultures, were done. Chi-square analysis was done to assess its prognostic and diagnostic significance. Data were analysed with Statistical Package for the Social Sciences (version 17.0 for Windows).

Results and conclusion: C-reactive protein was positive in 60 (75%) of the patients, and PCT was positive in 45 (56.25%) patients; 28 patients had PCT levels 0.5 to 1.5 ng/mL, 1 (3.6%) had CRP <6 mg/mL, 27 (96.4%) had CRP >6 mg/mL; 17 patients had PCT values >1.5 ng/mL and CRP was positive in all patients ($p < 0.001$). *Streptococcus pneumonia* was the most common and isolated in 8 (10%) patients. C-reactive protein is a useful and better adjuvant in the diagnosis of community-acquired pneumonia (CAP). 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, Prognosis, Prohormone.

How to cite this article: Prajwal KC, Krishna MV, Patil S. Study of Clinical Profile of Community-acquired Pneumonia with Special Reference to C-reactive Protein and Procalcitonin Levels. J Med Sci 2016;2(2):27-30.

Source of support: Nil

Conflict of interest: None

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INTRODUCTION

The Infectious Diseases Society of America (IDSA) defines community-acquired pneumonia (CAP) as "an acute infection of the pulmonary parenchyma, i.e., associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and or localized rales), in a patient not hospitalized or residing in a long-term care facility for more than 14 days before onset of symptoms."[1]

A rapid diagnosis of pneumonia and an accurate differentiation from viral respiratory illnesses and noninfectious causes have important therapeutic and prognostic implications. In the current prospective observational study, we intended to study the utility of procalcitonin (PCT) level in comparison with C-reactive protein (CRP) in the diagnosis and prognosis of pneumonia.

Procalcitonin in Community-acquired Pneumonia

In patients with CAP, improved diagnostic assessment by PCT is important in order to differentiate from other noninfectious infiltrates and to guide the duration of antibiotics.

The dynamics of PCT levels have prognostic implications, as persistently elevated levels are associated with adverse outcome. Conversely, decreasing PCT levels suggest a favorable outcome, usually showing a log-linear drop-off and a half-life of 20 to 24 hours. The prognostic accuracy of PCT in the ICU can be markedly improved by considering the course of PCT. Mortality increased with every day that PCT increased.

C-reactive Protein

C-reactive protein was first described by Tillett and Frances in 1930, as a serum component present in acutely ill patients that reacted with a specific *Streptococcus pneumoniae* extract and they termed Fraction C.[2] C-reactive protein is the prototypical acute phase protein in humans and is an important mediator of host defense. Normal baseline levels of circulating CRP are low, but increase up to 10,000-fold within hours of inflammation induced

by infection or injury. It binds a wide array of extrinsic (bacteria, fungus, parasite, and plant components) and intrinsic (damaged cell membranes, chromatin, histones, and apoptotic cells) ligands, and subsequently activates the classical complement pathway and binds immunoglobulin receptors on phagocytes.

C-reactive protein has recently received increased attention as numerous studies have implicated it as a predictive biomarker for cardiovascular disease risk.[3] However, because CRP is a nonspecific indicator of inflammation, its levels can be significantly influenced by a number of disease conditions as well as other parameters. Normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), and severe bacterial infections and burns (>200 mg/L).[4]

MATERIALS AND METHODS

Source of Data

Eighty patients, aged more than 18 years, admitted to RajaRajeswari Medical College and Hospital (RRMCH), Bengaluru, with the diagnosis of pneumonia from June 14 to May 15, were included in the study.

Methods of Collection of Data

Patients satisfying the inclusion criteria and admitted in the Department of Internal Medicine and Department of Pulmonology in RRMCH, Bengaluru were included in the study. This study enrolled 80 patients with CAP, above 18 years of age. Data was collected in a proforma.

Routine hemogram with hematocrit, routine urine analysis, renal function tests, random blood sugar, liver function tests, serum electrolytes, chest X-ray, sputum Gram's stain, sputum culture, sputum acid-fast bacilli, blood culture, CRP, and serum PCT were investigated for all patients. The proposed study is a prospective observational study and appropriate statistical analysis is carried out.

Inclusion Criteria

Consecutive patients of CAP, in medicine and pulmonology ward of RRMCH.

Exclusion Criteria

- Patients having upper respiratory tract infections
- Patients having pulmonary tuberculosis
- Patients having lung abscess patients
- Patients less than 18 years
- Hepatic failure patients
- Renal failure patients
- Congestive cardiac failure.

PROCALCITONIN TEST PROCEDURE

Methods

Chemiluminescence assay [immunoluminometric assay (ILMA)]: For the PCT assay, tubes were coated with a monoclonal antibody specific for the katacalcin part of PCT. This antibody binds to amino acids 102 to 111 of PCT. Coating of the antibody was done for 20 hours on polystyrene tubes (2.0 µg/tube) in 0.3 mL of buffer (10 mmol/L Tris–HCl, pH 7.8, 10 mmol/L NaCl). Tubes were blocked with 10 mmol/L sodium phosphate buffer containing 30 q/L Karion FP, 5 gm/L protease-free bovine serum albumin (Sigma), pH 6.8, and lyophilized. A polyclonal sheep antibody specific for the calcitonin part of PCT was used as tracer. This antibody was raised to peptide 69 to 79 (GTYTQDLNKFH) of PCT and was affinity-purified on a calcitonin-sulfo link column and subsequently labeled with acridinium ester as follows: 100 µg of antibody in 20 mmol/L sodium phosphate buffer, pH 8.0, was incubated for 20 minutes at room temperature with 10 µL of acridinium ester (1 gm/L in acetonitrile; Hoechst AG). Labeled antibody was purified by high performance liquid chromatography (HPLC) using a Knauer hydroxyapatite column (buffer gradient, 1–500 mmol/L potassium phosphate, pH 6.8; flow rate, 0.8 mL/min). Procalcitonin was measured in a coated tube assay in which 100 µL of a patient sample or calibrator was added in duplicate to each antibody-coated tube and incubated for 30 minutes at room temperature; 200 µL of tracer containing acridinium ester-labeled anti-PCT antibody was then added, followed by a 2-hour incubation at room temperature. Tubes were washed five times with 2 mL of standard LUMI test® washing buffer (B_R_A_H_M_S AG), and detection was performed in a luminometer (detection time per sample, 1 second). This assay system was named LUMI test PCT® (B_R_A_H_M_S AG). Relative light units for the chemiluminescence assay were expressed in ng/L. Procalcitonin is calculated from a calibration curve that was included in every analytical run. The PCT concentrations <0.5 ng/mL are negative.[5-8]

RESULTS

The results are tabulated in Tables 1 to 4.

Table 1: C-reactive protein mg/L normal <6 mg/L

C-reactive protein mg/L normal <6 mg/L	*Gender*		
	Female	*Male*	*Total*
<6	12 (29.3%)	8 (20.5%)	20 (25%)
>6	29 (70.7%)	31 (79.5%)	60 (75%)
Total	41 (100%)	39 (100%)	80 (100%)

Table 2: Procalcitonin (ng/mL) normal <0.5 ng/mL

Procalcitonin (ng/mL) normal <0.5 ng/mL	*Female*	*Male*	*Total*
<0.5	22 (53.7%)	13 (33.3%)	35 (43.8%)
0.5–1.5	10 (24.4%)	18 (46.2%)	28 (35%)
>1.5	9 (22%)	8 (20.5%)	17 (21.3%)

Table 3: Gender distribution of patients studied with PCT levels

	Procalcitonin			
Gender	*<0.5*	*0.5–1.5*	*>1.5*	*Total*
Female	22 (62.9%)	10 (35.7%)	9 (52.9%)	41 (51.3%)
Male	13 (37.1%)	18 (64.3%)	8 (47.1%)	39 (48.8%)
Total	35 (100%)	28 (100%)	17 (100%)	80 (100%)

p = 0.100, Not significant, Chi-square test

DISCUSSION

We studied a total of 80 patients of CAP. In our study the age of patients presenting with CAP ranged from 18 to 70 years and above. Of these 23 (28%) were between 51 and 60 years, 19 (23.8%) were between 61 and 70 years, 5 (6.3%) were above 70 years; mean ± SD: 52.21 ± 15.04.

In our study of 80 patients, 60 (75%) patients had positive CRP >6 mg/L, 29 were females, and 31 were males (Table 1). The mean age of the patients whose CRP was positive and is >6 mg/L is 50 to 60 years ± 10 years (p = 0.935).

In another study conducted by the Flanders et al they reported on a small subgroup of patients with pneumonia who had CRP of <11 mg/mL. In 54 patients with pneumonia with low CRP in our study, the estimated diagnostic risk of pneumonia was high (n = 3) or intermediate (n = 51) based on the history and the physical examination results as defined in our model. These findings emphasize that CRP test results should be interpreted together with clinical findings.[9]

We estimated PCT in the same above 80 patients on the day of admission; 35 (43.8%) had negative PCT <0.5 ng/mL, 28 (35%) had PCT 0.5 to 1.5 ng/mL, and 17 (21.3%) had PCT >1.5 ng/mL. In a similar study done by Huang et al,[10] (Tables 2 and 3) patients presenting with a clinical and radiographic diagnosis of CAP were enrolled, and stratified *a priori* according to PCT 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. Primary outcome was 30-day mortality and 1,651 patients formed the study cohort. The mean PCT level at presentation was 3.4 ng/mL, but levels were broadly spread, such that 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. Masiá et al[11] studied 185 patients of CAP from October 15, 1999 to October 14, 2000. The mean PCT at admission was 0.49 ng/mL. In another study in patients with CAP done by Holm et al,[12] 70% patients of a total of 48 had a positive PCT. Müller et al[13] conducted a study in Switzerland in which 373 patients of CAP had a mean PCT of 3.1 at admission.

Boussekey et al[14] in August 2005 did a study to determine the diagnostic and prognostic role of PCT in patients admitted in an intensive care unit for severe CAP. Moreover, 110 patients hospitalized in ICU were prospectively studied. Within 48 hours following ICU admission, the PCT serum level was measured with a quantitative method above a threshold value of 0.5 ng/mL. 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[15] studied 96 patients, 50 to 85 years of age, treated in the hospital for CAP. On admission, 60 patients (54%) had elevated PCT levels (>0.1 μg/L). In our study, the age wise distribution of PCT showed PCT value of >1.5 ng/mL seen evenly in all age group between 20 and 70 years, whereas the mean age of the patient was 50 to 60 ± 10 years that showed PCT value of 0.5 to 1.5 ng/mL. In the study done by Huang et al, the mean age was 65 years. In the Masiá et al study, the mean age of patients with PCT <0.5 ng/mL was 64 years. The mean age of patients with PCT >0.5 ng/mL patients was 73 years. In the study done by Müller et al, the mean age was 67 ± 18 years. In the study by Krüger et al,[16] the mean ± SD (range) age was 61 ± 18 (18–98) years.

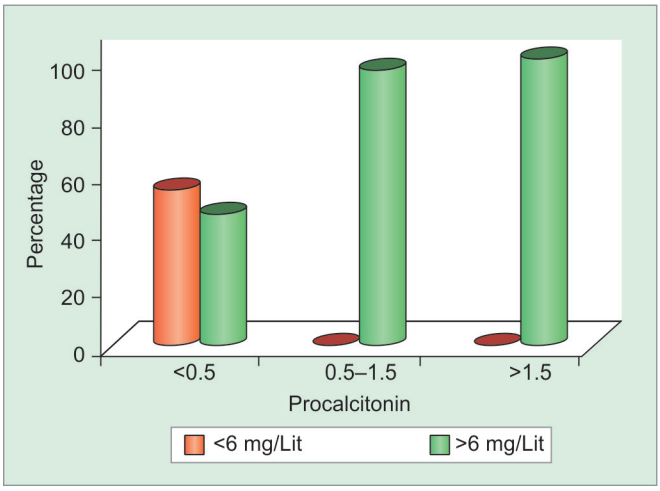
The PCT was positive in 26 (57.7%) male patients, and 19 (42.2%) female patients. In other studies done by Huang et al, Masiá et al, Müller et al, and Hedlund and Hansson mentioned above, the percentage of males was 52, 63, 63, and 48% respectively. A study done by Krüger et al[16] comprised 1,671 patients of CAP. Approximately 55% were males.

In our study of 35 patients PCT <0.5 ng/mL, out of which 19 (54.3%) had CRP <6 mg/mL, 16 (45.7%) had CRP >6 mg/mL. A total of 28 patients had PCT 0.5 to 1.5 ng/mL, 1 (3.6%) had CRP <6 mg/mL, 27 (96.4%) had CRP >6 mg/mL. Moreover, 17 patients had PCT values >1.5 ng/mL and CRP was positive in all patients (p < 0.001) Table 4. In our study, 16 patients had CRP >6 mg/mL and PCT <0.5 ng/mL. This can be explained by the increased incidence of the viral pneumonia (h1n1) during the study period. Thus, this study was helpful in distinguishing the viral and bacterial pneumonia as PCT is positive only in bacterial pneumonia.

Table 4: C-reactive protein in association with PCT levels

	Procalcitonin			
CRP	*<0.5*	*0.5–1.5*	*>1.5*	*Total*
<6 mg/L	19 (54.3%)	1 (3.6%)	0 (0%)	20 (25%)
>6 mg/L	16 (45.7%)	27 (96.4%)	17 (100%)	60 (75%)
Total	35 (100%)	28 (100%)	17 (100%)	80 (100%)

p < 0.001**, Significant, Chi-square test



Graph 1: C-reactive protein and PCT correlation

In a prospective study done by Luzzani et al,[17] the linear correlation between PCT plasma concentrations and the four categories of patients (sepsis negative, SIRS, localized infection, and sepsis group) was much stronger than in the case of CRP (Spearman's rho, 0.73 *vs* 0.41; $p < 0.05$). A rise in sepsis-related organ failure assessment score was related to a higher median value of PCT but not CRP. They concluded that PCT is a better marker of sepsis than CRP and course of PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction. Results of our study match with these findings (Graph 1).

In another study conducted by van Vugt et al[18] showed the measurement of PCT added no relevant additional diagnostic information. A simplified diagnostic score based on symptoms signs, and CRP >30 mg/mL resulted in proportions of the pneumonia of 0.7, 3.8, and 18.2% in the low, intermediate, and high-risk group respectively.

CONCLUSION

- C-reactive protein and PCT were positive in all age groups, but more positive in the age group of 40 to 70 years.
- C-reactive protein and PCT were uniformly positive in males and females.
- Majority of the patients with CAP had CRP positive (75%) than compared with PCT (56.3%).
- There was a linear correlation between PCT and CRP in patients with CAP; CRP was positive in all patients whose PCT was positive ($p < 0.001$).

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