European Review for Medical and Pharmacological Sciences 2020; 24: 8477-8482

Investigation of the clinical significance of detecting PTX3 for community-acquired pneumonia

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Abstract. – OBJECTIVE: To evaluate the value of PTX3 in the diagnosis of community-acquired pneumonia (CAP).

PATIENTS AND METHODS: We included 170 inpatients diagnosed with CAP from January 2016 to December 2018. The patients were divided into the severe pneumonia group and the mild pneumonia group according to their condition. According to the results of pathogen detection, they were divided into the bacterial infection group, the virus infection group, the mixed infection group, and the other pathogen infection group. Clinical data including C-reactive protein (CRP), procalcitonin (PCT), white blood cell count (WBC), and neutrophil-lymphocyte ratio (NLR) were collected. Blood was collected within 24 hours, 3 days, and 7 days after admission, and the serum PTX3 level was dynamically monitored. The correlation between different groups was compared, and expression differences and dynamic changes of PTX3 were analyzed.

RESULTS: PTX3, PCT, and CRP in the CAP group were higher than those in the healthy control group, and the difference was statistically significant ($p<0.05$). Compared with the mild group, the increase of PTX3, PCT, and CRP was also different in the severe group ($p<0.05$). The area under the ROC curve of PTX3 was 0.726 (sensitivity 76.08%, specificity 76.92%) when the threshold value was 32.26 ng/ml. Dynamic monitoring of PTX3 showed that the PTX3 level in severe CAP patients was significantly higher than that in mild patients ($p<0.05$), and the PTX3 level in both groups gradually decreased with treatment time, but the level in severe CAP patients remained at a high level on the 7th day. The main pathogens in CAP were bacteria (77 cases, 45.7%), and there was no significant difference in the PTX3 level among the patients infected with different pathogenic bacteria ($p=0.311$).

CONCLUSIONS: The serum PTX3 level, especially the dynamic monitoring results, can be used as a biomarker to reflect community acquired pneumonia, which can provide effective auxiliary diagnosis and efficacy in monitoring for clinical practice.

Key Words:
Pentraxin-3, Community-acquired pneumonia, Dynamically monitored.

Introduction

Community-acquired pneumonia (CAP) refers to infectious inflammation of the pulmonary parenchyma (including the alveolar wall, or in broad term the interstitial lung) that develops outside the hospital, including pneumonia with a defined incubation period of pathogen infection that develops in the incubation period after admission[1]. Despite many advances in antibiotic therapy, mortality in CAP remains high, with approximately 4% to 18% of inpatients and up to 50% of patients with severe CAP (SCAP)[2,3]. However, as many as 45% of pneumonia patients have no apparent severe symptoms when admitted, even those who eventually develop SCAP and are transferred to intensive care units[4]. Delays in assessing the severity of the disease can lead to the death of patients whose condition deteriorates without timely and effective treatment. Therefore, timely and accurate classification of patients according to the

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severity of CAP is the primary task of clinicians. Because serological markers are easy to measure, the objective results become an important reference to assist clinical diagnosis. Pentraxin-3 (PTX3) is an acute inflammatory protein that was discovered in recent years. It belongs to the long pentraxins family, which is a superfamily of the C-reactive protein (CRP)[5]. PTX3 can be detected at the infected site within a few hours after infection, and the plasma PTX3 level is correlated with the severity of various infectious diseases[6,7]. Thus, the objective of this study was to explore community acquired pneumonia in the course of the dynamic change of serum PTX3, peripheral blood PTX3 level changes in the condition of patients with community-acquired pneumonia, the severity, and significance in terms of pneumonia in patients with respiratory tract etiology identification.

Patients and Methods

Study Population and Design

The study was performed in Rizhao Hospital of TCM between January 1, 2016, and December 31, 2018. A total of 170 patients with CAP that met the inclusion criteria were selected. All patients met the diagnostic requirements of the guidelines for diagnosis and treatment of community-acquired pneumonia in China (2016 Edition)[8]. Based on the diagnostic criteria of severe CAP[9], patients were divided into the severe CAP group (SCAP) and the mild CAP group (MCAP). At the same time, 70 healthy people of the same age and gender who came to the preventive physical examination center of our hospital for a physical examination and had no respiratory diseases or related diseases that might affect the test results were selected as the control group. Inclusion criteria: patients diagnosed with CAP and not treated, who agreed to participate in this study, and had collected blood samples collected for testing related indicators. Exclusion criteria: patients with bronchial asthma, chronic obstructive pulmonary disease or other respiratory diseases, patients with tumors, hematological diseases, or immunosuppression, patients with acute immunological responses or severe infections such as bacterial meningoencephalitis, and patients with hospital-acquired pneumonia.

This investigation was approved by the Ethics Committee of Rizhao Hospital of TCM.

Data Collection

At the time of admission, clinical characteristics of the patients, including age, sex, admission time, and other general information were collected. Laboratory indicators such as PTX3, CRP, procalcitonin (PCT), white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), and pathogenic test results were recorded. Also, peripheral venous blood was collected for detection within 24 hours after admission, and on the 3th day and the 7th day. Venous blood was collected from healthy controls on the day of the physical examination.

Measurement of PTX3 Levels

Serum PTX3 was quantitatively determined by enzyme-linked immunosorbent assay (ELISA) (Human Pentraxin 3, R&D Systems, Minneapolis, MN, USA), the absorbance (OD value) was determined by microplate at 450 nm wavelength, and the correction wavelength was 570 nm. A standard curve was drawn to calculate the content of PTX3 in the sample using the standard materials provided in the kit. A positive, a negative, and a blank control were set for each test.

Statistical Analysis

All data were analyzed using SPSS 20.0 software (IBM, Armonk, NY, USA). Continuous values are presented as means when the data were normally distributed or as medians with 25th percentile-75th percentile interquartile range (IQR) with skewed data. The measurement data were expressed by mean ± standard error or median according to data distribution. Continuous variables were compared by the Mann-Whitney U test or the Student's *t*-test, and the Kruskal-Wallis test was used to compare PTX3 values between the different groups as appropriate. Categorical variables were compared by Pearson's Chi-square test or Fisher's exact test. Spearman rank correlation analysis was used for correlation analysis. $p<0.05$ was considered statistically significant.

Results

General Clinical Data and Detection Indexes

There was no significant difference in age, gender, composition, and other general clinical data among the three groups. Compared with the healthy control group, the inflammatory indicators in the severe CAP group were significantly

Table I. Comparison of general clinical data and detection indicators among the three groups.

Variables	SCAP (n=78)	MCAP (n=92)	Normal control (n=70)
Age (year)	64.0 (55.8-72.0)	63.5 (56.0-72.0)	62 (57.0-78.0)
Gender (female/male)	31/47	38/54	26/44
PTX3 (ng/ml)	45.18 (22.51-77.56)*#	25.16 (9.46-41.57)*	1.45 (0.91-2.33)
PCT (ng/ml)	4.51 (2.21-7.96)*#	2.31 (1.15-6.02)*	0.37 (0.19-0.64)
CRP (mg/L)	88.91 (55.88-151.17)*#	44.79 (22.67-83.37)*	3.71 (2.30-7.66)
WBC (10^9/L)	11.82 (5.58-19.25)*#	9.33 (4.90-17.52)	6.23 (3.88-9.49)
NLR	6.09 (4.88-9.19)*#	5.11 (3.52-8.57)*	2.16 (1.58-3.09)

#Compared with the mild CAP group, $p<0.05$; *compared with the healthy control group, $p<0.05$. SCAP: the severe CAP group, MCAP: the mild CAP group.

increased ($p<0.05$), while PTX3, PCT, CRP, and NLR in the mild CAP group were also higher than those in the healthy control group, with statistically significant differences ($p<0.05$). Compared with the mild group, the increase of PTX3, PCT, and CRP was also different in the severe group ($p<0.05$; Table I).

Value of PTX3 In Predicting Severity In CAP Patients

ROC curve analysis of CAP diagnosis by all indicators showed that PTX3 had the best diagnostic performance at 32.26 ng/ml, with an AUC of 0.726, a sensitivity of 76.08%, and a specificity of 76.92%. The AUC of PCT and CRP was 0.731 and 0.653, respectively, (Table II, Figure 1).

Dynamic Altering of PTX3 In CAP Patients

PTX3 levels were monitored within 24 hours of admission, and on the 3th and 7th day. The level of PTX3 in the severe pneumonia group was significantly higher than that in the mild pneumonia group ($p<0.05$). PTX3 in both groups gradually decreased with the treatment time, but the patients in the severe group remained at a high level on the 7th day, as shown in Figure 2.

Levels of PTX3 Across Multiple Pathogens Groups

The results showed that 77 cases (45.3%) were positive for bacterial culture, 46 cases (27.1%) were positive for respiratory virus antigens, 23 cases (13.5%) were mixed infections with bacteria, and 24 cases (14.1%) were infected with other pathogens. There was no significant difference ($p=0.311$) in the level of PTX3 among patients infected with different pathogens, as shown in Figure 3.

Discussion

The human body's defense against acute infectious pneumonia mainly focuses on the aggregation and activation of neutrophils through chemokines of inflammatory factors to generate an inflammatory response. Neutrophils can rapidly release stored PTX3 under the stimulation of inflammatory factors such as IL-1β and TNF-α, and expression of PTX3 is significantly enhanced during pulmonary infection[10]. PTX3 is a newly discovered early inflammatory protein that belongs to the same family as CRP. PTX3 plays an important role in the early stage of inflammation by identifying microorganisms, promoting the recognition of pathogens

Table II. Diagnostic performance of inflammatory indicators in severity in CAP patients.

Variables	Threshold	AUC	Sensitivity (%)	Specificity (%)	*p*-value
PTX3 (ng/ml)	32.26	0.726	76.08	76.92	<0.001
PCT (ng/ml)	2.88	0.731	62.38	73.88	0.002
CRP (mg/L)	41.22	0.653	71.55	67.92	0.007
WBC (10^9/L)	9.02	0.548	45.49	63.09	0.523
NLR	5.51	0.611	52.17	77.62	0.221

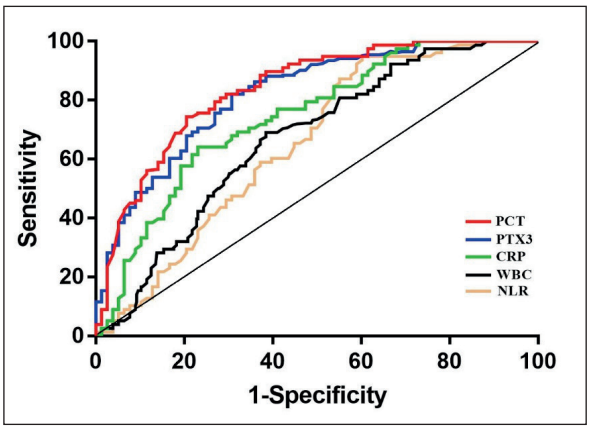

Figure 1. Receiver operating characteristic (ROC) curve analysis of various parameters to predict severe CAP.

by phagocytes, and activating the classical lectin complement pathway[11,12]. The expression level of PTX3 in normal human serum is relatively low, generally less than 2 ng/ml. When the body is infected, PTX3 is induced by Toll-like receptors and produced by monocytes, macrophages, and endothelial cells, and released into the blood[13]. Elevated PTX3 levels are associated with the severity and prognosis of infectious diseases[14]. Bastrup-Birk et al[15] reported that PTX3 significantly increased in patients with the systemic inflammatory response syndrome, which has certain diagnostic value. Tekerek et al[16] found that PTX3 can be combined with CRP and PCT to diagnose ventilator-related pneumonia.

In this study, the PTX3 level in CAP patients was significantly higher than that in healthy controls, and there were also differences in the expression level between severe and mild patients. ROC curve analysis also showed that the area

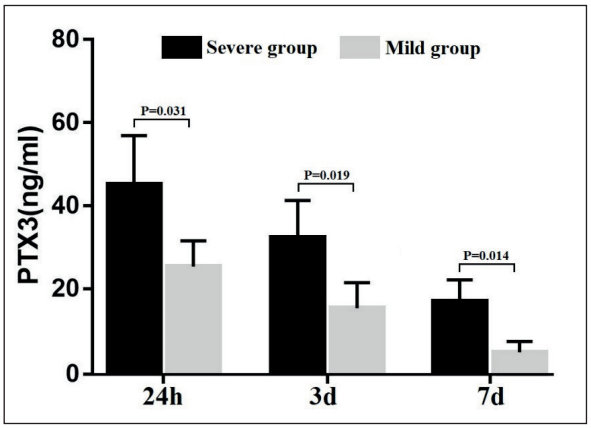

Figure 2. The dynamic altering of PTX3 in patients with CAP.

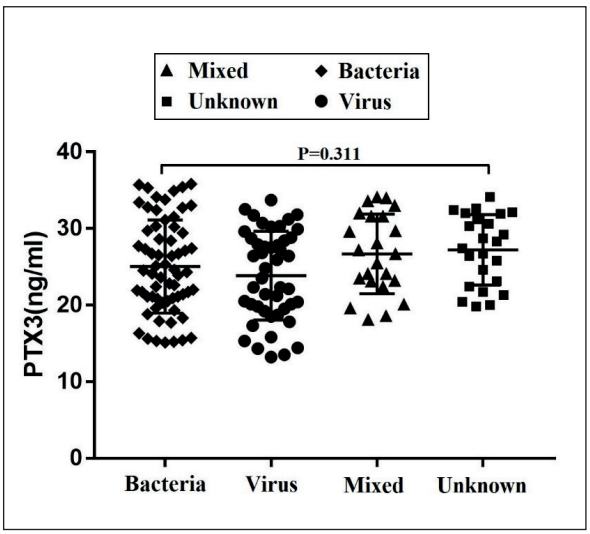

Figure 3. PTX3 expression among different pathogen groups.

under the curve was 0.726 when it was used to diagnose CAP, showing a good diagnostic effect. Compared with CRP, PCT and other inflammatory indicators, PTX3 also has certain advantages in the expression changes and sensitivity of CAP. CRP is mainly synthesized by hepatocytes in response to inflammatory stimuli. PCT is synthesized and released by thyroid C cells, which mainly reflects the active inflammatory response of the body[17]. It is also because of this synthesis and different sources of release, that PTX3 is relatively sensitive in the diagnosis of CAP, a local infection in the body.

In this study, the PTX3 level of hospitalized patients was dynamically monitored, and it was found that the PTX3 level was the highest within 24 hours after admission, and gradually decreased after 3 days of effective treatment, and significantly decreased after 1 week. The level of PTX3 in the severe group was higher at the beginning of admission and after treatment than in the mild group. PTX3 in both groups gradually decreased with the treatment time, but the patients in the severe group still maintained a high level at the 7th day. This indicates that PTX3 can be used to some extent to reflect the treatment situation. This is also consistent with previous studies on the prediction of infectious disease severity by the PTX3 level[18,19]. Severe pneumonia can cause a systemic inflammatory response, causing the body to release more PTX3 into the blood when stimulated. In addition, the treatment cycle is relatively long, the remission of symptoms is slow, and PTX3 exists in the body for a long time.

In addition, we investigated the correlation between PTX3 levels and infectious pathogens. The results showed that PTX3 levels were not affected by specific pathogenic factors in CAP patients. In this study, CAP patients were divided into the bacterial infection group, the viral infection group, the mixed infection group, and the other pathogens infection group according to the types of pathogens. Comparative analysis between different groups showed no statistically significant difference in the plasma PTX3 level. Previous studies were consistent with the results of this study[20,21], but there were also reports suggesting differences in PTX3 levels among patients infected with different pathogens[16]. The reasons for the differences in the conclusions of this study may be that, first of all, the pathogens of respiratory diseases infection are complex and diverse, and the results of pathogen detection are susceptible to the influence of sampling sites, population age structure, and other factors. Second, it may be related to the difference in the source of the disease in the medical institutions that carried out the study, and the low number of cases in the study. Therefore, to explore the correlation between CAP and PTX3 caused by different pathogenic microorganisms, a multi-center, large-sample study should be carried out.

Conclusions

Altogether, the abovementioned results demonstrate that the serum PTX3 level can be used as a biomarker to reflect community-acquired pneumonia, which can provide effective auxiliary diagnosis and efficacy in monitoring for clinical practice.

Funds

Key Research and Development Projects in Shandong (2018GSF118216); Development Plan of Medical and Health Science and Technology in Shandong Province (2017WS524).

Conflict of Interests

The Authors declare that they have no conflict of interests.

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