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Original Article

Significance of serum procalcitonin combined with C-reactive protein in diagnosis of acute exacerbation of chronic obstructive pulmonary disease and guidance of antibiotics therapy

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Abstract: Objective: To investigate the significance of serum procalcitonin (PCT) combined with C-reactive protein (CRP) in predicting acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and guiding antibiotic therapy. Methods: A total of 122 patients with chronic obstructive pulmonary disease (COPD) who were treated in the Department of Respiratory Medicine in Shanghai Putuo District Liqun Hospital from January to December of 2016 were recruited in this study and divided into AECOPD group (n=60) and stable COPD group (n=62). Serum PCT, CRP values and white blood cell count (WBC) of the AECOPD group and the stable COPD group were detected. Positive and negative sputum cultures, as well as the three markers (PCT, CRP and WBC) were compared between the two groups. The sensitivity, specificity and the area under receiver operating characteristic (ROC) curves of the markers in judging AECOPD were calculated and compared. Sixty patients with AECOPD who were treated from January to June of 2017 were randomly divided into PCT-CRP guided treatment group and usual care group. The use of antibiotics and other drugs, the total days of hospital stay, and deaths during hospitalization were compared between the two groups. Results: The PCT level was highest (0.45±0.39 ng/ml) in AECOPD patients with positive sputum culture, followed by 0.27±0.26 ng/ml in sputum culture-negative AECOPD patients, and lowest (0.08±0.09 ng/ml) in stable COPD patients, and there was significant difference in pairwise comparison (all P<0.001). The CRP and WBC levels were remarkably higher in the acute exacerbation phase than in the stable phase of COPD, but they were insignificantly different between AECOPD patients with negative sputum culture and those with positive sputum culture. The sensitivity and specificity of PCT in diagnosis of AECOPD were 70.0% and 74.2%, respectively. The sensitivity and specificity of CRP and WBC were 46.7%, 41.7%, 66.1%, and 64.5%, respectively. The area under the ROC curve for PCT was 0.721 (95% CI: 0.633-0.798), significantly higher than that (0.564, 95% CI: 0.471-0.654) for CRP and that (0.531, 95% confidence interval (CI): 0.438-0.622) for WBC (all P<0.001). The sensitivity and specificity of PCT-CRP combination were 91.7% and 59.7%, respectively, and the area under the ROC curve was 0.757 (95% CI: 0.671-0.831). Among patients with PCT-CRP parallel guided antibiotic treatment, no significant difference was seen in expectorant drugs, hormones, bronchodilators, and other drugs, as well as the number of patients with antibiotics use. The days of antibiotics use were significantly fewer (P=0.037); hospital stay was also considerably shorter (P=0.048). However, the deaths during hospitalization differed insignificantly. Conclusion: PCT-CRP combination contributes to the diagnosis of AECOPD with bacterial infections, and it is helpful to guide antibiotic medication and efficacy evaluation.

Keywords: Procalcitonin, C-reactive protein, chronic obstructive pulmonary disease, white blood cell count, antibiotic medication

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic pulmonary inflammatory disease characterized by airflow limitation. The prevalence of COPD in people older than 40 in China is as high as 8.6% as a result of high smoking rate and severe air pollution [1, 2]. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a process of acute onset of COPD when the patient's respiratory symptoms is deteriorated, which adversely impacts the

lung functions and quality of life in patients. AECOPD is also a leading cause of deaths. In China, COPD has become the third cause of deaths and induce severe disease and economic burden [3, 4].

Up till now, the etiology of AECOPD is still uncertain. AECOPD is related to smoking and air pollution [5]. The most common cause is airway inflammation caused by bacterial or viral infection, and approximately more than half of the cases of AECOPD are associated with bacteria and/or viral infections [6, 7]. As a result, antibiotic therapy is vital for management of AECOPD. Currently, diagnosis of AECOPD is primarily made based on the clinical manifestations of patients [8]. The examination of etiology of lower respiratory tract infection often lags behind, leading to clinical abuse of antibiotics [9]. Therefore, it is of great significance to find out one or more biomarkers which can be used for the early identification of AECOPD, confirmation whether bacterial infections are present, and guidance of therapy. All this can reduce CODP-induced death and burden. Multiple studies have shown that markers of inflammation including procalcitonin (PCT), C-reactive protein (CRP), and white blood cell count (WBC) are useful for diagnosis of AECOPD, distinguishing whether it is caused by bacterial infection, and guiding medications; however, the results of the studies are not similar [10-12]. This study was aimed to analyze the role of PCT and CRP in the diagnosis of AECOPD and guidance of antibiotic medication in AECOPD patients and those with stable COPD who were admitted to our hospital.

Materials and methods

Participants

A total of 182 patients with COPD admitted to our hospital between January 2016 and June 2017 were included in this study. Patients equal to or older than 18 years were included if they had the symptoms met the diagnostic criteria for COPD which were confirmed primarily based on comprehensive analysis of data including clinical manifestations, a history of exposure to risk factors, signs and laboratory tests. AECOPD was defined as a continuous exacerbation of the patients' respiratory symptoms that is beyond the normal daily variations and leads to a change in medication. Stable COPD was defined as the stability or mild symptoms of the patient's cough, sputum production, and shortness of breath, with the condition basically restored to the state before the acute exacerbation [13]. Exclusion criteria were: infections in other parts of the respiratory system; severe health-impacting diseases including severe cardiac insufficiency, malignancy or cardiac and cerebrovascular disease; combined with other lung disease; cognitive impairment and mental disorders. Of the 182 COPD patients, 62 had stable COPD and 120 had AECOPD. All patients submitted written informed consent and the study got approval from the Ethics Committee of Shanghai Putuo District Liqun Hospital.

Study design and assessment markers

Significance of PCT, CRP, and PCT-CRP combination in diagnosis of AECOPD: For the 62 patients with stable COPD and 60 patients with AECOPD admitted to the Shanghai Putuo District Liqun Hospital from January to December 2016, the concentrations of PCT, CRP and WBC were detected, and the accuracy of the three single markers, as well as PCT-CRP combination in diagnosis of AECOPD was assessed. The assessment markers comprised sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curves.

Role of PCT-CRP combination in guiding antibiotic therapy for AECOPD: In terms of a random number table, 60 patients with AECOPD admitted to Shanghai Putuo District Liqun Hospital from January to June 2017 were stratified into two groups, with 30 patients in each group. One group (usual care group) received conventional treatment including bronchodilators, corticosteroids, expelling phlegm, antibiotic therapy, and mechanical ventilation when necessary. The other group (PCT-CRP guided treatment group) received the same treatment as those in the conventional group. For the patients in the PCT-CRP guided treatment group, as far as antibiotic therapy was concerned, whether antibiotics were administered was based on serum PCT and CRP levels of the patients, which were measured every other day. Antibiotic drugs were given when PCT≥0.25 ng/ml or CRP>8 mg/L (it was considered to be the presence of bacterial infection); antibiotic drugs were discontinued when PCT<0.25 ng/ml and

Table 1. Basic characteristics of patients with AECOPD or stable COPD

Characteristic	Stable COPD (n=62)	AECOPD (n=60)	x^2/t	P
Age	65.12±7.81	67.36±8.43	1.523	0.130
Gender			0.382	0.536
Male	38 (61.29)	40 (66.67)		
Female	24 (38.71)	20 (33.33)		
Smoking			1.444	0.230
No	5 (8.06)	9 (15.00)		
Yes	57 (91.94)	51 (85.00)		
Course of disease	8.40±2.10	9.10±3.20	1.424	0.158
Comorbidity				
Heart disease			0.099	0.753
No	45 (72.58)	42 (70.00)		
Yes	17 (27.42)	18 (30.00)		
Hypertension			0.001	0.976
No	36 (58.06)	35 (58.33)		
Yes	26 (41.94)	25 (41.67)		
Diabetes			0.547	0.460
No	49 (79.03)	44 (73.33)		
Yes	13 (20.97)	16 (73.33)		
Frequency of hospitalization in the previous year			0.436	0.509
1	41 (66.13)	43 (71.67)		
≥2	21 (33.87)	17 (28.33)		
Sputum culture			13.262	<0.001
Negative	39 (62.90)	18 (30.0)		
Positive	23 (37.10)	42 (70.0)		

Note: COPD denotes chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

CRP<8 ng/ml. The assessment markers included the use of non-antibiotics, antibiotic medication, days of hospitalization, and deaths during hospitalization.

Marker testing

Fasting blood samples were collected from all the patients who had not undergone any treatment on the day of admission or the following day, and biochemical and hematological markers including PCT, CRP, and WBC were measured. Patients with AECOPD who had undergone PCT-CRP guided treatment continued to have blood PCT and CRP values measured every other day during hospital stay. PCT was detected using the sandwich immunofluorescence assay, with PCT>0.25 ng/ml suggesting the presence of bacterial infection [14, 15]. CRP was measured by immunoturbidimetry, and the normal reference value was 0-3 mg/L, with CRP>8 mg/L indicating the presence of bacterial infection [16]. WBC count was conducted using an automatic blood cell analyzer, with WBC>10^9/L indicating the presence of bacterial infection. The results of sputum cultures (at least twice) were applied to determine whether bacterial infection was present.

Statistical analysis

Measurement data were presented as mean ± standard deviation; one-way analysis of variance was employed to compare the means among more than two groups, and the pairwise comparisons were performed using the SNK q test. Categorical variables are represented as constituent ratios, and the differences in categorical variables were compared using a two-sided chi-square test. Sensitivity=True positive/(true positive + false negative)*100%; Specificity=rue negative/(true negative + false positive)*100%. The area under the ROC curve was utilized to assess the accuracy of different indicators for diagnosis of AECOPD, and the cut-off values for PCT and CRP were 0.25 ng/ml and 8

Table 2. Results of PCT, CRP and WBC detection in patients with AECOPD or stable COPD

Marker	AECOPD		Stable COPD (N=62)	F	P
	Positive sputum culture (n=42)	Negative sputum culture (n=18)			
PCT (ng/ml)	0.45±0.39	0.27±0.26	0.08±0.09	11.278	<0.001
CRP (mg/L)	21.67±11.62	18.24±19.46	4.28±2.45	40.070	<0.001
WBC (*10^9/L)	11.38±3.44	10.01±6.75	7.02±2.66	117.560	<0.001

Note: COPD denotes chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count.

Table 3. Accuracy of single PCT, CRP, WBC, and PCT-CRP combination in detection of AECOPD

Outcome		AECOPD	Stable CODP (%)	Sensitivity (%)	Specificity (%)	Area under ROC curve (95% CI)
PCT	Positive	42	16	70.0	74.2	0.721 (0.633-0.798)
	Negative	18	46			
CRP	Positive	28	21	46.7	66.1	0.564 (0.471-0.654)
	Negative	32	41			
WBC	Positive	25	22	41.7	64.5	0.531 (0.438-0.622)
	Negative	35	40			
PCT + CRP (Serial)	Positive	15	12	25.0	80.6	0.528 (0.436-0.619)
	Negative	45	50			
PCT + CRP (Parallel)	Positive	55	25	91.7	59.7	0.757 (0.671-0.831)
	Negative	5	37			

Note: COPD denotes chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ROC, receiver operating characteristic; CI, confidence interval; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count.

mg/L, respectively [17]. Statistically significant level was set to be two-sided (α=0.05). SPSS software, version 20.0, was used to perform all statistical analyses.

Results

Basic data of patients

Table 1 shows the individual and clinical characteristics of 62 patients with stable CODP and 60 with AECOPD. The average age of the two groups was 65.12±7.81 years and 67.36±8.43 years, respectively, and the proportions of males were 61.29% and 66.67%, respectively. The average age and the proportion of males were insignificantly different between the two groups. In addition, the two groups also differed insignificantly in smoking status, course of disease, comorbidities, and the frequency of hospitalization in the previous year. Of the patients with AECOPD, the rate of positive sputum culture was 70%, which was noticeably higher than that (37.10%) of patients with stable CODP (both P<0.001).

We tested PCT, CRP, and WBC in the blood of AECOPD patients with positive or negative sputum cultures and in the blood of patients with stable CODP. The overall differences of the above three markers were significant among the three groups (all P<0.001). Further studies revealed that PCT level was highest in AECOPD patients with positive sputum cultures (0.45±0.39 ng/ml), followed by that in AECOPD patients with negative sputum cultures (0.27±0.26 ng/ml), and the lowest (0.08±0.09 ng/ml) in patients with stable CODP, significantly different in pairwise comparisons among the three groups (all P<0.001). The CRP and WBC levels were substantively higher in AECOPD patients than in patients with stable CODP, but insignificantly different between the AECOPD patients with positive sputum cultures and those with negative sputum cultures (**Table 2**).

Accuracy of PCT, CRP and WBC in diagnosis of AECOPD

The diagnostic results of AECOPD by the above three markers are listed in **Table 3**. The sensi-

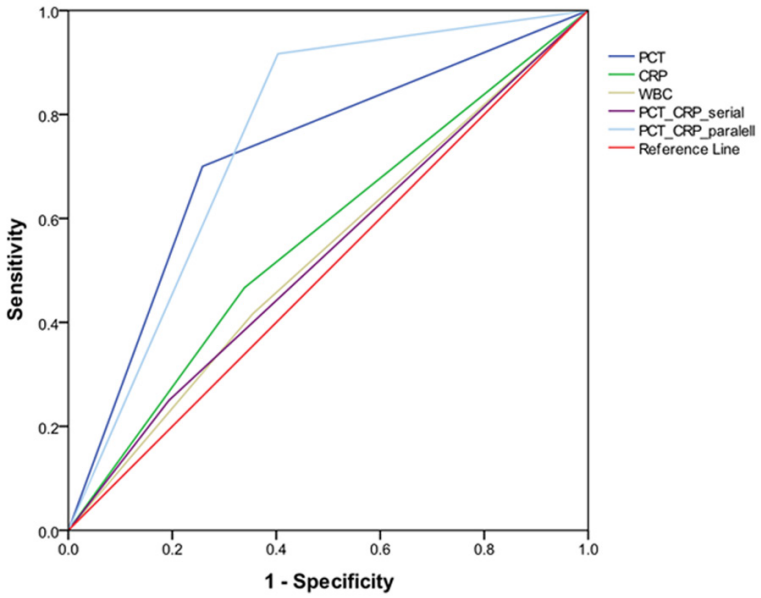

Figure 1. ROC curves for PCT, CRP and WBC as well as PCT-CRP combination.

tivity and specificity of PCT were 70.0% and 74.2%, respectively. The sensitivity and specificity of CRP and WBC were 46.7%, 41.7% and 66.1%, 64.5%, respectively. The sensitivity and specificity of PCT-CRP parallel combination were 91.7% and 59.7%, respectively, whereas the sensitivity and specificity of PCT-CRP serial combination were 25.0% and 80.6%, respectively. The area under the ROC curve for PCT was 0.721 (95% CI: 0.633-0.798), which was considerably higher than 0.564 (95% CI: 0.471-0.654) for CRP and 0.531 (95% CI: 0.438-0.622) for WBC (all P<0.001). However, the area under the ROC curve for CRP was not significantly different from that for WBC. The area under the ROC curve for PCT-CRP parallel combination was 0.757 (95% CI: 0.671-0.831), which was insignificantly different from that for PCT, but both had noticeably higher accuracy that that of PCT-CRP serial connection (all P<0.001; **Table 3**, and **Figure 1**).

Roles of PCT-CRP combination in guiding antibiotic mediation for AECOPD patients

We randomly divided 60 patients with AECOPD into two groups (usual care group and PCT-CRP guided treatment group) in terms of antibiotic medication. No remarkable disparity was found in individual and clinical characteristics between the two groups (all P>0.05, **Table 4**). **Table 5** shows medication and treatment of the two groups during the treatment period. The usual care group and the PCT-CRP guided treatment group varied insignificantly in the use of expectorant drugs, hormones, bronchodilators and other drugs, as well as the number of patients with antibiotic medications. However, the PCT-CRP guided treatment group had significantly fewer days of antibiotic medication (P=0.037), and shorter hospital stay (P=0.048). Nevertheless, the two groups differed insignificantly in the number of deaths during hospitalization.

Discussion

AECOPD may be caused by a variety of factors. Viral infection, air infection and other factors may aggravate airway inflammation and secondary bacterial infection. Seventy-eight percent of patients have definite bacterial or viral infections, of which bacterial infection accounts for approximately 40-60% [8]. In our current study, the positive rate of bacterial culture was 70%, which is similar to that reported in the above literature. Due to lack of accurate laboratory and auxiliary examination methods, diagnosis of AECOPD is completely determined by clinical manifestations. However, the diagnostic results vary greatly due to the uncertainties in both doctors and patients, making it difficult for doctors to make a timely assessment of the severity of patients' conditions. In recent years, multiple studies have found that inflammatory markers including PCT, CRP, WBC, and IL-6 are helpful in the diagnosis of AECOPD [11, 18].

Clinically, WBC and CRP are common markers used to evaluate most bacterial infections. CRP is a protein that is primarily synthesized by the liver. When there is infection or tissue injury in the body, serum CRP levels will elevate dramatically. However, in patients with AECOPD, serum CRP levels begin to rise gradually at the 12th hour in the acute phase, but viral infection may also lead to elevated CRP levels. As a result, it is still controversial whether elevated CRP levels can be applied for judging the presence or absence of infection during acute exacerbations [8, 18]. In a study with a small sample

Table 4. General characteristics of CT-CRP guided treatment group and usual care group

Characteristic	CT-CRP guided treatment (n=30)	Usual care (n=30)	x^2/t	P
Age	66.30±8.37	68.16±9.48	0.806	0.424
Gender			2.700	0.100
Male	17 (56.67)	23 (76.67)		
Female	13 (43.33)	7 (23.33)		
Smoking			1.920	0.166
No	3 (10.00)	7 (23.33)		
Yes	27 (90.00)	23 (76.67)		
Course of disease	8.60±3.20	9.50±4.10	0.948	0.347
Comorbidity				
Heart disease			0.318	0.753
No	20 (66.67)	22 (73.33)		
Yes	10 (33.33)	8 (26.67)		
Hypertension			1.714	0.190
No	15 (50.00)	20 (66.67)		
Yes	15 (50.00)	10 (33.33)		
Diabetes			1.364	0.243
No	24 (80.00)	20 (73.33)		
Yes	6 (20.00)	10 (33.33)		
Frequency of hospitalization in the previous year			2.052	0.152
1	19 (63.33)	24 (80.00)		
≥2	11 (36.67)	6 (20.00)		
Anthonisen criteria			1.990	0.370
I	7 (23.33)	4 (13.33)		
II	5 (16.67)	9 (30.00)		
III	18 (60.00)	17 (56.67)		

Table 5. Treatment of CT-CRP guided treatment group and usual care group

Treatment/Outcome	CT-CRP guided treatment (n=30)	Usual care (n=30)	x^2/t	P
Expectorant drugs			2.700	0.100
No	4 (13.33)	6 (20.00)		
Yes	26 (86.67)	24 (80.00)		
Hormones			0.601	0.438
No	14 (46.67)	17 (23.33)		
Yes	16 (53.33)	13 (76.67)		
Bronchodilators			0.417	0.519
No	5 (16.67)	7 (46.67)		
Yes	25 (83.33)	23 (46.67)		
No. of patients with antibiotics			0.098	0.754
No	6 (20.00)	7 (23.33)		
Yes	24 (80.00)	23 (76.67)		
Days of antibiotic use	11.30±5.40	14.50±6.20	2.132	0.037
Days of hospital stay	16.70±4.20	19.50±6.30	2.025	0.048
Deaths during hospitalization				1.000
No	28 (93.33)	29 (96.67)		
Yes	2 (6.67)	1 (3.33)		

size, with the same CRP positive criteria (≥8 mg/L), the sensitivity for distinguishing AECOPD from stable COPD were 60.4% and 52.2%, respectively [19]. In our current study, the sensitivity of CRP was 46.7% and the specificity was 66.1%, which were similar to those in the above-mentioned study, suggesting that the accuracy of CRP in diagnosis of AECOPD was not high. In our current study, the area under the ROC curve for CRP was 0.564 (95%: 0.471-0.654), similar to other studies [6, 20, 21].

PCT can be employed as an inflammatory marker

for bacterial infection and was first reported in 1990s. It is a pro-peptide of calcitonin and a hormone-free glycoprotein, usually produced by thyroid C cells. The PCT levels are extremely low in healthy people, and elevate significantly in case of bacteria infection, sedation, sepsis, and organ failure [22]. In our current study, serum PCT levels were noticeably higher in AECOPD patients with positive bacterial cultures than in those with negative bacterial cultures, while the serum PCT levels were substantially higher in AECOPD patients with negative bacterial cultures than those with stable COPD. Moreover, the area under the ROC curve of PCT was considerably greater than those of CRP and WBC. All this implies that PCT is superior to CRP and WBC in diagnosis of AECOPD and judgement of bacterial infections, which is consistent with the results of previous studies [12]. However, some studies suggest that PCT alone is an unsuitable marker for diagnosis of AECOPD, or it cannot distinguish between bacterial and viral infections [23, 24]. Additionally, in view of the consistency of AECOPD, the combination of markers contributes to more accurate etiological judgments [25, 26]. In our current study, we analyzed PCT-CRP serial and parallel combinations and found that although the area under the ROC curve in the PCT-CRP serial combination was significantly smaller than that of PCT, the specificity could rise to 80.6%, whereas PCT-CRP parallel combination can increase the sensitivity (70%) of single PCT use to 91%, which was similar to the results of other studies [19, 27]. Therefore, clinical diagnosis can be facilitated by comprehensive comparison in clinical practice.

Although bacterial infection is a major cause for AECOPD, antimicrobial therapy is not necessary for all patients with AECOPD [28]. A randomized, controlled, open-label study showed that PCT-directed antibiotic medication can significantly reduce mortality in patients with AECOPD [29]. The results of our current study indicate that antibiotic medication for treating AECOPD based on dynamic levels of PCT and CRP remarkably reduced the use of antibiotics and length of hospital stay. This result is similar to that of other studies and a meta-analysis [10, 11]. However, this analysis also revealed that due to the limitations of methodology and the small sample size of the study, more evidence is needed to explore the role of PCT in guiding AECOPD [10]. Moreover, other research demonstrates that PCT and CRP cannot distinguish viral infections from bacterial infections, so it is of little value for PCT and CRP used in guiding antibiotic medication in treating AECOPD [30].

In conclusion, the results of our current study suggest that PCT and CRP contribute to diagnosis of AECOPD. The randomized controlled trial also demonstrate that the PCT-CRP combination helps guide antibiotic medication in the treatment of AECOPD. Nevertheless, there are still some limitations in this study, such as the small sample size, no serological or molecular biological analysis focused on virus infection of individuals, and lack of long-term follow-up for exploring treatment effectiveness. Therefore, additional prospective studies with larger sample size are required to verify the significance of PCT-CRP combination in diagnosis of AECOPD and guidance of antibiotics medication.

Disclosure of conflict of interest

None.

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