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The risk stratification and prognostic evaluation of soluble programmed death-1 on patients with sepsis in emergency department

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ABSTRACT

Objective: To evaluate the efficacy of soluble programmed death-1 (sPD-1) for risk stratification and prediction of 28-day mortality in patients with sepsis, we compared serum sPD-1 with procalcitonin (PCT), C-reactive protein (CRP), and the Mortality in Emergency Department Sepsis (MEDS) score.
Methods: A total of 60 healthy volunteers and 595 emergency department (ED) patients were recruited for this prospective cohort study. According to the severity of their condition on ED arrival, the patients were allocated to the systemic inflammatory response syndrome group (130 cases), sepsis group (276 cases), severe sepsis group (121 cases), and septic shock group (68 cases). In addition, all patients with sepsis were also divided into the survivor group (349 cases) and nonsurvivor group (116 cases) according to the 28-day outcomes.
Results: When the severity of sepsis increased, the levels of sPD-1 gradually increased. The levels of sPD-1, PCT, CRP and the MEDS score were also higher in the nonsurvivor group compared to the survivor group. Logistic regression suggested that sPD-1, PCT, and the MEDS score were independent risk factors for 28-day mortality of patients with sepsis. Area under the curve (AUC) of sPD-1, PCT and the MEDS score for 28-day mortality was 0.725, 0.693, and 0.767, respectively, and the AUC was improved when all 3 factors were combined (0.843).
Conclusion: Serum sPD-1 is positively correlated with the severity of sepsis, and it is valuable for risk stratification of patients and prediction of 28-day mortality. Combining sPD-1 with PCT and the MEDS score improves the prognostic evaluation.

1. Introduction

Sepsis is a common life-threatening disease, and severe immunosuppression plays an important role in the deterioration of patients with sepsis [1]. Negative co-stimulatory molecules can negatively regulate cell proliferation, differentiation, and apoptosis, and play an important role in the immune function of patients with sepsis. As a member of the CD28 superfamily, programmed death-1 (PD-1) mediates a negative co-stimulatory signal [2]. In addition, PD-1 and programmed death ligand-1 (PD-L1) can effectively inhibit the function of T and B cells and suppress proliferation of T cells, thus playing an important part in immune regulation [3-5]. It has been reported that membrane-bound PD-1/PD-L1 plays an important part in immune suppression during sepsis [6]. Many co-stimulatory factors such as B7-H3 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) exist in both membrane-bound and soluble forms [7,8]. Similar to the membrane-bound molecules, the soluble molecules also have their corresponding biological function–they circulate in the blood stream like cytokines and play their part in the immune response. Two forms of PD-1 have been found: membrane-bound and soluble forms. Compared to membrane-bound PD-1, soluble PD-1 (sPD-1) lacks the third exon of PD-1 that encodes the transmembrane region and has its own biological function [9]. In recent years, sPD-1 has become the focus of increasing attention.

It is currently believed that sPD-1 can promote T-cell responses through blocking PD-1/PD-L1 pathway. Excessive sPD-1 can specifically block the PD-1/PD-L1 signaling pathway, leading to immune imbalance, so that auto-reactive T cells cannot be effectively inhibited or cleared, which results in pathological immune damage [9]. The level of sPD-1 is low in healthy individuals but is highly expressed in the serum of patients with rheumatoid arthritis (RA) [10], chronic hepatitis [11], and aplastic anemia [12]. Studies have shown that sPD-1 is also involved in anti-tumor [13] and anti-virus immunity [14]; however, the correlation between sPD-1 and sepsis has rarely been reported. Our research group has previously demonstrated the correlation between the expression of membrane-bound PD-1/PD-L1 and the prognosis of sepsis [15]. Thus, we speculate that sPD-1 in serum may also be associated with risk stratification and prognosis of patients with sepsis. In this study, we measured sPD-1 levels in the peripheral blood of patients in the

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emergency department (ED) with different degrees of sepsis severity, and we evaluated the usefulness of sPD-1 for risk stratification and prediction of 28-day mortality in patients with sepsis. We hoped that PD-1 could be used as an immunological marker for early assessment of the severity of sepsis and for monitoring disease progression.

2. Materials and methods

2.1. Study subjects

This prospective cohort study was conducted in the ED of an urban, tertiary care, teaching hospital with an average number of 260,000 ED visits per year. Consecutive patients who visited the ED with suspected infection and had 2 or more criteria of systemic inflammatory response syndrome (SIRS) were enrolled from January 2015 to December 2015. Exclusion criteria were as follows: being <18 years of age; presenting with surgical trauma, blood diseases, autoimmune diseases, HIV infection, liver disease (for example, hepatitis, cirrhosis), end-stage renal disease (requiring dialysis), tumors, and pregnancy; and receiving hormone therapy. The definitions of SIRS, sepsis, severe sepsis, and septic shock were consistent with the diagnostic criteria established by the 2001 International Sepsis Definitions Conference [16]. For patients who had been admitted to the ED twice or more during this study, only data obtained from the first admission were used. Patients included may have one or more previous comorbidities, including chronic obstructive pulmonary disease (COPD), cardiovascular disease (coronary heart disease and/or heart failure), chronic kidney disease (excluding those requiring dialysis), diabetes mellitus, and cerebrovascular disease. First, according to the patients' condition on ED arrival, all patients were allocated to a SIRS group (suspected infection on ED arrival, but eventually confirmed no infection), a sepsis group, a severe sepsis group, or a septic shock group. Second, all patients with sepsis (including sepsis, severe sepsis, and septic shock) were followed up for 28 days, and the survivor group and nonsurvivor group were identified according to the 28-day outcomes. Those discharged earlier than 28 days were followed up by telephone to define outcomes. This study was in line with medical ethics standards approved by the Ethics Committee of Beijing Chaoyang Hospital, and it was carried out with informed consent from the patients or their families.

2.2. Data collection

On arrival at the ED, the following patient information was recorded: age; gender; address; telephone number; vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature); altered conscious state; nursing-home resident status; comorbidities; medical history; routine blood data; white blood cell differential count; blood gas analysis; liver and kidney function test; coagulation function test; procalcitonin (PCT) levels; C-reactive protein (CRP) levels; chest X-ray; and bacteriological tests of sputum, blood, or urine. In addition, the Mortality in Emergency Department Sepsis (MEDS) score was calculated by summing the points of 9 variables: terminal illness, age >65 years, bands >5%, tachypnea or hypoxia, septic shock, platelet count, nursing-home resident, lower respiratory tract infection, and altered mental state [17]. Peripheral blood serum was collected immediately after the patient's arrival in the ED, and stored at −80 °C for the determination of sPD-1 level.

2.3. Measurements of sPD-1, PCT, and CRP levels

The level of sPD-1 was measured using an enzyme-linked immunosorbent assay kit (DuoSet Human PD-1, R&D systems, Minneapolis, MN, USA) on an automatic microplate reader (Multiskan MK3; Thermo, West Palm Beach, FL). The PCT level was measured using an enzyme-linked fluorescence immunoassay with a miniVIDAS immunoassay analyzer (BioMerieux, Durham, NC, USA). The CRP level was measured using the QuickRead CRP kit (Orion Diagnostica Oy, Espoo, Finland) by following the rapid immune turbidity method.

2.4. Statistical analysis

Data were analyzed by SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Age, score, and test results were all non-normally distributed. They were presented as medians with interquartile ranges [M (Q_L,Q_U)]. The Kruskal-Wallis test was applied for multigroup comparisons, and the Mann-Whitney *U* test was applied for comparison between 2 groups. Categorical clinical variables were tested using the chi-square test. Logistic regression was used to determine independent risk factors of 28-day mortality in patients with sepsis. New combinations of the MEDS score and relevant biomarker(s) were constructed by logistic regression model for conversion with the prediction probability (*P*) as the analysis indicator; the degree of fitness of the model was tested by the Hosmer-Lemeshow goodness-of-fit test. Receiver operating characteristic (ROC) curves were used to compare the predictive capacity of relevant variables, and the cutoff value of each variable was determined by the Youden index. The sensitivity, specificity, positive predictive values, and the negative predictive value were then calculated. The area under the ROC curve (AUC) was compared using MedCalc 11.6 statistical software (MedCalc Software, Ostend, Belgium). $P < 0.05$ indicates a statistically significant difference.

3. Results

3.1. Characteristics of the patients

A total of 595 patients and 60 healthy volunteers were enrolled in this study. There were 5 groups, 60 cases in the healthy control group, 130 cases in the SIRS group, 276 cases in the sepsis group, 121 cases in the severe sepsis group, and 68 cases in the septic shock group. White blood cell (WBC) count and platelet count were significantly different in the multigroup comparison among the 5 groups ($P < 0.001$), but WBC count showed no difference between the severe sepsis group and the septic shock group ($P = 0.848$), and platelet count showed no significant difference between the SIRS group and the healthy control group ($P = 0.051$). There were no significant differences in age, gender, and comorbidities among the 5 groups ($P > 0.05$). Among the 4 groups of SIRS, sepsis, severe sepsis, and septic shock, the CRP and PCT levels, MEDS score, and 28-day mortality were significantly different and the increase was higher according to the severity of sepsis ($P < 0.05$) (Table 1).

3.2. Levels of sPD-1 among the 5 groups

Levels of sPD-1 showed a significant difference among the 5 groups ($P < 0.001$). However, there was no significant difference in levels of sPD-1 between the SIRS group and the healthy control group ($P = 0.462$). The level of sPD-1 was higher in the sepsis group than in the SIRS and healthy control groups ($P < 0.05$), and sPD-1 levels of the sepsis, severe sepsis, and septic shock groups showed a significant difference in pairwise comparison ($P < 0.001$). As the severity of sepsis increased, the levels of sPD-1 gradually increased (Fig. 1).

3.3. Comparison between the survivor group and the nonsurvivor group

According to the 28-day outcomes, all the patients with sepsis (including sepsis, severe sepsis, and septic shock) were separated into the survivor group (349 cases) and nonsurvivor group (116 cases). Age, CRP, PCT, MEDS score, and sPD-1 level were higher in the nonsurvivor group than in the survivor group ($P < 0.001$), while gender, WBC count, platelet count, and site of infection showed no significant difference between the 2 groups ($P < 0.05$) (Table 2). Logistic regression analysis demonstrated that sPD-1, PCT, and the MEDS score were

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