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Immunoinflammation and Elevated Serum Procalcitonin In Patients with Resistant Strain Mycobacterium Tuberculosis in Benin Metropolis

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Abstract

Background: The utility of serum procalcitonin (PCT) for differentiating pulmonary tuberculosis (TB) from bacterial acquired pneumonia (AP) in Benin Metropolis (Nigeria), a country with an intermediate TB burden.

Aim: To determine the bacterial acquired Pnuemonia from Mycobacterium tuberculosis associated pneumonia with the aid of procalcitonin levels Methods: We conducted a prospective study, enrolling 170 participants with suspected AP in a community-based referral hospital. A clinical assessment was performed before treatment, serum and PCT were measured. The test results were compared to the final diagnoses.

Results: Of the 170 patients, 98 had bacterial acquired pneumonia and 52 had pulmonary TB. The median PCT level was 0.528 ng/mL (range, 0.01 to 27.75) with bacterial acquired pneumonia and 0.042 ng/mL (range, 0.01 to 0.87) with pulmonary TB ($p<0.001$). No difference was detected in the discriminative values of PCT ($p=0.733$).

Conclusions: The concentrations of PCT differed significantly in patients with pulmonary TB and bacterial acquired Pneumonia. The high sensitivity and negative predictive value for differentiating pulmonary TB from bacterial acquired pneumonia suggest a supplementary role of PCT in the diagnostic exclusion of pulmonary TB from bacterial AP in areas with an intermediate prevalence of pulmonary TB.

Keywords: Pneumonia; Acquired; Procalcitonin; Tuberculosis; Serum

Introduction

In countries with a high tuberculosis (TB) burden, *Mycobacterium tuberculosis* is a frequent cause of community-acquired pneumonia (CAP) [1-4], and the differential diagnosis of TB from common bacterial pneumonia is difficult. The varying clinical and radiographic presentation of CAP and TB according to patient age and comorbidity and the low sensitivity of acid-fast bacillus microscopy make it even more difficult to distinguish TB from common bacterial pneumonia [5-7]. Therefore, an adjunct diagnostic method that can determine whether CAP is caused by pulmonary TB or other bacterial pathogens would have a clinical role in terms of isolating patients with TB and administering appropriate anti-TB medication or antibiotic treatment at an early stage.

Acquired pneumonia (AP) is a major cause of hospital admission and the most important infectious cause of death [1]. A rapid diagnosis and appropriate antibiotic treatment are essential to reduce the morbidity and mortality from AP.

PCT (Procalcitonin) a 116 amino acid protein is a biomarker of severe systemic infectious bacterial disease [8-11]. Recently, PCT has also been introduced as a promising alternative to CRP in guiding the antibiotic treatment of CAP and acute exacerbations of chronic obstructive pulmonary disease [12,13] based on the ability of PCT to discriminate between patients with or without bacterial infection. In addition, PCT does not appear to be significantly elevated in patients with pulmonary TB [14-16], making it an attractive potentially rapid diagnostic method for differentiating pulmonary TB from bacterial AP.

Therefore, we investigated the utility of serum PCT for differentiating pulmonary TB from other bacterial AP in Benin Metropolis (Nigeria), a country with an intermediate TB burden.

Patients and Method

Patients

Of the 200 eligible patients, 30 were excluded because the final diagnosis was inconclusive or they had other diagnoses, such as pulmonary embolism, acute exacerbation of interstitial lung disease, or non-small cell lung cancer. One hundred and seventy patients were classified with pulmonary TB or bacterial CAP. None of the patients in this study was HIV-positive.

Patients were recruited between April 2013 and April 2014 after the study protocol had been approved by the Ethics Review Committee. Adult patients who visited the emergency department or outpatient clinic with respiratory symptoms and chest radiograph abnormalities were eligible for enrollment in this study.

Patients were considered to have pulmonary TB when *M. tuberculosis* was cultured from their sputum or lavage fluid, and the concentration of adenosine deaminase in the effusion was >65 IU/dL in lymphocyte-predominant exudative pleural effusions combined with a lung parenchymal lesion. Bacterial CAP was diagnosed when the subjects had clinical signs of pneumonia and a new infiltrate on

chest X-ray, and these resolved completely with antibiotic treatment and cultures of sputum or lavage fluid were negative for *M. tuberculosis* during follow-up. For the microbiologic evaluation of the patients with AP, sputum Gram stains and cultures was performed, two blood cultures, and urinary antigen assays to detect *Legionella pneumophila* and *Streptococcus pneumoniae*.

Additionally, demographic data, a white blood cell (WBC) count and differential, and the Pneumonia Patient Outcomes Research Team (PORT) [17] score were collected. The results of these tests were compared to the final diagnostic group scores.

Methods

The PCT level was measured using a monoclonal immunoluminometric assay (LIA PCT sensitive; BRAHMS Diagnostica, Berlin, Germany). After separating the serum, it was aliquoted and frozen at -70˚C until analyzed. The functional assay sensitivity for PCT with a 20% inter-assay variation coefficient was 0.05 ng/mL.

Statistics

Differences between the two groups were tested using the nonparametric Mann-Whitney *U*-test for continuous variables. Pearson's $\chi 2$ test or Fisher's exact test was used for categorical variables, and the Spearman rank correlation coefficient was calculated. Optimal cutoffs for predicting pulmonary TB or bacterial AP were investigated using receiver-operating characteristics (ROC) analysis, and the diagnostic accuracy was assessed from the area under the ROC curves (AUCs). A $p<0.05$ was regarded as statistically significant, and analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 170 patients who met the inclusion criteria, 98 had bacterial AP and 52 had pulmonary TB. The median age of the bacterial AP and pulmonary TB groups was 68 years (range, 18 to 88) and 46 years (range, 18 to 82), respectively. The responsible pathogen was determined in 42 patients (24.7%) with bacterial AP.

Fourty eight (93%) with pulmonary TB had positive respiratory specimen cultures for *M. tuberculosis*. The patients' demographic characteristics, symptoms, and laboratory results are compared in Table 1.

The respective median PCT level was 0.528 ng/mL (range, 0.013 to 27.754) and 0.042 ng/mL (range, 0.01 to 0.873) ($p<0.001$). A significant positive correlation was detected with the PCT concentrations (r=0.648, $p=0.01$).

Diagnostic accuracy for discriminating TB from bacterial AP

Discriminative value of 0.857 (95% confidence interval [CI], 0.778 to 0.936), and the PCT concentration had a discriminative value of 0.872 (95% CI, 0.792 to 0.951). No difference was found in the discriminative value of PCT ($p=0.733$). At a cutoff value of 12.5 mg/dL, the PCT concentration had a sensitivity of 93.1% and a specificity of 59.6% (Table 2).

Discussion

The results of this study are suggestive that PCT can help to discriminate between pulmonary TB and other common bacterial AP in a setting of intermediate TB prevalence. Significantly lower PCT serum concentrations were found with pulmonary TB compared to the other bacterial AP in the initial diagnosis stage. About 46,000 cases of TB are newly diagnosed annually in South Korea [18], and the rapid, accurate differential diagnosis of TB from common bacterial AP has important public health implications for the isolation care of patients with TB and early appropriate anti-TB medication or antibiotic treatment.

Bacterial pneumonia (n=98)	**Tuberculosis (n=52)**	**p value**
Demographic characteristics		
Age, yr 68 (18-88)	46 (18-82)	<0.001*
Sex, male/female 36/21	18 / 12	0.77†
History of tuberculosis 14 (24.6)	6 (20.0)	0.63†
Symptoms		
Cough 62 (63.2)	48 (93.0)	0.10†
Sputum 48 (84.2)	22 (73.3)	0.22†
Fever 52 (91.2)	15 (50.0)	<0.001†
Dyspnea 34 (59.6)	12 (40.0)	0.08†
Night sweats 0 (0)	7 (23.3)	<0.001‡
Weight loss 1 (1.8)	8 (26.7)	0.001‡
Chest pain 11 (19.3)	9 (30.0)	0.30†
Laboratory test		
White blood cell, $\times 10^3/\mu L$ 15.21 (2.30-39.92)	8.38 (5.07-22.99)	<0.001
Neutrophils, $\times 10^3/\mu L$ 11.06 (1.70-37.92)	5.85 (3.07-20.23)	<0.001*
Monocyte, μL 503 (0-1210)	535 (253-5009)	0.053*
Procalcitonin, ng/mL 0.528 (0.013-27.754)	0.042 (0.01-0.873)	<0.001*
Upper lobe dominance 18 (28.1)	23 (76.7)	<0.001†
Cavitary lesion 0 (0)	11 (36.7)	<0.001‡
Effusion 11 (19.3)	9 (30.0)	0.26†
PORT score 94 (18-187)	76.4 (10-126)	<0.001*
Values are presented as number (%) or median (range).		
PORT, Pneumonia Patient Outcomes Research Team.		
* Mann-Whitney U-test.		
† Pearson $\chi 2$ test. ‡ Fisher's exact test.		

Table 1: Patients and Laboratory diagnosis

Discriminating pulmonary TB from bacterial AP is frequently impossible based on patient history, physical examination, and radiographic findings. Therefore, PCT might have a role in the diagnostic algorithm as rapid, noninvasive tests.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT, ng/mL				
<0.1	86.2	78.9	67.6	91.8
<0.25	93.1	59.6	54.0	94.4
<0.5	93.1	50.9	49.1	93.5
<1.0	100.0	31.6	42.6	100.0

Table 2: Diagnostic validity of procalcitonin (PCT) in differentiating pulmonary tuberculosis from bacterial acquired pneumonia according to the different value

There was no difference observed in the discriminating power of PCT for differentiating pulmonary TB and other bacterial infections in this study. PCT has also been investigated as a predictor of bacterial infection and is considered a more accurate marker of various bacterial infections [9,19]. Therefore, the absence of a difference of PCT in our study should be considered in light of several factors. First, the low yield of a causative pathogen in bacterial AP (24.7%) suggests the possibility of including bacterial AP with an atypical etiology, such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and respiratory viruses. These atypical pathogens produce lower PCT levels than classical bacterial pneumonia such as pneumococcal pneumonia [20,21]. Second, because the hospital in which this study was conducted is a secondary referral hospital, although it is a community-based hospital, more than 24 hours had passed from the onset of symptoms to the time some patients visited the hospital. The variable time interval from the onset of symptoms before evaluating PCT might have affected the results because of the kinetics of each inflammatory marker [22,23].

Conclusion

In conclusion, serum PCT concentrations differed significantly in patients with pulmonary TB and those with bacterial AP at the initial diagnosis stage. The high sensitivity and negative predictive value for differentiating the diagnosis of pulmonary TB from bacterial AP suggest a supplementary role for PCT in the diagnostic exclusion of pulmonary TB from bacterial AP in areas with an intermediate prevalence of active pulmonary TB.

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