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Original article

Serial quantification of procalcitonin (PCT) predicts clinical outcome and prognosis in patients with community-acquired pneumonia (CAP)☆

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ABSTRACT

Procalcitonin (PCT), a calcitonin precursor, is commonly measured in the setting of community-acquired pneumonia (CAP). However, the clinical significance of serial PCT changes has not been established. We conducted a prospective observational study of 122 patients with CAP. Thirty-day mortality was the primary endpoint. Secondary endpoints included: (1) initial treatment failure, (2) 30-day mortality and/or initial treatment failure, and (3) intensive care unit (ICU) admission. In subgroup analysis, we classified patients into pneumococcal pneumonia and non-pneumococcal pneumonia groups. The baseline frequency of 30-day mortality was 10.7%. Increases in serum PCT levels from admission to Day 3 were observed with statistically higher frequency in patients with 30-day mortality ($P = 0.002$). For secondary endpoints, only the 30-day mortality and/or initial treatment failure group was statistically significant ($P = 0.007$). Subgroup analysis revealed statistically significant changes in the non-pneumococcal pneumonia group ($N = 85$) across several endpoints, including 30-day mortality ($P = 0.001$), initial treatment failure ($P = 0.013$), and 30-day mortality and/or initial treatment failure ($P < 0.001$). No significant changes in endpoint measurements were found in the pneumococcal pneumonia group ($N = 28$). Interestingly, serum PCT levels at the time of diagnosis were higher in patients with pneumococcal pneumonia than those with non-pneumococcal pneumonia ($P = 0.006$), and this positively correlated with disease severity scores for all patients (PCT vs. PSI: $R = 0.380$, $P < 0.001$; PCT vs. A-DROP: $R = 0.422$, $P < 0.001$) and for non-pneumococcal pneumonia (PCT vs. PSI: $R = 0.468$, $P < 0.001$; PCT vs. A-DROP: $R = 0.448$, $P < 0.001$), but not for pneumococcal pneumonia. In conclusion, serial quantification of PCT can predict clinical outcomes for patients with CAP.

1. Introduction

Procalcitonin (PCT), the precursor of calcitonin (CT), was originally found as a serum marker of bacteremia [1]. It consists of 116 amino acids and is encoded by the *CACL-1* gene located on chromosome 11 [2,3]. PCT has demonstrated consistent expression in the thyroid gland (C cells) and lung (neuroendocrine cells), but temporal expression has also been observed in other organs during bacteremia [4]. Thyroid C cells and lung neuroendocrine cells have secretory granules in which PCT is processed into mature CT, while other organs lack these secretory organs and directly release PCT without any processing [2]. Thus, the main PCT production sites during bacterial infection may involve multiple organs other than the thyroid gland and lung. Studies have also shown that the production and secretion of PCT is up-regulated by lipopolysaccharides (LPS), interleukins (IL)-1β and -6, and tumor necrosis factor (TNF)-α, whereas it is down-regulated by interferon (IFN)-γ [2,5–7]. Thus, elevated levels of serum PCT would be highly suggestive of a bacterial infection, rather than a viral infection.

In community-acquired pneumonia (CAP), the significance of serum PCT levels at the time of diagnosis has been well established. PCT levels tend to be high and are associated with increased clinical disease severity scores [8,9], while lower levels of PCT indicate a favorable prognosis, even if clinical severity scores indicate severe CAP [8,9]. However, these reports only examined serum PCT levels

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at the time of diagnosis, and did not screen for causative pathogens or serial changes in PCT levels.

We conducted a prospective observational study to clarify whether serial PCT quantification predicts the clinical outcome of CAP. We assessed the predictive values of serial PCT quantification for 30-day mortality risk, treatment efficacy, and intensive care unit (ICU) admission risk. In an additional subgroup analysis, we classified patients by the presence of pneumococcal and non-pneumococcal pneumonia (that is, whether the pneumonia was caused by *Streptococcus pneumoniae* or by other pathogens, respectively). The relationship between PCT and disease severity was also evaluated. The purpose of the subgroup analysis was to maximize the predictive value of serial PCT change for pneumonia outcomes by taking into consideration the differences in the causative pathogens of CAP.

2. Patients and methods

2.1. Participants

This was a prospective observational study of patients with CAP who were hospitalized and treated with antimicrobial agents at the Department of Respiratory Medicine, Kyorin University Hospital (Tokyo, Japan). CAP diagnosis and antimicrobial agent selection were performed according to the Guidelines for the Management of Community-Acquired Pneumonia in Adults (i.e., CAP guidelines) [10] and/or Nursing and Healthcare-Associated Pneumonia (i.e., NHCAP guidelines) [11] formulated by the Japanese Respiratory Society (JRS). All patients who were diagnosed with CAP and treated in our department from 2009 to 2011 were included in the study and assessed with regard to our eligibility criteria. Exclusion criteria were as follows: (1) minors (<20 years old); (2) patients with malignant neoplasms, but whose family wished them to remain uninformed; (3) patients with severe immunosuppression (e.g., HIV/AIDS, chemotherapy, or treatment with high-dose corticosteroids and/or immunosuppressive agents); (4) hospital-acquired pneumonia (HAP); (5) a confirmed alternative diagnosis; and (6) coexistent illness interfering with radiological evaluation of CAP (e.g., advanced lung fibrosis, advanced lung cancer, severe heart failure, active tuberculosis, or active fungal infection). This study was approved by the institutional review board of Kyorin University School of Medicine. All participants provided written, informed consent.

2.2. Study settings

Patients were diagnosed with CAP based on the following criteria: when a new infiltration shadow was detected in a chest X-ray or CT scan, if symptoms were suggestive of lower respiratory tract infection, and when blood tests were positive for acute inflammatory reaction [10]. All patients were assessed for disease severity using the Pneumonia Severity Index (PSI) [12,13] and A-DROP score [age >70 years old for men and >75 years old for women, dehydration, respiration (SpO_2 <95% or PaO_2 <60 mmHg), orientation disturbance (confusion), and blood pressure (systolic value <90 mmHg or diastolic value <60 mmHg)] [10]. Serum levels of PCT, C-reactive protein (CRP), serum amyloid A (SAA), and white blood cells (WBC) were serially quantified at diagnosis (Day 0) and after administration of an antimicrobial agent (Days 3, 7, and 14). Two sets of blood cultures and urinary antigen tests for *S. pneumoniae* and *Legionella pneumophila* were obtained from all patients (122/122) at hospitalization. A sputum culture (111/122) and IgM blood antibody testing against *Mycoplasma pneumoniae* (120/122) were obtained from most patients. Specific antibodies against *M. pneumoniae* were measured with both particle agglutination (PA) and complement fixation (CF) tests at Days 0 and 14. Specific antibodies against *Chlamydophila pneumoniae* (IgG, IgA, and IgM) were measured at Days 0 and 14. The etiologic pathogen was determined as described below and pathogen-specific PCT ranges at the time of diagnosis were calculated. Within patients with CAP caused by *S. pneumoniae*, serum PCT levels were compared among those who were diagnosed by (1) a positive urinary antigen test, (2) a positive sputum culture, and (3) a positive blood culture (indicating bacteremia).

The primary endpoint was 30-day mortality and the secondary endpoints were (1) initial treatment failure, (2) 30-day mortality and/or initial treatment failure, and (3) ICU admission. Serial changes in PCT, WBC, CRP, and SAA were analyzed for their potential to estimate the clinical prognosis/outcome. In an additional subgroup analysis, we classified the patients into pneumococcal and non-pneumococcal pneumonia groups, and compared the predictive values of serial changes in PCT and the other markers between them. In all patients, attending physicians selected, started, and terminated antimicrobial agents according to the CAP and NHCAP guidelines of JRS [10,11]. The physicians comprehensively evaluated the efficacy of the antimicrobial agents using the patient's vital signs, chest X-rays, and laboratory data (e.g., WBC, neutrophil count, and CRP) according to CAP and NHCAP guidelines [10,11]. If the initial antimicrobial agent administered was not effective, the physicians switched or added alternative antimicrobial agents in accordance with the recommendations of the CAP and NHCAP guidelines [10,11]. In this case, the outcome of the initial antibiotics treatment was classified as "treatment failure". All clinical decisions were made independent of serum PCT levels as PCT levels were measured at a laboratory external to the hospital. Thus, the physicians were blind to all patient serum PCT levels for several days after sampling.

2.3. Microbiology

The etiologic pathogens of CAP were determined when a candidate pathogen was detected and at least one of the following criteria was met: (1) a positive blood culture (in the absence of an apparent extra-pulmonary focus), (2) a positive sputum culture (with Geckler classification 4 or 5), (3) a positive pleural fluid culture, (4) a positive urinary antigen test for *L. pneumophila* or *S. pneumoniae* or (5) seroconversion for *M. pneumoniae* or *C. pneumoniae* (i.e., more than a four-fold increase in the antibody levels). Test results positive for IgM antibodies against *M. pneumoniae* alone were not considered as diagnostic and PA and CF levels of *M. pneumoniae* were further confirmed at Days 0 and 14.

PCT was measured using Elecsys BRAHMS PCT automated immunoassays (Roche Diagnostics GmbH, Mannheim, Germany). Urinary antigen tests for *S. pneumoniae* and *L. pneumophila* were performed using Binax Now® *S. pneumoniae* and Binax Now® *L. pneumophila* urinary antigen tests (Alere Scarborough, Maine, USA), respectively. Antibodies against *M. pneumoniae* were measured by ImmunoCard® (IgM; Meridian Bioscience, Ohio, USA), Serodia®-Myco II (PA; FUJIREBIO, Tokyo, Japan), and *M. pneumoniae* CF test reagent (CF; Denka Seiken, Tokyo, Japan). Antibodies against *C. pneumoniae* were measured using the Hitazyme® assay (IgM; Hitachi Chemical, Tokyo, Japan) and SeroCP Quant ELISAs (IgG, A; Savyon Diagnostics, Ashdod, Israel).

2.4. Statistical analysis

Parametric data are presented as mean ± SD and nonparametric data are presented as median (interquartile range; IQR). Pairings of groups of nonparametric data were compared using the Mann–Whitney *U* test; multiple groups of nonparametric data