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Presepsin as a novel diagnostic biomarker for differentiating active pulmonary tuberculosis from bacterial community acquired pneumonia

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ABSTRACT

Background: The expression of presepsin in active pulmonary tuberculosis (APTB) is unknown. We observed the expression of presepsin in APTB, and to evaluate the value for discriminating between APTB and bacterial community acquired pneumonia (BCAP).

Methods: Consecutive APTB patients who were accurately diagnosed by sputum culture and BCAP patients were enrolled from August 2013 to July 2015. Clinical data were collected, and plasma presepsin concentrations were tested. Receiver operating characteristic (ROC) curves were performed for diagnostic analysis.

Results: In all, 133 healthy individuals, 103 APTB and 202 BCAP patients were enrolled. Presepsin concentrations in APTB group (218.0 [146.0, 368.0] pg/ml) were higher than those in the healthy control group (128.0 [101.5, 176.5] pg/ml, $P < 0.001$), and lower than the concentrations measured in the BCAP group (532.0 [364.0, 852.3] pg/ml, $P < 0.001$). Simple APTB and miliary tuberculosis patients showed no significant differences in presepsin concentrations. Compared with both Gram-positive and negative bacteria, *Mycobacterium tuberculosis* caused a limited increase of presepsin. With the cut-off value set at 401 pg/ml, presepsin demonstrated high positive predictive value, allowing initial discriminating between APTB and BCAP. Presepsin combined with CURB-65 score could significantly improve the discrimination ability.

Conclusions: Presepsin concentrations in APTB patients were slightly increased, and may be helpful for initial discrimination between APTB and BCAP.

1. Introduction

Fever, cough, acute dyspnea, and changes in white blood cell count are common nonspecific clinical manifestations of respiratory system infection in emergency departments. Bacteria are common pathogens of community acquired pneumonia (CAP); therefore, early identification of pathogens is essential for targeted therapy. Bacterial culture detection from blood and sputum usually takes at least several days, while positive detection rate is low, especially for blood samples [1,2]. *Mycobacterium tuberculosis* is a special kind of bacteria which causes tuberculosis, the second leading cause of death from infectious disease worldwide. For the detection of *M. tuberculosis*, routine direct microscopic examination and molecular detection are associated with high false positive rates [3]. Culture-based diagnosis of active pulmonary tuberculosis (APTB) is not widely available, because *M. tuberculosis* culturing requires specific conditions, and nearly 2 weeks are needed to obtain results [3,4]. Therefore, the identification of a biomarker that is an early indicator, and allows for the discrimination between *M. tuberculosis* and other common bacteria, is necessary for early diagnosis and the determination of the initial therapy.

Currently, the new biomarker presepsin is well known for general bacterial infections, and demonstrates good diagnostic and prognostic value for bacterial CAP (BCAP) [5–10]. Immunity against microorganisms relies primarily on the activity of monocytes and macrophages, which recognize pathogen-associated molecular patterns, partly via cluster-of-differentiation marker protein 14 (CD14), which mediates an immediate response against lipopolysaccharides (LPS) [11]. Following the binding of LPS to CD14 through LPS-binding protein, a subtype of soluble CD14 (sCD14) is released into the blood [5]. The proteolysis of sCD14 by circulating cathepsin D leads to the generation of a small soluble peptide (64 amino acids, 13 kDa), designated as presepsin. Presepsin concentrations have been shown to be significantly higher in CAP patients [6–8]. To date, no previous studies have investigated presepsin expression in APTB.

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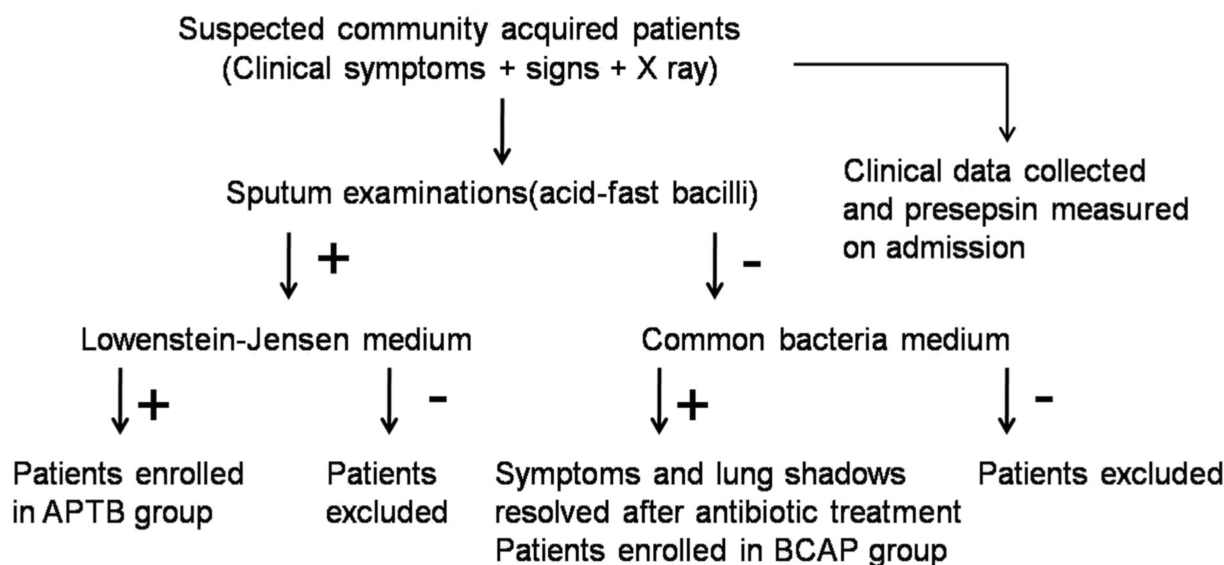

Fig. 1. Flow chart of patient inclusion.

2. Materials and methods

2.1. Patient inclusion and exclusion criteria

This study was conducted in the Emergency Departments of Beijing Chao-Yang Hospital and Beijing Tuberculosis Research Institute. China. From August 2013 to July 2015, patients who fulfilled the APTB criteria as defined by the World Health Organization (2013) and whose sputum cultures yielded positive results were enrolled [14], together with BCAP patients whose sputum examination yielded positive results for bacteria. Exclusion criteria were as follows: patients < 18 y; terminal stage of disease (malignant cancer of any type, acquired immunodeficiency syndrome, or end-stage liver or renal disease); or patients (or their relatives) who did not provide consent for participation in the study. Additionally, 133 healthy individuals with normal chest X-ray findings, were enrolled in the healthy control group, and their serum or plasma samples, remaining after routine tests, were collected. Fig. 1 shows the flow chart of patient inclusion in the study. This study was approved by the Beijing Chao-Yang Hospital Ethics Committee and Beijing Tuberculosis Research Institute Ethics Committee, and was performed in accordance with the ethical standards outlined in the Declaration of Helsinki and its later amendments. Written informed consents were obtained from all enrolled patients.

2.2. Diagnostic criteria

APTB diagnostic criteria were defined as follows [12]: one or more initial sputum smear examinations (Ziehl-Neelsen staining and direct smear microscopy) positive for acid-fast bacilli, plus chest X-ray abnormalities consistent with APTB. Meanwhile, the culture of *M. tuberculosis* in Lowenstein-Jensen medium yielded positive results in the following days.

BCAP was diagnosed when patients had clinical symptoms of pneumonia and new focal chest signs [1]. Meanwhile, chest X-ray demonstrated new lung shadows, and these resolved with antibiotic treatment. For the microbiological evaluation of patients with BCAP, we performed sputum or protective specimen brush Gram staining and culturing. Sputum smear examinations yielded negative results after Ziehl-Neelsen staining.

The criteria for sputum smear examination and sputum culture [13] were: Sputum samples were considered of good quality if they had < 10 squamous epithelial cells and > 25 leukocytes per low power field, or the ratio between the 2 is < 1:2.5. Other samples were that did not meet this criteria were excluded from the evaluation. The following test results were considered important references for etiological diagnosis: (1) Significant growth of dominant bacteria in qualified lower respiratory tract samples (except for normal flora); (2) Small amount of bacterial growth in qualified lower respiratory tract samples, but results were consistent with smear microscopy results; (3) Apparent bacterial phagocytosis by neutrophils was seen in smear microscopy of qualified lower respiratory tract samples. The presence of many morphologic microorganisms without an identifiable predominant morphotype was considered as polymicrobial flora.

2.3. Data collection

Patients' data including age, gender, and vital signs were recorded on admission. Laboratory examinations, including white blood cell counts, microbiological detection, and X-ray scans, were carried out within 24 h after admission. CURB-65 score (confusion, serum urea > 7 mmol/l, respiratory rate ≥ 30/min, systolic blood pressure < 90 mm Hg and/or diastolic blood pressure ≤ 60 mm Hg, and age ≥ 65 y) was calculated to evaluate severity of pneumonia [1,14]. Venous blood samples were obtained, collected in tubes containing EDTA and centrifuged, and the supernatant plasma samples were collected for rapid analysis. Plasma presepsin concentrations were determined using a compact automated immunoanalyzer (PATHFAST; Mitsubishi Chemical Medience Corp.) based on a chemiluminescent enzyme immunoassay [7] with lower and upper detection limits of 20 pg/ml and 200,000 pg/ml, respectively with a reference range of 60–365 pg/ml.

2.4. Statistical analysis

All data were analysed using SPSS ver 22.0. For normally distributed data, continuous variables were presented as mean ± SD. One-way analysis of variance and least significant difference test were applied for multi-group comparisons. For skewed-distribution data, variables were expressed as the median (25th to 75th percentiles). Kruskal-Wallis test was applied for multi-group comparisons, and independent sample test was performed for 2-group comparisons. Qualitative parameters were analysed using a 2 × 2 contingency table

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