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Optimal cut-off value of serum procalcitonin in predicting bacterial infection induced acute exacerbation in chronic obstructive pulmonary disease: A prospective observational study

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Abstract

Objective: To explore the optimal cut-off value of serum procalcitonin (PCT) level in predicting bacterial infection in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods: 204 hospitalized patients with AECOPD were enrolled in this study. Their diagnoses and treatments followed routine protocols in Fu-Xing Hospital affiliated to Capital Medical University, Beijing, China. Extra blood samples were taken for serum PCT level testing and the results were blinded to the treating physicians. On discharge, clinical data were collected and the treating physicians made comprehensive analyses to determine whether the AECOPD were triggered by respiratory tract bacterial infection or non-bacterial causes according to the "new diagnostic criteria" defined in this study. In the AECOPD patients with bacterial infection, treating physicians decided whether they had bacterial pneumonia based on imaging studies. Receiver operating characteristic curve (ROC) was used to analyze the accuracy of serum PCT level in predicting bacterial infection.

Results: In the 173 AECOPD patients who did not have pneumonia, 115 had evidences of bacterial infection while 58 did not. The median PCT levels were 0.1(0.08, 0.18) ng/ml and 0.07 (0.05, 0.08) ng/ml for each group, which were statistically different. The proposed optimal cut-off value of serum PCT level in predicting bacterial infection was 0.08 ng/mL according to this study, with a sensitivity of 81%, specificity of 67% and area under the ROC curve (AUC) of 0.794. There were 31 AECOPD patients diagnosed with pneumonia, their median PCT level was 0.23 ng/mL.

Conclusions: The serum PCT levels slightly increased in the majority of hospitalized patients with AECOPD compared with reference range. When PCT level was ≥0.08 ng/mL, AECOPD was more likely to be caused by bacterial infection. A significantly elevated PCT levels may indicate combination of AECOPD and bacterial pneumonia.

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Introduction

The prevalence of Chronic Obstructive Pulmonary Disease (COPD) is currently up to 13.7% in people 40 years or older in China.[1] Exacerbations of COPD are mainly triggered by respiratory viral infections although bacterial infections and environmental factors such as air pollution and ambient temperature may also initiate and/or amplify these events.[2] Research has shown that the overall prevalence of bacterial infection was approximately 50% in AECOPD patients,[3] however nearly 90% of hospitalized AECOPD patients were given antibiotics.[4,5] Overuse of antibiotics seemingly indeed exist in our clinical work which likely results in increased medical cost, side effects and bacterial resistance, due to sometimes ambiguity in discriminating bacterial from nonbacterial reasons causing AECOPD in our clinical settings.

One early study had indicated that Procalcitonin (PCT) as a biomarker had a high diagnostic accuracy in distinguishing bacterial from non-bacterial infections,[6] but two recent studies[7,8] came to an opposite conclusion. While the usefulness of PCT in predicting bacterial infection in AECOPD patients still remains controversial, no one universal cut-off value of PCT was proposed for this purpose,[9] as diagnosis of respiratory bacterial infection is often hampered by lack of ideal "gold standard".[10] The current GOLD guidelines recommend antibiotics use in patients of Anthonisen Criteria I and II with sputum purulence, assuming purulence of sputum indicating bacterial infection. Also sputum culture positivity was traditionally regarded as the conventional "gold standard" for diagnosis of bacterial infection. These approaches are sometime difficult to achieve in real clinical settings as some AECOPD patients have no sputum excretion or are given antimicrobial treatments before sputum samples are collected, which can lead to false negative culture results.

In this study, we redefined the "new diagnostic criteria" for bacterial infection based on clinical work. Different from previous studies that used sputum culture as the "gold standard" for the diagnosis of bacterial infection, the "new diagnostic criteria" included sputum purulence, elevated blood WBC and antibody positive for atypical pathogens in addition to positive sputum culture. Based on the new criteria we explored the optimal cut-off value of serum PCT level in predicting bacterial infection in hospitalized AECOPD patients. We hope it can help clinicians in rational antibiotic prescription and avoidance of antibiotic overuse.

Methods

Study design and patients

Prospective observational diagnostic study design. 237 consecutive patients with suspected AECOPD who were admitted to the respiratory medicine ward were recruited to this study from September 2013 to December 2015 in Fuxing hospital, a 820-bed general hospital located in Beijing, China. and affiliated to Capital Medical University.

COPD was diagnosed and managed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[11] AECOPD was defined as worsening of the patient's respiratory symptoms exceeding normal daily variations and requiring a change in regular treatment.

Exclusion criteria: (1) patients have confirmed diagnosis other than AECOPD such as chronic heart failure, acute pulmonary embolism, pneumothorax, bronchiectasis, asthma, etc., (2) patients have comorbidities affecting serum PCT levels such as chronic renal failure, trauma or surgery within past week, thyroid cancer and bacterial infection outside the respiratory system. (3) patients who are unable to provide accurate medical history. (4). patients are currently infected by special pathogens such as tuberculosis or fungi.

For those who were hospitalized multiple times during a year, patients with two hospitalization interval less than 1 month were excluded in this study.

Implementation of clinical diagnoses and treatments

Medical histories, symptoms and signs for enrolled patients who were suspected with AECOPD were collected and recorded by admitting residents. The attending physicians arranged a panel of related tests according to the patients' conditions, which included laboratory tests of blood, sputum, urine and stool, other tests such as electrocardiogram, pulmonary function test, chest radiographs, etc. were ordered accordingly.

Most of pulmonary function tests were performed after recoveries. For those patients who could not tolerate pulmonary function tests, previous results can be retrieved and used in the Electronic Medical Record System.

"Purulent" sputum was defined as a change in the color from "uncolored" to "yellow-green colored" of spontaneously expectorated samples.

Pneumonia was defined as a new pulmonary infiltrate on chest X-ray or CT.

Confirmation and differential diagnosis of AECOPD was made by the attending physicians, and appropriate treatments were given to each patient simultaneously. The end point was discharge and the clinical data were drawn and filled in the Clinical Research Form.

Pathogenic microorganism assessments

Sputum bacterial culture was performed according to the standard hospital procedures for microbiological surveys. Gram stain was performed and sputum quality was assessed. The presence of ≥25 neutrophils and ≤10 squamous epithelial cells per low-power field in gram-stained sputum, and/or white blood cell/squamous cell ratio ≥2.5 were defined as a qualified specimen. The concentration of pathogenic bacteria or conditional pathogenic bacteria isolated from sputum semi-quantitative culture was +++ or ++++ was considered positive for sputum culture.

The presence of IgM antibodies for *Mycoplasma*/*Chlamydia*/legionella, or a fourfold or greater rise of IgG antibody titers were regarded as positive atypical pathogen infection.

Definition of "new diagnostic criteria (standard)" for bacterial infection

We defined a set of new diagnostic criteria for bacterial infection in AECOPD patients. The diagnostic criteria are as followings:

(1) purulent sputum appearance during the current exacerbation, (2) positive bacterial culture results of qualified sputum specimens, (3) blood WBC≥10x10^9/L and/or neutrophil/leucocyte ratio≥ 85% with exclusion other causes for the increase; (4) serum atypical pathogen antibody positive (IgM+ or double serum antibody IgG four-fold increase over 2 weeks). Patient meet any one of items 1–4 item was diagnosed with bacterial infection, others were diagnosed with non-bacterial infection.

Before discharge, the definitive diagnosis of bacterial infection was made by the attending physicians according to the new defined diagnosis standard and filled in the Clinical Research Form.

Serum PCT measurement

An additional 3 mL blood sample was collected for PCT level assay at the first venous blood collection for each patient. Serum PCT level was measured on Roche's automatic electrochemical luminescence immunoassay system (cobas e601), Elecsys BRAHMS PCT reagent, range of measurement 0.02–100 ng/mL, and the functional sensitivity ≤0.06 ng/mL, normal reference value of PCT level in healthy people is 0–0.05 ng/mL. The results of PCT were blinded to the physician till the end of the study.

Statistical analyses

Statistical analyses were performed using SPSS 21.0 software(Chicago, Illinois, USA). Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and non-normally distributed variables were expressed as median (interquartile range, IQR). Categorical data were expressed as number (percent %). Two independent sample T tests were used to compare means and the Mann-Whitney U test was used to compare ranks. Categorical data were compared using Chi-Square test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the accuracy of PCT level for predicting bacterial infection in hospitalized patients with AECOPD. All statistical tests were two tailed and the significant level was set at 0.05.

Results

A total of 237 hospitalized patients with suspected AECOPD were recruited, 204 patients were enrolled eventually. According to chest X-ray or CT, 173 patients were qualified with non-pneumonia-AECOPD, 31 cases were diagnosed with pneumonia-AECOPD.

Of the 173 non-pneumonia AECOPD patients, 115 were diagnosed with bacterial infection and 58 without according to the "new defined criteria" mentioned above. Flow Chart of inclusion and exclusion was shown in Figure 1.

In all patients diagnosed with non-pneumonia-AECOPD, 81 were reported with purulent sputum, 37 patients had positive sputum bacterial culture (49 isolates), 42 patients had elevated WBC and/or neutrophils and seven patients had positive IgM/IgG antibodies of atypical pathogens.

In positive sputum culture, bacteria distribution was as follows: *Escherichia coli* 6, *Enterobacter cloacae* 7, *Klebsiella pneumoniae* 5, *Serratia marcescens* 3, *Haemophilus influenza* 1, *Pseudomonas aeruginosa* 11, *Acinetobacter baumannii* 8, *Stenotrophomonas maltophilia* 5, *Staphylococcus epidermidis* 1, *Staphylococcus aureus* 2.

Baseline characteristics and clinical finding were compared between bacterial and nonbacterial group patients. There was no significant difference between the two groups except for that patients with bacterial infection were more likely to appear with crackle sound and patients with nonbacterial were more likely to have wheezing sound on auscultation. The detailed information was shown in Table 1.

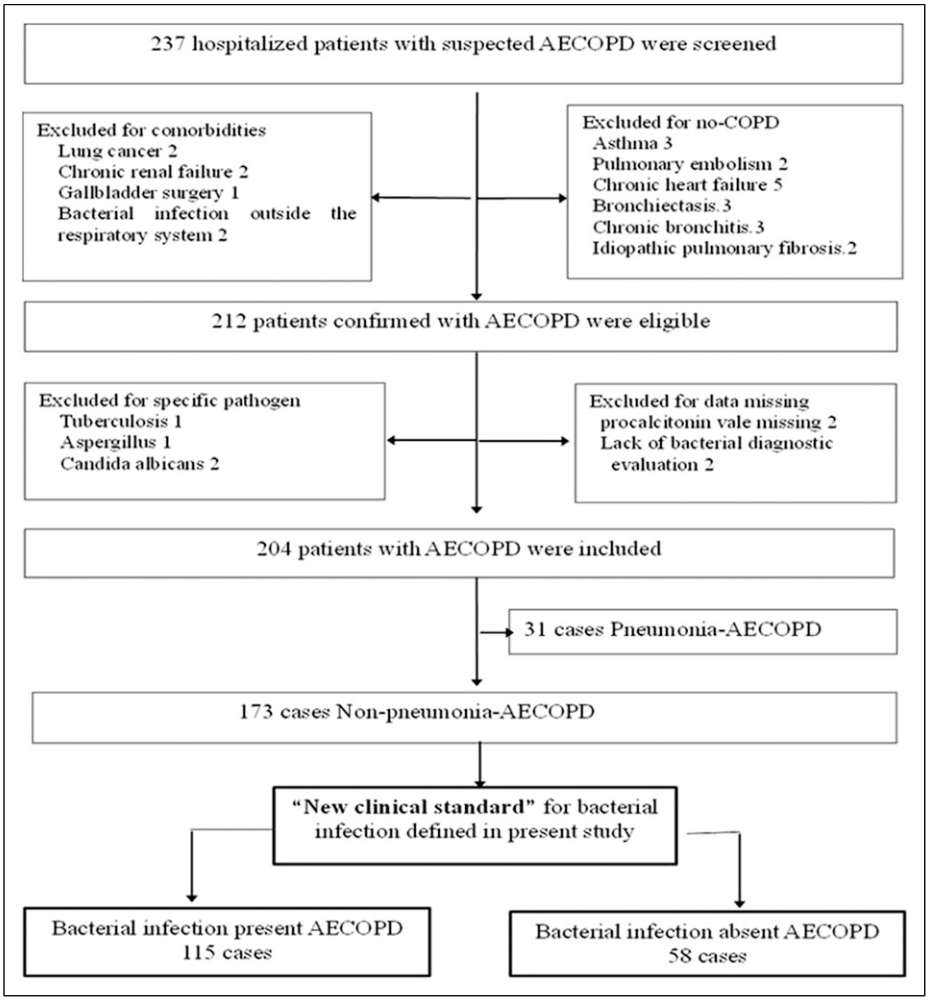

Figure 1. Flow chart of the study population with AECOPD AECOPD: acute exacerbation of obstructive pulmonary disease.

Under different diagnostic standards for bacterial infections, the ROC curves for PCT in predicting bacterial infections in patients with AECOPD are different. When positive sputum culture was regarded as diagnostic standard (conventional standard A), 37 cases were diagnosed with bacterial infection. When purulent sputum was regarded as diagnostic standard (conventional standard B), 81 cases were diagnosed with bacterial infection. According to the "new defined standard" for the diagnosis of bacterial infection mentioned above in our study, 115 cases were diagnosed with bacterial infection. ROC curves were shown in Figure 2.

The different cut-off values of PCT level in predicting bacterial infection under the "new diagnostic criteria" were showed in Table 2.

Using conventional diagnostic standard A and B for diagnosing bacterial infection, the optimal cut-off values of serum PCT level were 0.15 ng/mL and 0.1 ng/mL respectively. Using 0.25 ng/mL as the cut-off value appears high in specificity but too low in sensitivity.

We use "new defined diagnostic criteria" of bacterial infection in this study. The accuracy of serum PCT level in predicting bacterial infection in AECOPD patients was evaluated. Receiver Operating Characteristic (ROC) curve was drawn, and the area under the curve (AUC) was 0.794, 95% confidence interval [CI] (0.727, 0.860, $p < .001$). Based on the maximization of the Youden's index, the optimal cut-off value of PCT for the diagnosis of bacterial infection was 0.08 ng/mL with the sensitivity and specificity as 81% and 67% respectively. The detailed information about the accuracy of serum PCT level for detecting bacterial infection in AECOPD was shown in Table 3.

The median serum PCT level was 0.08(0.06, 0.13) ng/ml for patients with non-pneumonia-AECOPD, 0.1(0.08, 0.18) ng/ml and 0.07 (0.05, 0.08) ng/ml for subgroups of bacterial infection and non-bacterial infection respectively. Mann-Whitney U test was used to compare the difference between the two groups. $Z = -6.331$, $p < 0.001$, PCT levels were significantly higher in patients with bacterial infection than in patients without bacterial infection.

Table 1. Baseline characteristics and clinical findings in AECOPD patients with bacterial infection group compared with patients without bacterial infection group.

Groups Variables	Bacterial infection *N* = 115	Nonbacterial infection *N* = 58	*p* value
Baseline characteristics			
Age, y, median(IQR)	82(8)	81(6)	.067
Male, *n* (%)	75(65.2)	34(58.6)	.396
Smoking history, *n* (%)	91(79.3)	42(72.4)	.344
Current smokers, *n* (%)	18(15.6)	10(17.2)	.619
Comorbidity, diabetes, *n* (%)	16(13.9)	9(15.5)	.777
Congestive heart failure, *n* (%)	31(26.9)	16(27.6)	.930
Length of illness prior to admission, d	5(3)	6(2)	.424
Antibiotic use prior to admission, *n* (%)	35(30.4)	10(17.2)	.069
Chronic oral steroid use, *n* (%)	6(5.2)	2(3.4)	.889
Chronic inhaled steroid use, *n* (%)	93(80.8)	41(70.1)	.130
GOLD stage, lung function, *n* (%)			
I (FEV1 ≥ 80% of predicted)	7(6.1)	3(5.2)	1.000
II(50%≤FEV1<80% of predicted)	43(37.4)	20(34.5)	.741
III(30% ≤ FEV1 < 50% of predicted)	47(40.9)	22(37.9)	.745
IV(FEV1 < 30% of predicted)	18(15.7)	13(22.4)	.298
Clinical findings at admission			
Dyspnea, *n* (%)	109(94.8)	54(93.1)	.234
Increased volume of sputum, *n* (%)	81(70.4)	38(65.5)	.510
Upper respiratory tract infection, *n* (%)	59(51.3)	33(56.8)	.521
Temperature, °C,mean(SD)	36.8(0.8)	37.2(0.6)	.075
Respiratory rate, breaths/min, median(IQR)	22(5)	21(6)	.526
Heart rate, beats/min, median(IQR)	100(13)	98(14)	.419
systolic Blood pressure, mmHg, mean(SD)	130(15)	132(15)	.365
diastolic Blood pressure, mmHg, mean(SD)	75(15)	78(13)	.327
Oxygen saturation,%, median(IQR)	92(5)	91(5)	.263
Moist rale, *n* (%)	76(66.1)	25(41.3)	.005※
Dry rale, *n* (%)	65(56.5)	43(74.1)	.030※

Values are presented as *n* (%), median ((IQR) or mean (SD); groups are based on the new diagnostic criteria. AECOPD: acute exacerbation of chronic obstructive pulmonary disease; FEV1: forced expiratory volume in the first second; GOLD: Global Initiatives for Chronic Obstructive Lung Disease; IQR: interquartile range; SD: standard deviation.

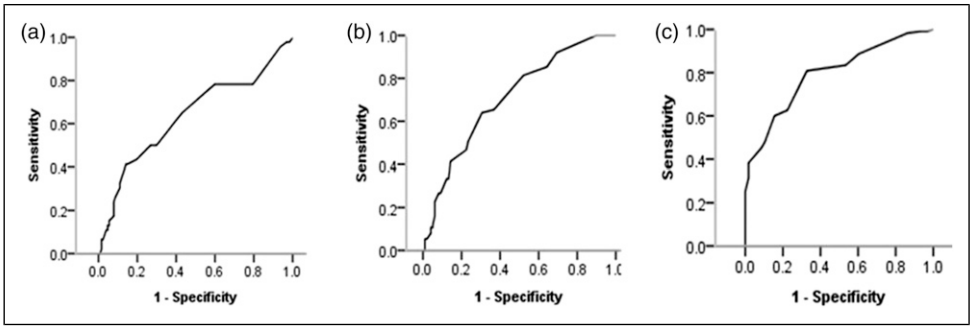

Figure 2. Under different diagnostic standard, the ROC curves for PCT in predicting bacterial infections in hospitalized patients with AECOPD (a) positive sputum culture as the diagnostic standard for bacterial infection (b) purulent sputum as the diagnostic standard for bacterial infection (c) new clinical standard for bacterial infection defined in the present study.

Table 2. Diagnostic efficiency of PCT level in predicting bacterial infection in patients hospitalized with AECOPD under different diagnostic standard.

Diagnostic standard	PCT cut-off value(ng/ml)	Sensitivity (%)	Specificity (%)	AUC	95% CI
Conventional standard A	0.1	61	60	0.635	0.534–0.736
	0.25	24	92		
	*0.15	41	86		
Conventional standard B	0.1	64	69	0.707	0.631–0.784
	0.25	20	94		
	*0.1	64	69		
New defined clinical standard	0.1	60	85	0.794	0.727–0.860
	0.25	18	96		
	*0.08	81	67		

Conventional standard A: positive bacterial culture of qualified sputum specimens as diagnostic standard for bacterial infection.
Conventional standard B: purulent sputum appearance during the current exacerbation as diagnostic standard for bacterial infection.
New defined clinical standard: (1) purulent sputum appearance during the current exacerbation, (2) positive bacterial culture results of qualified sputum specimens, (3) blood WBC≥$10x10^9$/L and/or neutrophil/leucocyte ratio≥ 85% with exclusion other causes for the increase; (4) serum atypical pathogen antibody positive (IgM+ or double serum antibody IgG four-fold increase over 2 weeks) Hospitalized patients with AECOPD meet any one of items 1–4 was diagnosed with bacterial infection.
*optimal cut off value; AUC: area under the curve; 95% CI: 95% confidence interval.

Table 3. Efficiency of the serum PCT level for detecting bacterial AECOPD based on the new diagnostic criteria (optimal cut-off value of 0.08 ng/mL) (*N* = 173).

Evaluation index	Value	Standard error	95% confidence interval
Accuracy	0.763	0.032	(0.700,0.826)
Sensitivity	0.809	0.037	(0.736,0.882)
Specificity	0.672	0.062	(0.550,0.794)
Youden index	0.481	0.072	(0.340,0.622)
Positive likelihood ratio	2.466	1.213	(1.689,3.601)
Negative likelihood ratio	0.284	1.260	(0.181,0.447)
Positive predictive value	0.830	0.035	(0.761,0.899)
Negative predictive value	0.639	0.061	(0.519,0.759)

The median serum PCT level was 0.23(0.12, 1.4) ng/ml in patients with AECOPD combined with pneumonia (pneumonia-AECOPD), which was significantly higher than serum PCT level 0.08(0.06, 0.13) ng/ml in patients with non-pneumonia-AECOPD. Comparison of distribution of PCT values in different groups was shown in Figure 3.

In patients with non-pneumonia-AECOPD, 21 out of 173 (12%) patients had serum PCT level ≥0.25 ng/ml, and 95/173 (55%) with PCT level <0.1 ng/ml.

Discussion

This was a real-world study. The result showed that majority of the hospitalized AECOPD patients have slight elevated serum PCT levels, and the optimal cut-off value of serum PCT level in predicting bacterial infection in those patients might be around 0.08 ug/mL.

Different from previous studies in which sputum culture was used as the "gold standard" for the diagnosis of bacterial infection in low respiratory tract infection,[12,13] we defined a "new diagnostic criteria" of bacterial infection in this study. Besides positive sputum culture, purulent sputum, increased blood WBC and atypical pathogens antibody positivity were all included in the diagnostic criteria. The "new diagnostic standard" was established for the following reasons:

First of all, sputum culture was regarded as the conventional "gold" standard for diagnosis of bacterial infection with obviously limitations. As many patients had been given with antimicrobial treatments before sputum samples were collected for bacterial culture in clinical practice, which will result in false negative culture. Meanwhile, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella* catarrhiae are the top three pathogens of lower respiratory tract infection, but routine sputum culture often reaches false negative results as they are fastidious to the culture environments. Real-life data on antibiotic prescriptions and sputum cultures in AECOPD showed that pathogens relevant in AECOPD were only detected in 19% of cultures[14]

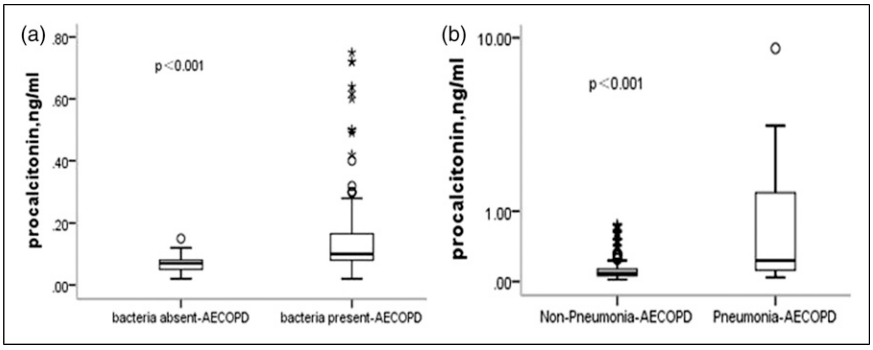

Figure 3. Distribution of PCT values in different group patients. *bacterial absent/present groups are based on the new defined diagnostic criteria for bacterial infection (a): comparison of PCT level between bacterial and non-bacterial infection patients(non-pneumonia-AECOPD) (b): comparison of PCT level between pneumonia-AECOPD and non-pneumonia-AECOPD patients.

Secondly, Sputum purulence is the best indicator of presence of bacteria pathogens in low respiratory infection. Soler et al.[15] reported that with quantitative cultures of protected specimen brush samples as the gold standard, the self-reporting presence of purulent sputum can predict the presence of bacterial infection in the distal airways. Another pooled analysis[16] also revealed that sputum color was a stronger predictor of potentially pathogenic bacteria in chronic bronchitis exacerbations. Similar results[17,18] were reported recently and GOLD 2020 highlights that purulent sputum is important in the decision to prescribe antibiotics for AECOPD.

Thirdly, increased blood WBC count/neutrophils and positive serum antibody of atypical pathogens have good diagnostic values for bacterial infection and atypical pathogen infection respectively. *Mycoplasma* infection was categorized as bacterial infection in our study as they play an important role in AECOPD in China[19] and antibiotics are needed for its treatment.

Based on reasons mentioned above and reference to the diagnostic criteria of pneumonia,[20] we defined a "new diagnostic standard" for determining bacterial infection in hospitalized patients with AECOPD in our study. Under the "new diagnostic standard", the AUC value of ROC for diagnosis of bacterial infection was 0.794, which was superior to 0.635 and 0.707 when under the conventional diagnostic standards.

Under the "new diagnostic criteria", the optimal PCT cut-off value was 0.08 ng/mL for predicting bacterial infection in the present study, which was lower than previous studies advocated. Chang et al.[12] showed that the optimal threshold of PCT for predicting bacterial infection in AECOPD patients was 0.155 ng/ml. Stolz et al.[21]reported that the optimal cut off level of PCT indicating bacterial infection was 0.1 ng/mL. One study on 63 patients with severe AECOPD admitted to the ICU showed the optimal threshold level for identifying bacterial infection with PCT was 0.25 ng/mL[22]. Another two studies reported that the best cutoff value of serum PCT levels were 0.4 ng/mL and 0.5 ng/mL respectively.[23,24]

The optimal cut off value of serum PCT for predicting bacterial infection varied from study to study and reasons may be as follows. Firstly, standards for diagnosing bacterial infections were different. Secondly, there was great heterogeneity among different studies. Thirdly, the PCT detection methodologies and the reference ranges varied in different studies. So, when reported optimal cut off value of serum PCT level in predicting bacterial infection, first of all, we should indicate the standard of diagnosis of bacterial infection.

In our opinion, the fundamental purpose of investigating the threshold of PCT level for predicting bacterial infection is for better antibiotic use in clinical practice. Early studies reported that PCT-based protocols can decreased antibiotic prescription without affecting clinical outcomes.[25,26] But a recent study indicate that PCT-directed antibiotic therapy does not significantly reduce antibiotic-days.[27]

It is seemingly that this controversy still exists regarding the value of PCT level and antibiotic use in patients with AECOPD. In fact, the presence of bacterial infections does not mean that antibiotic treatment is necessarily required, as many mild infections with self-limiting. Just as the results of the classic double-blind randomized controlled trial (RCT) led by Anthonisen showed that AECOPD patients who received placebo also had a high remission rates.[28] Although the serum PCT level has a good capability in distinguish bacterial from non-bacterial infections, decisions of antibiotic use in patient are complex, beside the probability of bacterial infection and the serum PCT level, the severity of the clinical condition of the patients should be considered.

Moreover, in agreement with previous studies, serum PCT level can distinguish pneumonia-AECOPD patients from non-pneumonia-AECOPD patients.[29,30] In addition, our study results show that 67% (115/173) of the studied patients were diagnosed with bacterial infection, which was

higher than 50% reported in the previous study. The reasons may be as followings. Firstly, patients in our study were older with the median age as over 80 year old. Secondly, seven patients with positive IgM/IgG antibodies of atypical pathogens were included. Thirdly, bacterial and viral co-infections were more frequent at exacerbation state, as a recent study reported.[31]

In all, on account of the obvious limitation of using positive sputum culture as the "gold standard" for the diagnosis of bacterial infections, we defined new clinical diagnostic criteria and re-evaluated the optimal threshold value of serum PCT level in trying to predict bacterial infection in those patients. The results showed that the possible optimal cut-off value of serum PCT level in predicting bacterial infection in AECOPD was 0.08 ng/mL.

Limitations of the present study are as followings. First of all, it is a single center study. Secondly, some cases with antibiotics use prior to hospitalization were not excluded. Thirdly, purulent sputum was defined according to the patients' own reports without color card comparison. Further studies needed to confirm the conclusions drawn from current study.

Conclusion

Under the new defined diagnostic criteria for bacterial infection, the optimal cut-off value of serum PCT level in predicting bacterial infection in hospitalized patients with AECOPD is 0.08 ng/mL. Serum PCT level ≥0.08 ng/mL might indicate AECOPD is caused by bacterial infection, with an accuracy rate of 76%. The serum PCT levels slightly increased in the majority of hospitalized patients with AECOPD. A significantly elevated PCT level often indicates combination of AECOPD and bacterial pneumonia.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was approved by the ethics committee of Fu-Xing hospital affiliated to Capital Medical University.

Informed consent

All patients was informed consent.

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