

Original Article

Diagnostic values of C-reactive protein, procalcitonin and serum amyloid A in predicting bacterial infection in patients with acute exacerbations of chronic obstructive pulmonary disease

Ge Xiong, Bin Qiao, Zegang Wu, Yan Li

Department of Clinical Laboratory, Renmin Hospital of Wuhan University, Wuhan City, China

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Abstract: Objective: To investigate the diagnostic values of C-reactive protein (CRP), procalcitonin (PCT) and serum amyloid A (SAA) in predicting bacterial infection in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Methods: 78 patients diagnosed as AECOPD treated in Renmin Hospital of Wuhan University during 2014 January to 2016 January were included. Baseline information (age, sex, accompanied diseases, GOLD grade) was recorded in details. Sputa were collected on admission and were cultured for 72 hours. Blood samples were drawn for CRP, PCT and SAA. Results: 38 patients were diagnosed as bacterial infection and another 40 patients had no evidence of bacterial infection after sputum culturing. Differences of baseline information between two groups had no statistical significance. CRP, SAA and PCT level of patients with bacterial infection were significantly higher than that of patients with no bacterial infection. Besides, purulent sputum, elevated SAA and PCT were significantly associated with bacterial infection after univariate and multivariate regression analysis. Results of sputum culture showed that the three main pathogens were haemophilus influenzae (10 patients), Pseudomonas aeruginosa (6 patients) and Streptococcus pneumoniae (5 patients). SAA of patients in haemophilus influenzae (Hi) and Haemophilus parainfluenzae (Hpi) (Hi&Hpi) group were significant higher than that of patients in other pathogens group, but no difference were observed between the two groups in level of CRP and PCT. AUCs of CRP, PCT and SAA in the diagnosis of bacterial infection in patients with AECOPD was 0.875, 0.941 and 0.854, respectively. Conclusion: We found that PCT was better than CRP and SAA in predicting bacterial infection in patients with AECOPD and therefore might be a useful clinical marker in guiding antibiotic therapy.

Keywords: C-reactive protein, procalcitonin, serum amyloid A, bacterial infection, exacerbations, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious disease with high mortality. It was reported that there were 3 million people in the UK [1] had COPD and 8.2% adults older than 40 years suffered from COPD in China. It was estimated that COPD would become the third cause of global death in 2020 [2]. Exacerbations of COPD (AECOPD) is an acute worsening condition of COPD, which always accompanied by clinical symptoms such as, shortness of breath and increased production of sputum. Respiratory infection (bacteria or viruses or mixed) is thought to be the main cause in most exacerbations. Studies had showed that about 30-50%

of exacerbations were caused by bacterial infections [3]. It was still difficult to discriminate bacterial or viral infections in exacerbations. Patients with exacerbations of COPD caused by bacteria will be advised to receive antibiotic treatment as soon as possible, but difficulties in differential diagnosis make it impossible, especially in patients with no purulent sputum [4].

In recent years, biomarkers had been widely used as a diagnostic markers of bacterial infection in exacerbations. Several studies had confirmed that C-reactive protein (CRP) increased during exacerbations of COPD and the CRP level was strongly associated with viral detec-

Table 1. Baseline information of the total population

Variables	Bacteria detected n (%)	No bacteria detected n (%)	P value
Number of patients	38	40	-
Gender (male)	24 (63.16)	22 (55.00)	0.46
Age	61.13±7.49	62.63±8.40	0.41
Smoking history			
Current	11 (28.95)	10 (25.00)	0.45
Former	14 (36.84)	13 (32.50)	-
Never	13 (34.21)	17 (42.50)	-
Hypertension	10 (26.32)	9 (22.50)	0.69
Diabetes	5 (13.16)	8 (20.00)	0.42
Temperature on admission	36.95±0.44	36.83±0.39	0.21
GOLD I-II	11 (28.95)	24 (60.00)	0.006
GOLD III-IV	27 (71.05)	16 (40.00)	
Purulent sputum	20 (52.63)	13 (32.50)	0.07
Duration of hospitalization	10.55±2.53	8.28±2.41	<0.001
Biomarkers			
CRP	56.65±31.65	19.62±8.78	<0.001
SAA	53.73±23.33	25.20±14.44	<0.001
PCT	1.63±0.85	0.35±0.27	<0.001
WBC	10.56±2.33	9.73±2.36	0.12

tion rate [5] and bacterial infection [6]. Interesting, in other clinical studies, CRP level showed no association with bacterial infection [4] and whether it could be used as a diagnostic marker in bacterial infection in exacerbations is still unclear [7]. Besides, procalcitonin (PCT), as an inflammatory blood marker, had a important role in the guidance of antibiotic treatments in patients with exacerbations of COPD [8]. But the role of PCT in differentiating bacterial from viral causes is still unknown. Serum amyloid A (SAA) is an acute phase protein, which is similar to CRP and SAA, may be a better marker in early diagnosis of bacterial infections [9-11]. Study showed that patients with neutrophilic exacerbations of COPD were accompanied by higher concentrations of serum SAA and CRP [12]. But no clinical study had conducted to investigate to the role of SAA in predicting bacterial infection in patients with exacerbations of COPD.

Therefore, we conducted this prospective study to compare CRP, PCT and SAA levels in patients with bacterial infection and no bacterial infections. And also we aimed to explore the diagnostic roles of CRP, PCT and SAA of bacterial infection in patients with exacerbations of COPD.

Patients and methods

Patients

We performed this prospective clinical study in Renmin hospital of Wuhan University during 2014 January to 2016 January. Patients included were all diagnosed as COPD and exacerbation of COPD was defined as an increase in breathlessness, cough or increased volume of sputum, or increased sputum purulence according to the Anthonissen's criteria. All patients would receive a chest X ray or computed tomography (CT) on admission. Patients who were older than 18 years and had no use of any antibiotics or steroids in the last two weeks were included. We excluded patients who had severe organ dysfunction or systematic disease or malignancy disease. The severity of COPD was graded according to the Global Initiative for

Chronic Obstructive Lung Disease (GOLD) guidelines as it described in previous study [13]. Patients were grouped according their sputum culture. Patients with positive sputum culture results were in Bacteria detected group, otherwise patients would be included in no-Bacteria detected group. All patients signed an informed consent.

Samples

Blood and sputum were collected on admission. Sputum was examined by Gram stain and was cultured for 72 hours. Blood samples were drawn for CRP, PCT and SAA. These biomarkers were all measured by standard methods in the department of Clinical laboratory in Renmin hospital of Wuhan University. Normal value of biomarkers were as follows: CRP 0~10 mg/L, PCT <0.05 ng/ml, SAA 0~10 mg/L.

Statistical analysis

The descriptive analysis (mean, standard deviation, median) was used for continuous variables and percentage for categorical variables. Comparisons used the t test or One-Way ANOVA analysis for continuous variables. Details of results of culture sputum were recorded and

CRP, PCT and SAA in AECOPD patients

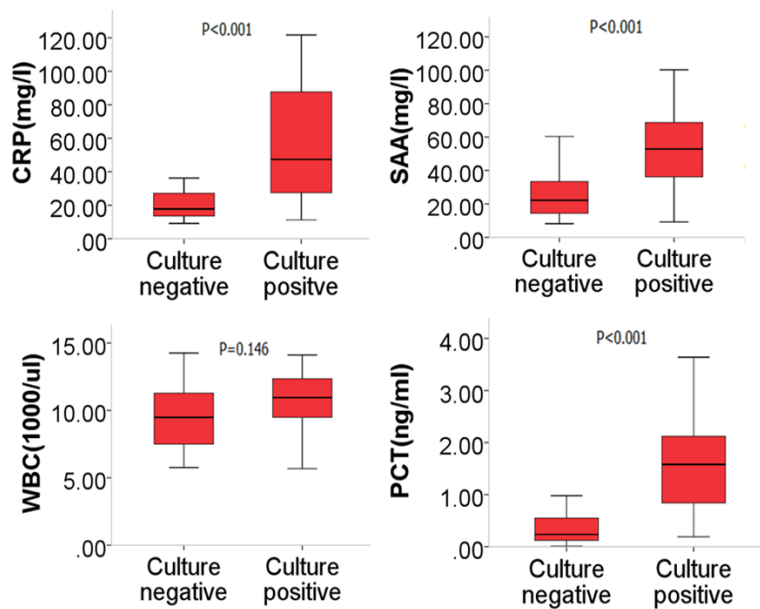


Figure 1. Comparison of CRP, SAA, WBC and PCT between culture positive and culture negative group of AECOPD. CRP, SAA and PCT level of patients with bacterial infection were significant higher than that of patients with on bacterial infection (56.65 ± 31.65 vs 19.62 ± 8.78 , 53.73 ± 23.33 vs 25.20 ± 14.44 , 1.63 ± 0.85 vs 0.35 ± 0.27 , all $p < 0.001$, respectively).

we used Box-plot to present levels of biomarkers between different bacterial group. The association between variables and bacteria was evaluated by using univariate and multivariate logistic analysis. Receiver operating characteristic (ROC) curves was used to accessed the variables' prediction ability. Statistical analyses were conducted using SPSS 21 and Medcalc and P value < 0.05 were considered statistically significant.

Results

Baseline demographic data of patients with AECOPD

78 patients with AECOPD were included in this study. There were 38 patients were diagnosed as bacterial infection and another 40 patients had no evidence of bacterial infection after sputum culturing. Patients in two groups had no difference in gender, age, accompanied diseases, temperature. There were 27 patients of AECOPD with bacterial infection in GOLD stage III-IV. Only 13 patients were in GOLD stage III-IV in culture negative group. There were no patients died during hospitalization. Details of baseline information of patients included in this study were showed in **Table 1**.

Biomarkers' level in different patients with AECOPD

Comparison of CRP, SAA, WBC and PCT between culture positive and culture negative group of AECOPD were shown in **Figure 1**. CRP, SAA and PCT level of patients with bacterial infection were significantly higher than that of patients with no bacterial infection (56.65 ± 31.65 vs 19.62 ± 8.78 , 53.73 ± 23.33 vs 25.20 ± 14.44 , 1.63 ± 0.85 vs 0.35 ± 0.27 , all $p < 0.001$, respectively).

Univariate and multivariate regression

After the analysis of univariate and multivariate regression, we found that purulent sputum, elevated SAA and PCT were significantly associated with bacterial infection. Details were showed in **Table 2**.

Pathogens of sputum culture

We recorded the results of sputum culture and the results showed that the three main bacteria in sputum culture were haemophilus influenzae, Pseudomonas aeruginosa and Streptococcus pneumoniae. Details of causative pathogens in patients of AECOPD with bacterial infection were showed in **Table 3**. In order to investigate if there were any differences among patients with different causative pathogens in CRP, SAA and PCT, we merged patients infected with haemophilus influenzae (Hi) and patients infected with Haemophilus parainfluenzae (Hpi) into one group and patients infected with other pathogens in another group. The results showed that SAA of patients in Hi&Hpi group were significant higher than that of patients in other pathogens group (62.88 ± 22.37 vs 47.76 ± 21.97 , $p = 0.043$). But no difference were observed between the two groups in level of CRP and PCT (61.84 ± 28.83 vs 53.27 ± 32.93 , $p = 0.41$; 1.62 ± 0.69 vs 1.64 ± 0.93 , $p = 0.94$, respectively). Comparison of CRP, SAA, WBC and PCT between different bacteria positive group were show in Box plot (**Figure 2**).

Table 2. Univariate and Multivariate analyses for influencing factors of bacterial infection in AECOPD patients

Variables	Univariate analyses		Multivariate analyses	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	0.98 (0.92-1.03)	0.41	-	-
Male	0.95 (0.66-2.62)	0.82	-	-
Current smoking	2.50 (1.42-7.49)	0.13	-	-
Hypertension	1.23 (0.44-3.46)	0.70	-	-
Diabetes	0.61 (0.18-2.05)	0.42	-	-
Temperature on admission	2.08 (0.66-6.58)	0.22	-	-
GOLD III-IV	3.68 (1.43-9.47)	0.007	7.21 (0.20-26.22)	0.28
Purulent sputum	2.31 (0.92-5.78)	0.074	4.51 (2.18-6.05)	0.04
CRP	1.13 (1.05-1.20)	<0.001	1.21 (0.95-1.52)	0.12
SAA	1.08 (1.04-1.12)	<0.001	1.21 (1.01-1.44)	0.04
WBC	1.19 (0.97-1.45)	0.09	1.43 (0.80-2.55)	0.23
PCT	16.42 (5.69-59.14)	<0.001	5.47 (1.32-9.05)	0.03

Table 3. Bacterial species in culture positive group

Pathogen	Bacteria detected, n (%)
Haemophilus influenzae	10 (26.32)
Haemophilus parainfluenzae	4 (10.53)
Pseudomonas aeruginosa	6 (15.79)
Acinetobacter baumannii	3 (7.89)
Streptococcus pneumoniae	5 (13.16)
Klebsiella pneumoniae	4 (10.53)
Escherichia coli	1 (2.63)
Staphylococcus aureus	4 (10.53)
Enterobacter cloacae	1 (2.63)

Diagnostic value of biomarkers in predicting bacterial infections

We performed the receiver operating characteristic curves (ROC) to assess the relationship between biomarkers and the bacterial infection in patients with AECOPD (**Figure 3**). Area under curves (AUCs) were calculated and as well as the sensitivity and specificity. The results showed that AUCs of CRP, PCT and SAA in the diagnosis of bacterial infection in patients with AECOPD were 0.875, 0.941 and 0.854, respectively. Diagnostic value of SAA was lower than PCT ($P=0.03$), but made no difference from CRP ($P=0.74$). The resulting specificity of PCT were as high as 92.50% and sensitivity of SAA were the highest among three biomarkers (sensitivity of SAA, 84.21%). Details were showed in **Table 4**.

Discussion

We confirmed the fact that CRP and PCT had an important role in predicting bacterial infection in patients with AECOPD and also found that SAA had higher sensitivity in predicting bacterial infection than CRP and PCT in patients with AECOPD. Besides, AECOPD patients seemed to have higher level of SAA on admission if they were infected with Hi or Hpi.

CRP level had been reported to be elevated in patients with AECOPD, especially in patients with increased sputum purulence on admission [14]. Ahmet Bircan found that the level of CRP in patients with AECOPD were significantly higher than that of patients with stable COPD. What's more, the value of CRP in discriminating bacterial AECOPD from nonbacterial AECOPD was acceptable. In another study, higher level CRP was observed in bacterial AECOPD compared with nonbacterial AECOPD and the cutoff values for CRP was 19.65 mg/L with a sensitivity of 78.18% and specificity of 84.61% [15]. It was interesting that we obtained similar results with Chunhong peng. ACU of CRP in predicting bacterial infection in patients with AECOPD was 0.875 and sensitivity and specificity was 68.42% and 85.00%, respectively. But the cutoff for CRP in our study was 31.68 mg/l. So it was obvious that results varied among studies. The reasons for the differences might be that patients with COPD in different studies were treated with different dosage and kinds of antibiotics and systemic steroids. Besides, inclu-

CRP, PCT and SAA in AECOPD patients

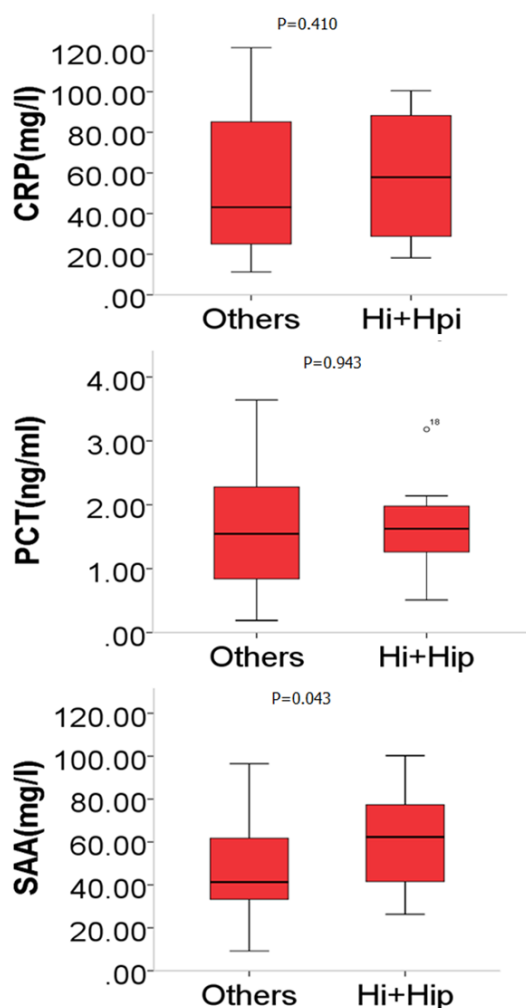


Figure 2. Comparison of CRP, SAA, WBC and PCT between different bacteria positive group. SAA of patients in Hi&Hpi group were significant higher than that of patients in other pathogens group (62.88 ± 22.37 vs 47.76 ± 21.97 , $p=0.043$). But no difference were observed between the two groups in level of CRP and PCT (61.84 ± 28.83 vs 53.27 ± 32.93 , $p=0.41$; 1.62 ± 0.69 vs 1.64 ± 0.93 , $p=0.94$, respectively).

sion and exclusion criterion differed among studies and thus brought additional influence to the level of CRP. So we should be cautious in dealing with these results. It was sure that CRP, as an inflammatory and acute phase protein, was certainly elevated in bacterial exacerbation which might causing more systemic inflammation than nonbacterial exacerbations [16]. But the role of CRP in predicting bacterial infection in patients with AECOPD were still unclear and more clinical studies with strict inclusion and exclusion criterion should be performed to investigate the role of CRP in AECOPD.

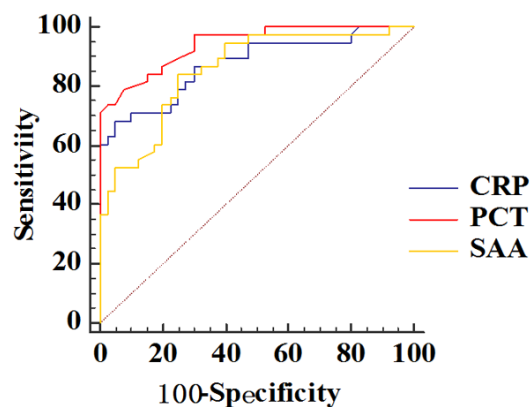


Figure 3. Comparison of the areas under the curve (AUC) of CRP, PCT and SAA in the diagnosis of bacterial infection in patients with AECOPD. AUCs of CRP, PCT and SAA in the diagnosis of bacterial infection in patients with AECOPD was 0.875, 0.941 and 0.854, respectively.

In previous study, Christ-crain found that patients in PCT group had a relative risk of 0.49 compared with standard group of antibiotic exposure [17]. Despite the fact that PCT is an important biomarker in guiding antibiotic therapy in AECOPD patients with bacterial infection, there were still several studies demonstrated no differences in PCT level between bacteria and nonbacterial AECOPD [18, 19]. Daniels JM found that PCT was no different between bacterial and nonbacterial AECOPD and patients with low PCT do benefit from antibiotic therapy. What's more, they found CRP was a more value biomarker in bacterial AECOPD patients. While in our study and several studies conducted by others, results showed that patients with bacterial infection had significant higher level of PCT than nonbacterial infection patients. Besides, PCT was significantly associated with bacterial infection in AECOPD patients after univariate and multivariate analysis. Similar results were reported in the previous study [20]. Specificity of PCT in discriminating bacterial from nonbacterial AECOPD varied from studies. GEIJN found specificity of PCT in predicting bacterial infection was 39% with AUC of 0.735, which was quite different from the results in other studies. Cut-off value for procalcitonin was 1.03 ng/ml with a specificity of 83% and sensitivity of 40% in previous study [21]. In our study, we demonstrated that PCT had a highest specificity in predicting bacterial infection in AECOPD patients compared with SAA and CRP. Interestingly, the cutoff values for PCT

Table 4. Diagnostic value of variables for bacterial infection in AECOPD

Variables	AUC	P vaule	95% CI	Cut-off	Sensitivity	Specificity	NPV	PPV
CRP	0.875	0.04	0.78-0.94	31.68	68.42	85.00	58.35	89.81
PCT	0.941	0.02	0.86-0.98	0.76	78.95	92.50	74.21	96.74
SAA	0.854	0.04	0.76-0.92	31.28	84.21	75.00	78.85	74.01

was 0.76 and the AUC was as high as 0.941. So we believed that PCT was a valuable biomarker in predicting bacterial infection in AECOPD patients.

Serum Amyloid A (SAA) were strongly induced in the liver by systemic infection. Several studies had demonstrated that SAA could be used as a predictable biomarker in patients with infection related diseases [22, 23]. But Junyan QU found that SAA was not a valuable biomarker in discriminating bacterial infection from nonbacterial infection [24]. Few studies were performed to investigated SAA and its role of SAA in predicting bacterial infection in AECOPD patients was still unclear. Gao, P found that patients with exacerbations of COPD were accompanied by higher concentration of serum SAA. This was the first studies to investigate SAA as predictable biomarker in bacterial AECOPD. We found that SAA was significantly higher in patients with bacterial AECOPD than nonbacterial AECOPD. What's more, the AUC of SAA was 0.854, which was comparable with CRP in AECOPD patients. The cutoff value was 31.28 mg/l with a specificity of 75.00% and sensitivity of 84.21%. Interestingly, AECOPD patients seemed to have higher level of SAA on admission if they were infected with Hi or Hpi. The results in our study showed SAA was a promising biomarker in predicting bacterial AECOPD, although more studies were still needed.

Study focused on comparison between CRP and PCT in predicting bacterial AECOPD were limited. Chih-Hao Chang reported that CRP and PCT had no difference in differentiate bacterial or viral infection in AECOPD [25]. While in another study, they demonstrated that PCT was better than CRP and neutrophil/lymphocyte ratio in predicting bacterial AECOPD, but the specificity was less than 80% and AUC was relatively low. AUC of PCT was higher that CRP in discriminating bacterial and nonbacterial AECOPD and PCT was better both in sensitivity and specificity when compared with CRP in our study. Still there was no other study performed to compared the diagnostic role of CRP, PCT and SAA in AECOPD patients.

Although studies varied in results, but the roles of CRP, PCT and SAA in predicting bacterial infection in patients with AECOPD were still promising. Our study provided more evidences to support the fact that CRP, PCT and SAA could be used as biomarkers in predicting bacterial infection in patients with AECOPD and therefore might be useful clinical markers in guiding antibiotic therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Yan Li, Department of Clinical Laboratory, Renmin Hospital of Wuhan University, No. 238 Jiefang Road of Wuchang District, Wuhan 430060, China. Tel: +86-27-88071553; E-mail: 2590246443@qq.com

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