

The diagnostic value of serum levels of C-reactive protein and procalcitonin in differentiation between active pulmonary TB and CAP

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Introduction C-reactive protein (CRP) and procalcitonin (PCT) levels are elevated in patients with community-acquired pneumonia (CAP), but PCT does not increase in patients with pulmonary tuberculosis (TB).

Aim To evaluate the diagnostic value of serum levels of CRP and PCT in differentiating between active pulmonary TB and CAP.

Participants and methods The present study was carried out on 90 individuals divided into the following groups: group I included 10 control participants, group II included 40 patients with active pulmonary TB, and group III included 40 patients with CAP. Serum levels of CRP and PCT were measured.

Results CRP was significantly increased in group III compared with groups I and II. PCT was significantly increased in group III compared with groups I and II; also, there was a significant increase in group II compared with group I. The cut-off value of CRP between group II and

group III was more than 24 (mg/dl), with a sensitivity of 100%, a specificity of 70%, and that of PCT was more than 530 (pg/ml), with a sensitivity of 67% and a specificity of 97.5%.

Conclusion Measurements of CRP and PCT were complementary to each other to differentiate between pulmonary TB and CAP.

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Introduction

Tuberculosis (TB) continues to be a major public health concern, with nine million incident cases and estimated 1.3 million deaths reported worldwide in 2007 [1]. The diagnosis of TB is made on the basis of clinical symptoms, chest radiograph, skin tuberculin test, and finally, the detection of the causative agent by direct microscopy of biological specimens and culture on solid and in liquid media. Smear examination and in-vitro culture of *Mycobacterium tuberculosis* bacilli has remained the gold standard [2].

Community-acquired pneumonia (CAP) is a major cause of hospital admission and the most important infectious cause of death [3]. A rapid diagnosis and appropriate antibiotic treatment are essential to reduce the morbidity and mortality caused by CAP.

In countries with a high TB burden, *Mycobacterium tuberculosis* is a frequent cause of CAP and the differential diagnosis of TB from common bacterial pneumonia is difficult [3].

C-reactive protein (CRP) is an acute-phase protein produced primarily in the liver and is stimulated by cytokine release [4]; CRP levels are elevated in patients with CAP compared with healthy control

participants [5]. Procalcitonin (PCT) is an acute-phase reactant protein and consists of 116 amino acids; it has been reported to be a sensitive marker of severe bacterial infection [2].

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 [1] on the basis of the ability of PCT to discriminate between patients with or without bacterial infection. In lower respiratory tract infections, measurement of serum PCT may enable physicians to differentiate between typical bacterial and nonbacterial causes of inflammation using a cut-off value of 0.5 ng/ml [6–9]. In addition, PCT does not appear to be significantly elevated in patients with pulmonary TB, making it an attractive potentially rapid diagnostic method for differentiating pulmonary TB from bacterial CAP [1]. Identification of the etiology of CAP is a clinical difficulty because single clinical, radiologic, or laboratory parameters have limited value in predicting the infectious organism [10], and no rapid test has been standardized for the diagnosis of 'atypical' or viral pathogens. As a result, broad-spectrum initial antibiotic therapy is usually empirically chosen [11,12]. PCT serum levels or other biological markers of bacterial infection might enable clinicians to choose targeted antibiotic

therapy in patients with CAP by differentiating between classic bacterial and atypical or viral etiology.

This work aims to evaluate the diagnostic value of serum levels of CRP and PCT in differentiating between active pulmonary TB and CAP.

Participants and methods

The present study was carried out on 90 participants; they were recruited from the chest department, Tanta University Hospital, and Abbassia chest hospital during the period from April 2012 till April 2013 and divided into three groups. Group I included 10 apparently healthy normal nonsmoker volunteers, six men and four women, mean age 37.1 ± 10.816 years. Group II included 40 patients with active pulmonary TB, 40 men and no women, mean age 38.1 ± 6.368 years. Group III included 40 patients with CAP caused by bacterial infection, 36 men and four women, mean age 49.425 ± 6.687 years. Informed consents were obtained from all the participants in this study.

Inclusion criteria

- (1) Patients with active pulmonary TB fulfilled the following criteria:
 - (a) Patients with clinical symptoms and signs of pulmonary TB.
 - (b) Examination of sputum by Ziehl–Neelsen stain (three successive times) was positive for acid-fast bacilli.
- (2) Patients with CAP fulfilled the following criteria [13]:
 - (a) Acute illness characterized by symptoms and signs of lower respiratory infection.
 - (b) New radiological shadowing for which there was no alternative explanation.
 - (c) Acquired outside hospital.
 - (d) Sputum Gram stain and culture showed that the causative organisms were bacteria. Sputum samples should fulfill the following criteria to maintain a sensitivity of 62% and a specificity of 85% to ensure that organisms present in the smear were not commensals: squamous epithelial cells (normally exfoliated from the oropharynx) less than 10 cells per low-power microscopic field, polymorphonuclear neutrophils 10–25 cells per low-power microscopic field, and there should be at least 10 organisms per oil immersion field [14].

Exclusion criteria

- (1) Patients with lung infections other than pulmonary TB or CAP caused by bacterial infection.

- (2) Bacterial CAP on top of viral infections of respiratory tract. This was diagnosed as pneumonia after flu manifestation although many studies found that serum level of PCT is not increased or even low in viral infections [15,16].
- (3) Patients with negative smear pulmonary TB or extrapulmonary TB (diagnosed by history, clinical examination, and any investigation, available with the patients, proved this diagnosis).
- (4) HIV patients.
- (5) Patients with a history of other chronic respiratory diseases, for example chronic obstructive pulmonary disease, bronchial asthma, lung cancer, and IPF.
- (6) Patients with chronic metabolic, endocrine, cardiovascular, or inflammatory diseases.
- (7) Patients with CAP or active pulmonary TB under antimicrobial therapy.

The following were carried out for all participants:

Thorough assessment of history, full clinical examination, plain chest radiograph posteroanterior view, sputum examination for acid-fast bacilli by Ziehl–Neelsen stain three successive times for patients suspected of having tuberculous. In patients with CAP, sputum examination by gram stain and culture was performed to detect causative microorganisms; also, blood culture was required in severe cases. Five milliliters of venous blood was withdrawn from each participant to measure the serum levels of CRP and PCT. Serum levels for CRP were measured using qualitative measurement of CRP (Biosystems S.A. Costa Brava 30, 08030 Barcelona-Spain on the basis of the latex agglutination method as follows:

- (1) All reagents, controls, and serum samples were brought to room temperature.
- (2) The CRP latex reagent was shaken gently before use. One drop of reagent was placed in the test circle. Using disposable pipettes, one drop of undiluted patient serum was placed on the same circle and both were mixed together with the paddle end of the pipette.
- (3) Positive and negative controls were obtained with each series of test serum in the same way as in step 2.
- (4) The slide was rotated back and forth for 2 min and the result was read under an indirect oblique light source [9].

Serum levels of PCT were measured using a commercially available ELISA kit supplied by 'Raybiotech Inc.' (3607 Parkway Lane, Suite 100, Norcross GA 30092, USA) according to the manufacturer's instructions as follows:

- (1) All reagents and samples were brought to room temperature (18–25 °C) before use.
- (2) One hundred microliter of the standard and the sample were added to appropriate wells, covered, and incubated for 2.5 h at room temperature or overnight at 4°C with gentle shaking.
- (3) The solution was discarded and washed four times with 1×wash solution by filling each well with wash buffer (300 µl) using a multichannel pipette or autowasher. Complete removal of the liquid at each step was performed and was important to achieve good performance. After the last wash, any remaining wash buffer was removed by aspirating or decanting. The plate was then inverted and blotted on clean paper towels.
- (4) One hundred microliter of 1×prepared biotinylated antibody was added to each well and incubated for 1 h at room temperature with gentle shaking.
- (5) The solution was discarded and the wash was repeated as in step 3.
- (6) One hundred microliter of prepared Streptavidin solution was added to each well and incubated for 45 min at room temperature with gentle shaking.
- (7) The solution was then discarded and the wash was repeated as in step 3.
- (8) One hundred microliter of TMB One-Step Substrate Reagent was added to each well and incubated for 30 min at room temperature in the dark with gentle shaking.
- (9) Fifty microliter of stop solution was added to each well and was read at 450 nm [9].

Statistical analysis

Mean values, SD, range, sensitivity, and specificity were determined in this study, and ANOVA test and Tukey's test were used.

Results

The participants were older and there was a significant increase in serum CRP in group III compared with groups I and II, but there was no significant difference between groups I and II; also, there was a significant increase in serum PCT in group III compared with groups I and II, but there was significant increase in group II compared with group I. There was a significant positive correlation between serum PCT and serum CRP in groups II and III. The cut-off point of serum CRP between group II and group III was more than 24 mg/dl with a sensitivity of 100% and a specificity of 70%, but the cut-off point of serum PCT between both the groups was more than 530 pg/ml, with a sensitivity of 67% and a specificity of 97.5% (Tables 1–5 and Figs. 1–4).

Table 1 Range, mean value ± SD, and statistical comparison of age in the three groups studied

| Group | Age (years) | | ANOVA | |
|----------------------|-----------------------|----------------|------------------------|---------|
| | Range | Mean ± SD | F | P-value |
| Group I | 27.0–55.0 | 37.1 ± 10.816 | 29.406 | <0.001 |
| Group II | 25.0–50.0 | 38.1 ± 6.368 | | |
| Group III | 35.0–61.0 | 49.425 ± 6.687 | | |
| Tukey's test | | | | |
| Group I and group II | Group I and group III | | Group II and group III | |
| 0.916 | <0.001 | | <0.001 | |

Table 2 Range, mean value ± SD, and statistical comparison of serum C-reactive protein level in the three groups studied

| Group | Serum CRP (mg/dl) | | ANOVA | |
|----------------------|-----------------------|-----------------|------------------------|---------|
| | Range | Mean ± SD | F | P-value |
| Group I | 6.0–6.0 | 6.0 ± 0.0 | 22.101 | <0.001 |
| Group II | 12.0–48.0 | 27.0 ± 14.822 | | |
| Group III | 48.0–384.0 | 132.0 ± 101.823 | | |
| Tukey's test | | | | |
| Group I and group II | Group I and group III | | Group II and group III | |
| 0.915 | 0.048 | | <0.001 | |

Table 3 Range, mean value ± SD, and statistical comparison of serum procalcitonin level in the three groups studied

| Group | Serum procalcitonin (pg/ml) | | ANOVA | |
|----------------------|-----------------------------|------------------|------------------------|---------|
| | Range | Mean ± SD | F | P-value |
| Group I | 14.0–48.0 | 30.60 ± 10.814 | 13.22 | <0.001 |
| Group II | 293.0–583.0 | 409.30 ± 72.755 | | |
| Group III | 112.0–3016.0 | 711.85 ± 599.781 | | |
| Tukey's test | | | | |
| Group I and group II | Group I and group III | | Group II and group III | |
| 0.026 | <0.001 | | 0.003 | |

Table 4 ROC curve of C-reactive protein level in serum between group II and group III

| Cut-off | Sensitivity | Specificity | PPV | NPV | Accuracy (%) |
|---------|-------------|-------------|------|-------|--------------|
| >24 | 100.0 | 70.0 | 76.9 | 100.0 | 94.8 |

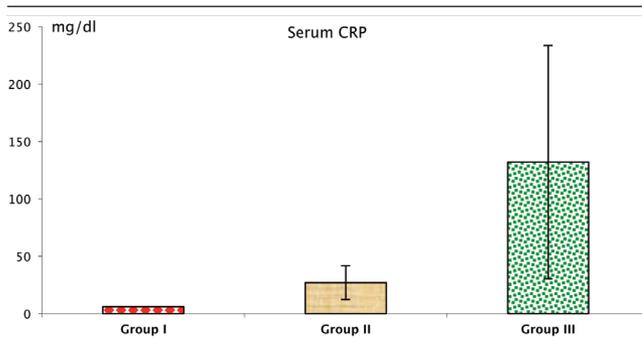
Table 5 ROC curve of procalcitonin level in serum between group II and group III

| Cut-off | Sensitivity | Specificity | PPV | NPV | Accuracy (%) |
|---------|-------------|-------------|------|------|--------------|
| >530 | 67.0 | 97.5 | 96.4 | 75.0 | 80.3 |

Discussion

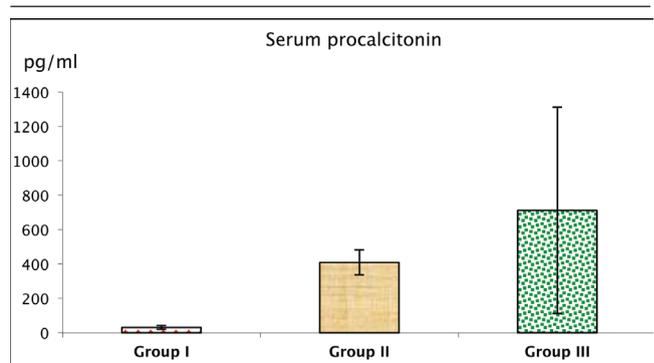
Sahin and Yildiz [17] concluded that CRP is useful in the differential diagnosis of TB and pneumonia; the best serum CRP cut-off value was 9.4 mg/dl; also, a study by Yoon *et al.* [18] found that the mean values of serum CRP were significantly higher in CAP patients compared with pulmonary tuberculosis (PTB) patients, with a sensitivity of 67.5% and a specificity of 85.1%. The CRP level is a nonspecific marker of acute-phase inflammation because it is subjected to the influence of other factors such as the general characteristics of

Fig. 1



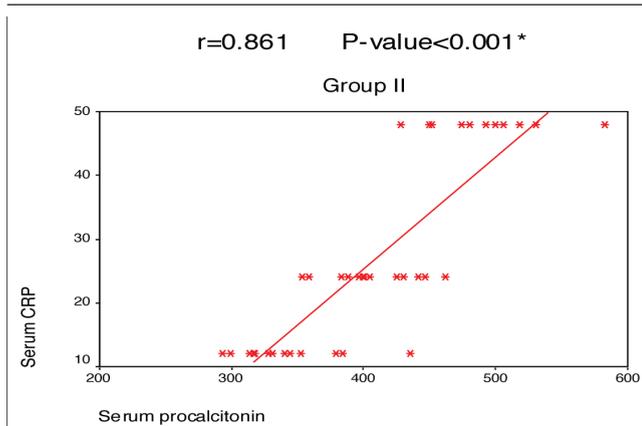
Serum C-reactive protein (CRP) level in the three groups studied.

Fig. 2



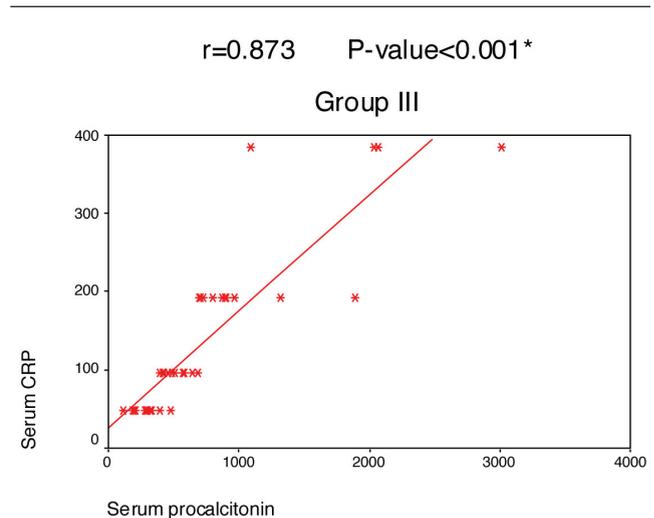
Serum procalcitonin level in the three groups studied. CRP, C-reactive protein.

Fig. 3



Correlation between serum procalcitonin and serum C-reactive protein (CRP) in group II.

Fig. 4



Correlation between serum procalcitonin and serum C-reactive protein (CRP) in group III.

patients such as age and sex; thus, cut-off levels may be different from study to another. Ugajin *et al.* [19] found that the serum level of PCT was significantly lower in PTB patients compared with CAP patients, and concluded that serum PCT is not habitually increased in HIV-negative PTB patients and is a useful biomarker for differentiating between PTB and CAP. The poor response of serum PCT in PTB is because (a) secreted cytokine patterns are different between tuberculous infection and common bacterial infection and (b) serum PCT concentration increases slightly in intracellular infection, including that caused by mycoplasma and viruses. Kang *et al.* [3] studied 87 participants with suspected CAP in a community-based referral hospital. A clinical assessment was performed before treatment, and serum CRP and PCT were measured. The test results were compared with the final diagnosis. Of the 87 patients, 57 had bacterial CAP and 30 had pulmonary TB. The median CRP concentration was 14.58 mg/dl in patients with bacterial CAP and 5.27 mg/dl in those with pulmonary TB; also, the median PCT level was 0.514 pg/ml in patients with bacterial CAP and 0.029 pg/ml in those with pulmonary TB. They concluded that

the concentrations of CRP and PCT were significantly higher in patients with bacterial CAP compared with pulmonary TB, and also found that PCT is superior in predicting the severity of bacterial CAP compared with CRP. Rasmussen *et al.* [1] concluded that in West African PTB patients, PCT levels were low but increased significantly with increasing severity of disease, and can predict the risk of mortality. As PCT synthesis and release are determined by the inflammatory cytokine cascade during systemic infection, the intensity depends on the number of organisms entering the systemic circulation; the number of organisms in PTB is probably lower than in bacterial pneumonia. The present study showed that there was a positive correlation between the serum PCT and serum CRP in patients with pulmonary TB and CAP. This was in agreement with the study of Rasmussen *et al.* [1] as they found positive correlations between both PCT and CRP. The current study showed, that the cut-off value of serum PCT of more than 530 pg/ml

had a sensitivity of 67% and a specificity of 97.5% between group II and group III. Nyamande and Lalloo [20] concluded that PCT has a fairly high specificity for diagnosing CAP because of common bacterial pathogens (88%) as well as PTB (82%); however, the sensitivity is relatively low. They also concluded that PCT was more sensitive and specific than CRP in differentiating between both diseases. Ugajin *et al.* [19] concluded that serum PCT has better diagnostic validity than CRP for differentiation between PTB and CAP, with a higher sensitivity and specificity. In this study, the low sensitivity and the high specificity of PCT as well as the high sensitivity and the low specificity of CRP in comparing between CAP and pulmonary TB prove that they are complementary tests for differentiation between both diseases. However, there are several limitations in this study; the sample size was not large, CAP bacterial causative pathogens were not clearly defined, and this work did not study the relation between PCT and CRP concentrations and the severity of CAP or the effect of antimicrobial therapy. Therefore, further studies should be carried out taking into consideration the above-mentioned points.

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Conflicts of interest

None declared.

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