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Usefulness of serum procalcitonin levels in pulmonary tuberculosis

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ABSTRACT: There are very few data on serum procalcitonin (PCT) levels in pulmonary tuberculosis (PTB) patients who are negative for HIV.

We assessed serum PCT in consecutive patients diagnosed with pulmonary tuberculosis or community-acquired pneumonia (CAP) on admission to discriminate between PTB and CAP, and examined the value of prognostic factors in PTB.

102 PTB patients, 62 CAP patients, and 34 healthy volunteers were enrolled. Serum PCT in PTB patients was significantly lower than in CAP patients (mean±SD 0.21±0.49 *versus* 4.10±8.68 ng·mL^{-1}; p<0.0001). By receiver-operating characteristic curve analysis, serum PCT was an appropriate discrimination marker for PTB and CAP (area under the curve 0.866). PTB patients with ⩾0.5 ng·mL^{-1} (normal cut-off) had significantly shorter survival than those with <0.5 ng·mL^{-1} (p<0.0001).

Serum PCT is not habitually elevated in HIV-negative PTB patients and is a useful biomarker for discriminating between PTB and CAP; however, when serum PCT is outside the normal range, it is a poor prognostic marker.

KEYWORDS: Procalcitonin, prognosis, pulmonary tuberculosis

Procalcitonin (PCT), the precursor molecule of calcitonin, is known as a systemic inflammatory protein. Several studies have reported that serum PCT is a useful biomarker for diagnosis and for estimating the severity of community-acquired pneumonia (CAP) [1, 2]. In particular, high serum PCT with CAP is associated with a high mortality rate [3–7]. In contrast to CAP, there are very few data on PCT levels in pulmonary tuberculosis (PTB). According to the limited information available from small scale studies, which included 27 PTB patients [8], 30 PTB patients [9], and 34 HIV-positive PTB patients [10], serum PCT was not elevated; however, the clinical significance of serum PCT levels in PTB patients has not been well documented. In this study, we examined serum PCT levels in HIV-negative PTB patients to discriminate between PTB and CAP. Moreover, we investigated whether serum PCT levels in PTB patients are related to disease prognosis.

METHODS

Patients

From June 2008 to September 2009, consecutive patients admitted to our hospital (Tenryu Hospital, Hamamatsu, Japan) with PTB or CAP were included in this study. PTB was defined by sputum smear-positive and culture-positive *Mycobacterium tuberculosis* in the presence of new radiographic pulmonary infiltration. According to the European consensus on the surveillance of tuberculosis [11], PTB patients with tuberculous involvement of other organ systems were defined as having disseminated tuberculosis. Patients with other infections, such as urinary tract infection, meningitis and infectious endocarditis, were excluded. All PTB patients were initially treated with a standard four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin.

Pneumonia was diagnosed by the presence of new radiographic pulmonary infiltration and the following clinical findings: 1) axillary temperature >37.5°C; and 2) a cough, purulent sputum, pleuritic chest pain or shortness of breath. CAP was defined if pneumonia had occurred at home without antibiotic use in the previous 14 days.

As the severity index, the Pneumonia Patients Outcome Research Team score [12] was used in all PTB and CAP patients. Healthy volunteers free from respiratory disease were included as normal controls.

This study was prospective and was approved by the ethics committee of our hospital, and informed consent was obtained according to the hospital's guidelines.

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Methods

Venous blood samples were drawn from PTB and CAP patients on admission. Serum PCT and C-reactive protein (CRP) were measured within 24 h of admission. Serum PCT was determined by an immunoluminometric assay (Sphere Light B.R.A.H.M.S PCT; Wako Diagnostics, Tokyo, Japan). The normal range of PCT is <0.5 ng·mL^{-1} and the lower limit of detection is 0.1 ng·mL^{-1} [13, 14]. Serum CRP was determined by a turbidimetric assay (Nanopia CRP; Sekisui Medical, Tokyo, Japan). The lower limit of detection was 0.1 mg·dL^{-1}. White blood cell (WBC) and differential cell counts were determined by flow cytometry (XT-2000*i*; SYSMEX Corporation, Kobe, Japan). If serum PCT and CRP were lower than their detection limit, we defined them as 0.05 ng·mL^{-1} and 0.05 mg·dL^{-1}, respectively.

Statistical analysis

Data are expressed as mean±SD. Differences between groups were tested using the nonparametric Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables, respectively. PTB and CAP were discriminated using receiver-operating characteristic (ROC) analysis. Mortality within 60 days of admission was analysed by Kaplan–Meier survival curves and by the log-rank test, according to cut-off values of 10.00 mg·dL^{-1} serum CRP [15, 16] and 0.5 ng·mL^{-1} serum PCT [13, 14], respectively. A probability value of <0.05 was regarded as significant.

TABLE 1 Patient characteristics on admission

	PTB	CAP	Control	p-value
Demographics				
Patients n	102	62	34	
Age yrs	71.5±18.5	75.2±17.0	64.7±15.3	0.2194
Males/females n	63/39	38/24	11/23	>0.9999
Symptoms				
Fever	48 (47.1)	62 (100)		<0.0001
Cough or sputum	53 (52.0)	44 (71.0)		0.0216
Dyspnoea	22 (21.6)	38 (61.3)		<0.0001
Chest pain	4 (3.9)	5 (8.1)		0.3005
Weight loss	19 (18.6)	2 (3.2)		0.0035
Laboratory test				
PCT ng·mL^{-1}	0.21±0.49	4.10±8.68	0.05±0	<0.0001
CRP mg·dL^{-1}	6.18±5.75	15.67±9.59	0.14±0.27	<0.0001
WBC 10^9 cells·L^{-1}	7.87±3.12	13.01±8.23	5.95±1.33	<0.0001
Neutrophils 10^9 cells·L^{-1}	6.23±3.10	11.57±8.20	3.62±1.43	<0.0001
Lymphocytes 10^9 cells·L^{-1}	1.04±0.73	1.02±0.55	1.70±0.47	0.7207
Radiography findings				
Cavitary lesion	44 (43.1)	8 (13.0)		0.0001
Pleural effusion	21 (20.6)	10 (16.1)		0.5418
PORT score	89.8±35.3	106.4±41.6		0.0116

Data are presented as n (%) or mean±SD, unless otherwise stated; p-values are given for the comparison between pulmonary tuberculosis (PTB) and community-acquired pneumonia (CAP). PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell; PORT: Pneumonia Patients Outcome Research Team.

RESULTS

Patient characteristics and serum PCT levels

102 PTB patients, 62 CAP patients, and 34 healthy volunteers were enrolled. All were seronegative for HIV. The causative micro-organism was identified in 33 CAP patients (53.2%), with the most frequently isolated micro-organism being *Streptococcus pneumoniae* (n=13), followed by *Haemophilus influenzae* (n=7), *Pseudomonas aeruginosa* (n=5), *Klebsiella pneumoniae* (n=4), *Escherichia coli* (n=2), and *Moraxella catarrhalis* (n=2). The characteristics of the enrolled patients are

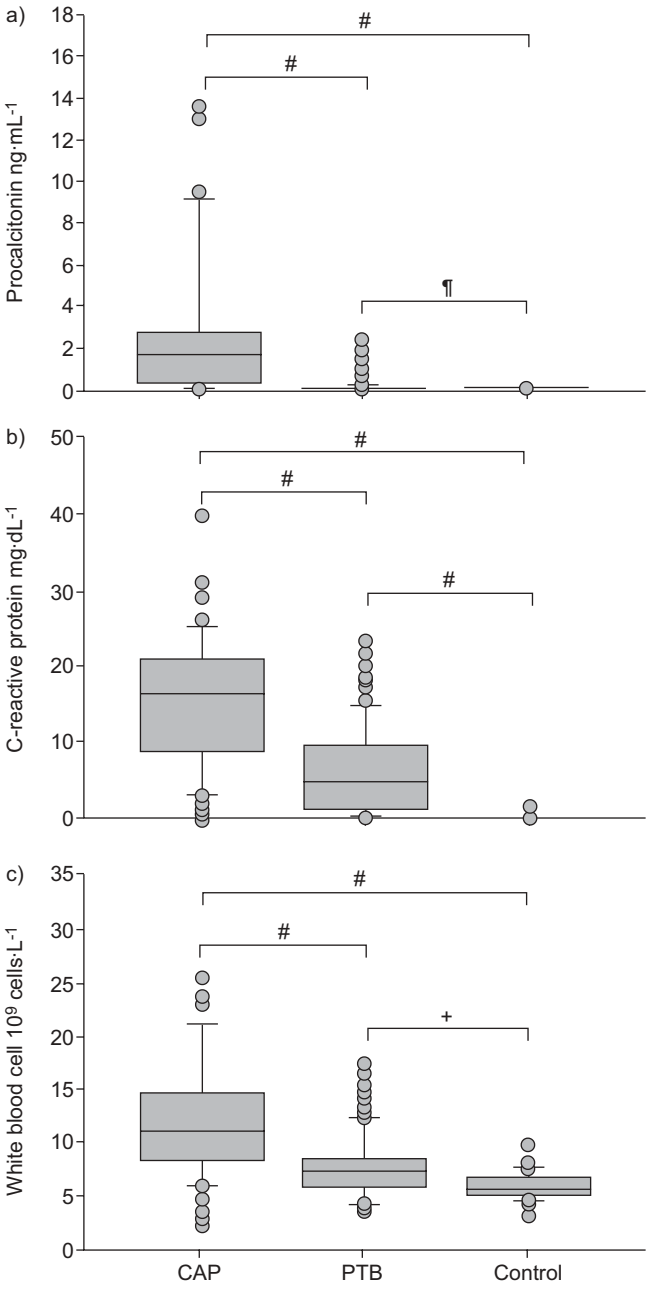

FIGURE 1. a) Serum procalcitonin, b) serum C-reactive protein and c) white blood cell count compared among pulmonary tuberculosis (PTB), community-acquired pneumonia (CAP) and healthy controls. #: p<0.0001; ¶: p=0.0034; +: p=0.0009.

TABLE 2 Characteristics of disseminated tuberculosis patients and non-disseminated tuberculosis patients

	Disseminated tuberculosis	Non-disseminated tuberculosis	p-value
Demographics			
Patients n	12	90	
Age yrs	76.9±9.9	70.8±19.4	0.5676
Males/females n	7/5	56/34	>0.9999
Laboratory test			
PCT ng·mL^{-1}	0.75±0.79	0.14±0.39	<0.0001
CRP mg·dL^{-1}	11.19±7.28	5.52±5.26	0.0059
WBC 10^9 cells·L^{-1}	8.41±5.31	7.80±3.01	0.8762
Neutrophils 10^9 cells·L^{-1}	7.27±3.29	6.07±3.05	0.1686
Lymphocytes 10^9 cells·L^{-1}	0.73±0.68	1.09±0.73	0.03
PORT score	131.1±31.6	84.5±32.2	0.0001
Death within 60 days	7 (58.3)	5 (5.6)	<0.0001

Data are presented as mean±SD or n (%), unless otherwise stated. PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell count; PORT: Pneumonia Patients Outcome Research Team.

shown in table 1. There were no significant differences in age (71.5±18.5 *versus* 75.2±17.0 yrs; p=0.2196) and sex (63/39 males/females *versus* 38/24; p>0.9999) between PTB and CAP patients. Serum PCT in PTB patients was significantly lower than in CAP patients (0.21±0.49 *versus* 4.10±8.68 ng·mL^{-1}; p<0.0001) (fig. 1a). PTB patients had significantly lower serum CRP and WBC count than CAP patients (6.18±5.75 *versus* 15.67±9.59 mg·dL^{-1}; p<0.0001 and 7.87±3.12 *versus* 13.01±8.23×10^9 cells·L^{-1}; p<0.0001) (fig. 1b and c). Healthy volunteers (11/23 males/females aged 64.7±15.3 yrs) had 0.05±0.0 ng·mL^{-1} serum PCT, 0.14±0.27 mg·dL^{-1} serum CRP, and 5.95±1.33×10^9 cells·L^{-1} WBC count.

12 of 102 PTB patients had disseminated tuberculosis (11.8%). As shown in table 2, disseminated tuberculosis patients had higher serum PCT (0.75±0.79 *versus* 0.14±0.39 ng·mL^{-1}; p<0.0001) and serum CRP (11.19±7.28 *versus* 5.52±5.26 mg·dL^{-1}; p=0.0059) than non-disseminated tuberculosis patients. The PORT score (131.1±31.6 *versus* 84.5±32.2; p=0.0001) and mortality within 60 days of admission (58.3% *versus* 5.6%; p<0.0001) were significantly higher in disseminated than non-disseminated tuberculosis patients.

Discrimination between PTB and CAP

On ROC curve analysis (fig. 2), the area under the ROC curve was 0.866 for serum PCT, 0.815 for serum CRP and 0.749 for the WBC count. Using different cut-off values, sensitivity, specificity and positive (PPV) and negative predictive values (NPV) are shown in table 3. With a cut-off value of 0.25 ng·mL^{-1}, serum PCT had a sensitivity of 86.3%, specificity 74.2%, PPV 84.6% and NPV 76.7%; with a cut-off value of 10.00 mg·dL^{-1}, serum CRP had a sensitivity of 76.5%, specificity 72.6%, PPV 82.1%, and NPV 65.2%. Serum PCT was a better discriminative marker for PTB and CAP than the WBC count or serum CRP, but there was no significant difference among them.

Prognosis

Mortality within 60 days of admission was 11.8% (12 out of 102) in PTB patients. Two died of severe tuberculous intestinal involvement and the others of respiratory failure. All 12 patients had drug-sensitive tuberculosis. With a cut-off value of 10.00 mg·dL^{-1} serum CRP, there was no significance between groups (p=0.1074) (fig. 3a). Using a cut-off value of 0.5 ng·mL^{-1} serum PCT, patients with ⩾0.5 ng·mL^{-1} had significantly shorter survival than those with <0.5 ng·mL^{-1} (p<0.0001) (fig. 3b). The characteristics of patients with PCT ⩾0.5 or <0.5 ng·mL^{-1} are shown in table 4. A significant proportion of patients with PCT ⩾0.5 ng·mL^{-1} had disseminated TB compared with PCT <0.5 ng·mL^{-1} (55.6% *versus* 7.5%).

DISCUSSION

The current study demonstrates that serum PCT in HIV-negative PTB patients is basically low and is a useful biomarker for discriminating PTB and CAP; however, when serum PCT is above the normal cut-off point (0.5 ng·mL^{-1}), it is a poor prognostic marker in PTB patients.

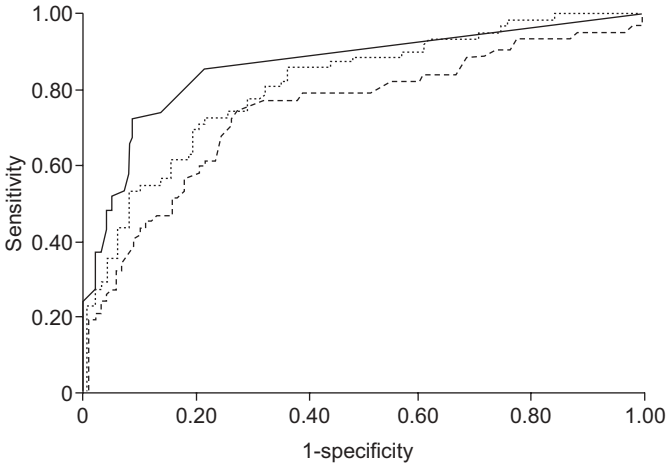

FIGURE 2. Receiver-operating characteristics curve for discrimination between pulmonary tuberculosis and community-acquired pneumonia using procalcitonin (——), C-reactive protein (· · · · ·) and white blood cell count (– – – –).

TABLE 3 Diagnostic validity of procalcitonin (PCT) and C-reactive protein (CRP) in differentiating pulmonary tuberculosis from community-acquired pneumonia according to different values

	Sensitivity %	Specificity %	PPV %	NPV %
PCT ng·mL^{-1}				
<0.1	78.4	85.4	89.9	70.7
<0.25	86.3	74.2	84.6	76.7
<0.5	91.2	67.7	82.3	79.2
<1.0	92.2	58.0	78.3	81.8
<2.0	96.1	43.5	73.7	87.1
CRP mg·dL^{-1}				
<5.0	52.0	88.7	88.3	52.9
<10.0	76.5	72.6	82.1	65.2
<12.5	85.3	56.5	76.3	70.0
<15.0	90.2	54.8	76.7	77.2
<20.0	97.1	29.0	69.2	85.7

PPV: positive predictive value. NPV: negative predictive value.

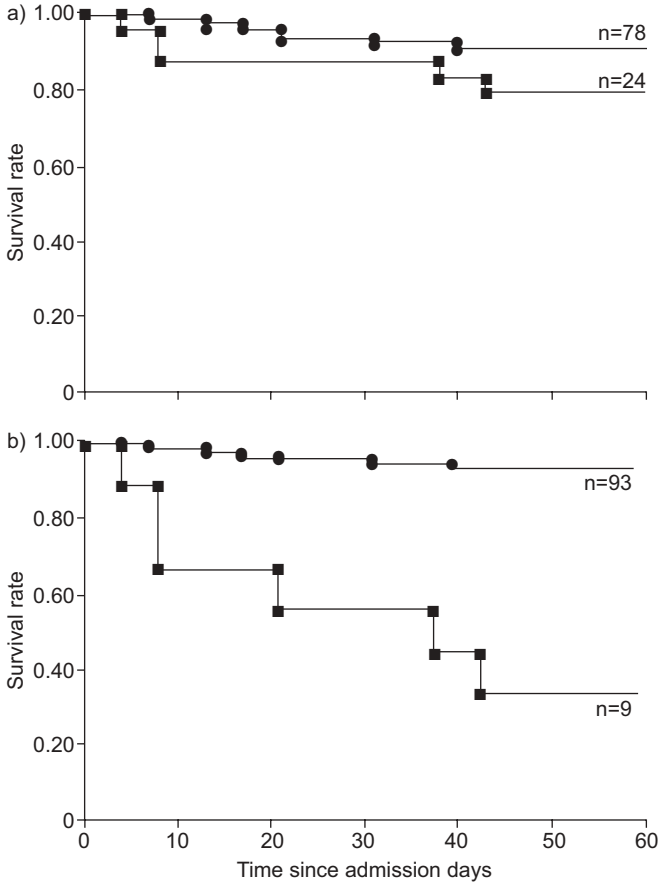

FIGURE 3. Kaplan–Meier curves for 60-day mortality with pulmonary tuberculosis patients grouped according to a) 10 mg·dL^{-1} C-reactive protein (●: <10 mg·dL^{-1}; ■: ⩾10 mg·dL^{-1}) and b) 0.5 ng·mL^{-1} procalcitonin (●: <0.5 ng·mL^{-1}; ■: ⩾0.5 ng·mL^{-1}).

TABLE 4 Characteristics of pulmonary tuberculosis patients with serum procalcitonin (PCT) levels ⩾0.5 or <0.5 ng·mL^{-1}

	PCT ⩾0.5 ng·mL^{-1}	PCT <0.5 ng·mL^{-1}	p-value
Demographics			
Patients n	9	93	
Age yrs	72.7±9.5	71.4±19.3	0.4973
Males/females n	4/5	59/34	0.2975
Laboratory test			
PCT ng·mL^{-1}	1.64±0.70	0.08±0.07	<0.0001
CRP mg·dL^{-1}	16.95±4.90	5.14±4.71	<0.0001
WBC 10^9 cells·L^{-1}	9.02±3.26	7.76±3.11	0.2451
Neutrophils 10^9 cells·L^{-1}	8.29±3.00	6.00±3.04	0.0181
Lymphocytes 10^9 cells·L^{-1}	0.38±0.20	1.11±0.73	0.0001
PORT score	121.6±25.8	86.5±34.6	0.0033
Disseminated tuberculosis	5 (55.6)	7 (7.5)	0.0009
Death within 60 days	6 (66.7)	6 (6.5)	<0.0001

Data are presented as mean±SD or n (%), unless otherwise stated. CRP: C-reactive protein; WBC: white blood cell count; PORT: Pneumonia Patients Outcome Research Team.

It has been reported that serum PCT is not elevated in PTB compared with in CAP [8–10, 17]. Although the reasons why the serum PCT response in PTB is poor remain to be clarified, there are several possible explanations. First, secreted cytokine patterns are different between tuberculous infection and common bacterial infection; for example, interferon (IFN)-γ is a more critical cytokine for growth inhibition of mycobacteria than common bacteria [18–20]. According to *in vitro* observation, IFN-γ attenuates the secretion of PCT from human adipose tissue [21]. Secondly, as previously reported, serum PCT concentration increases slightly in intracellular infection, including that caused by *Mycoplasma*, viruses and *Pneumocystis jiroveci* [22, 23]. Since 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 typical bacterial pneumonia.

Conversely, NADERI *et al.* [24] reported that serum PCT is not a reliable marker to discriminate between PTB and non-PTB disease due to its low sensitivity and specificity; however, since the study included mild cases, such as bronchitis, and used semi-quantitative serum PCT measurement, we consider that it differed from our study.

Several studies have shown a factor related to prognosis in tuberculous patients. Regarding nutritional status, it is reported that malnutrition is a risk factor for fatality in patients with miliary tuberculosis [25], and low serum albumin levels are strongly and independently associated with death in tuberculous patients [26]. In addition to these findings, our study demonstrated that serum PCT levels over the normal cut-off point (0.5 ng·mL^{-1}) predict a poor prognosis. To our knowledge, this is the first report on serum biomarkers determining prognosis in PTB patients.

Our study has several limitations. First, since outpatients were excluded, the enrolled patients might have had relatively severe conditions. As a result, serum PCT was elevated compared with previous studies including outpatients [1, 5]. Secondly, PTB patients could be associated with bacterial co-infection. In severe cases, we performed non-tuberculous culture of blood, urine or sputum, but pathogenic bacteria were not found. Additionally, PCT levels in PTB patients who died were significantly lower than in CAP (0.90 ± 0.92 *versus* 12.26 ± 18.54 ng·mL^{-1}; $p=0.0073$). Taken together, we do not consider that bacterial co-infection was a factor in severe PTB patients; however, we cannot completely reject the possibility of bacteria co-infection with PTB.

In conclusion, serum PCT is a better biomarker than CRP or WBC count for the differentiation between PTB and CAP in HIV-negative patients. However, it is important to realise that elevated PCT values were observed in a limited number of patients with disseminated tuberculosis, which was associated with higher mortality.

STATEMENT OF INTEREST

None declared.

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