Int J Clin Exp Pathol 2016;9(7):6804-6812
www.ijcep.com /ISSN:1936-2625/IJCEP0025186

Original Article

PCT, CRP, Ang-2 expressions and SGRQ scores for assessing post-treatment health status of AECOPD patients

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Received January 29, 2016; Accepted May 20, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: Background and aim: Our study is aimed at clarifying the interrelationship among PCT, CRP, Ang-2 and SGRQ in post-treatment patients with AECOPD. This study also confirmed that whether or not PCT, CRP, Ang-2 and SGRQ are appropriate biomarkers for assessing the efficacy of AECOPD treatments. Material and methods: The case group incorporated 88 patients with AECOPD and another 40 patients with stable-stage COPD admitted in our hospital during the period between April 2015 and October 2015. We also recruited a total of 50 healthy individuals as the control group in order to carry out this case-control study. All patients in the case group have received conventional symptomatic treatments. Serum samples were collected from all study subjects for detecting PCR, CRP and Ang-2 expressions. Meanwhile, the Saint George's respiratory questionnaire was specifically designed to assess and quantify the health status and life wellbeing of all individuals who participated in this study. Statistical analysis was carried out using the SPSS 19.0 statistical software. Results: PCT, CRP and Ang-2 expression levels were all increased in COPD patients compared to normal people. Furthermore, PCT, CRP and Ang-2 expression levels in AECOPD patients were much higher than those in stable-stage COPD patients (all $P < 0.05$). PCT, CRP and Ang-2 expression levels in the better group appeared to be gradually decreased as time of treatment increased. By contrast, Ang-2, PCT and CRP expression levels were increased in the worse group as time of treatment increased (all $P < 0.05$). Results from statistical analysis indicated that both CRP and PCT expression levels were positively correlated with Ang-2 expression. As suggested by correlation analysis, PCT, CRP and Ang-2 expression levels were closely related to the health status and wellbeing of patients with AECOPD. Conclusion: Serum PCT, CRP and Ang-2 are effective biomarkers of acute exacerbated COPD and they can be used to determine the severity of COPD as well as the effectiveness of treatments on AECOPD.

Keywords: PCT, CRP, Ang-2, SGRQ, AECOPD patients, treatment effect

Introduction

Chronic obstructive pulmonary disease (COPD) was a major global health issue characterized by progressive irreversible airflow obstruction which is typically caused by smoking and continuous exposure to indoor biomass fuels [1, 2]. COPD is usually presented with the onset of chronic respiratory symptoms and exercise limitation which may trigger undesirable effects on health status and exacerbate over the short, medium and long-term [3, 4]. Recently, both the morbidity and mortality of COPD were steadily rising and COPD has been ranked as the most life-threatening chronic disease over the world [5, 6]. Acute exacerbation of COPD (AECOPD) is presented if symptoms of COPD patients including cough and shortness of breath exacerbation, increased sputum volume and purulent sputum were progressed to severe fever and inflammation which may have substantially negative impact on lung function and wellbeing of patients [7]. Several risk factors for COPD have been identified and respiratory infections, particularly bacterial infection is the most critical one. Antibiotics are often used to relieve symptoms, shorten the duration of AECOPD and reduce airway bacterial load in patients with COPD caused by bacterial infection [8]. As a result, it is worthwhile to discover other indicators for early detection and diagnosis of COPD.

Procalcitonin (PCT), a propeptide of calcitonin, is a glycoprotein without hormone activity [9]. PCT expression synthesized and secreted from liver macrophages, lung lymphocytes and endocrine cells was significantly increased when infections occur. However, autoimmune inflammation or virus infection is not able to elevate PCT expression. Thus, PCT was considered to be a valuable marker for detecting inflammation [10]. Meanwhile, plasma CRP exhibited a sharp rise in acute phase when tissue injury and infection occurred. As a non-specific inflammatory marker, CRP is able to activate and strengthen the role of phagocytic cells. Moreover, CRP concentration was closely correlated with infection degree and it offers greater sensitivity than white blood cells with respect to neutrophil count, erythrocyte sedimentation rate and temperature. Apart from that, hormones, immunosuppressive agents or an anti-inflammatory drug is not able to affect CRP concentration [11]. Formal studies have suggested that serum hs-CRP concentration in patients with AECOPD was related to infection severity [12]. Ang-2 is an endothelial cell-specific angiogenic factor and it is able to combine with the endothelial-specific receptor tyrosine kinase Tie-2 for triggering the degradation of vascular basement membrane and loss of endothelial cell homeostasis. Furthermore, Ang-2 plays an important role in pathological angiogenesis by increasing vascular leakage, inducing endothelial cell division and forming new blood vessels in a non-sprouting style [13]. Ang-2 was mainly expressed in vascular endothelial cells and stored in Weibel-Palade bodies (WPB). Ang-2 expression is increased and released from WPB in the case of inflammation, ischemia, hypoxia and other unusual circumstances [13]. Therefore, the above molecules might be used as predictive markers for detecting patients with AECOPD.

Clinical indicators such as lung function are difficult to be comprehensively evaluated due to different physical, emotional and social status of patients. Life wellbeing status is a comprehensive assessment index which thoroughly reflects patients' physiological function, mental health and other health status with a high sensitivity [14]. Currently, SGRQ is the most widely accepted questionnaire for assessing health status of respiratory disease and it has become extremely popular for quantifying and evaluating patients' wellbeing. Scores of SGRO not only provide reliable information for lung function and clinical symptoms but also are superior over other respiratory questionnaires [15]. Therefore, SGRO is a desirable criterion for evaluating treatment efficacy as well as health status and life wellbeing of patients with COPD.

However, how the interrelationship among PCT, CRP and Ang-2 influences the health status and life quality of patients with AECOPD is still unknown. As a result, this case-control study may address this issue and clarify the prognostic value of PCT, CRP and Ang-2 in AECOPD.

Materials and methods

Study objects

A total of 128 patients with chronic pulmonary obstruction disease (CODP) were recruited from the China-Japan Union Hospital of Jilin University from April 2015 to October 2015. The case group included 82 males and 46 females. As suggested by clinical conditions, CODP patients were divided into 2 groups: AECOPD group (88 acute exacerbation COPD patients) and stable COPD group (40 stable-stage COPD patients). In addition, we also recruited 50 healthy people as the control group (23 males, 27 females). All patients received conventional symptomatic treatments such as oxygen, anti-infection, reduce phlegm and smooth wheezing after admission. Patients with respiratory disease, systemic inflammatory disease or history of allergies were excluded from this study. All subjects agreed to participate in this study and signed a written consent form. This study was unanimously approved by the ethics committee of China-Japan Union Hospital of Jilin University.

Collection of patient general information

Patient information such as such as age, sex, clinical symptoms, health status and wellbeing were recorded before and after the treatment.

Blood samples collection

Normal physical examinations were conducted for all patients and 5 mL venous blood samples were collected. Then samples were performed with water bath for 30 min and centrifugal separation of serum was carried out with 3000 r/min in 15 min. In addition, 5 ml venous blood were collected again from patients in 1, 3, 7

Table 1. Basic information of individuals in AECOPD group, Stable COPD group and Control group

Group	AECOPD (n = 88)	Stable COPD (n = 40)	Control (n = 50)	Test value	*P* value
Age	70.66±8.20	68.64±6.09	67.88±7.26	F = 2.464	0.088
Gender					
Male	55	27	23	X^2 = 5.312	0.076
Female	33	13	27		

F: Test value of One-way ANOVA test; X^2: Test value of Chi-square test.

Table 2. The expression level of PCT, CRP and Ang-2 of patients in three groups with SGRQ score before radiotherapy

Group	No	PCT (μg/L)	CRP (mg/L)	Ang-2 (ng/L)	SGRQ score
AECOPD	88	30.18±3.87	29.17±10.47	144.74±22.88	69.78±10.37
Stable COPD	40	14.40±1.08	9.00±3.98	83.56±30.77	43.22±9.85
Control	50	0.33±0.16	2.94±1.08	70.61±20.16	6.45±2.39
H value		1891	218.2	181.0	836.4
P value		< 0.001*	< 0.001*	< 0.001*	< 0.001*

*: $P < 0.05$.

days after treatment. After that, all blood samples were added into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes and centrifugal separation was conducted with speed of 1000 * g for 15 min. Then supernatant were stored at in a -70°C refrigerator for further experiments.

Detection of PCT, CRP and ANG-2 expressions

Electrochemiluminescence immunoassay (Roche cobase 411 electrochemical luminescence analyzer and reagent) was performed to detect PCT expression extracted from the serum of patients with a normal value of 0~0.5 ng/ml. Double optical path immune turbidity analyzer together with other related reagents were used to detect the expression level of CRP with a range of 0~10 mg/L. Double antibody sandwich enzyme-linked immunosorbent assay (ELISA) was developed for determining Ang-2 expression level in plasma and the operation was strictly complied with the specified instruction. The experiment Kit was provided by Beijing Branch Surplus Technology Co., LTD and all specimens were performed by the same experienced researcher.

Life wellbeing assessment

Saint George's respiratory questionnaire (SGRQ) was submitted for self-assessment of health status on the same day when blood samples were collected. SGRQ included 50 questions which were divided into three main areas: respiratory symptoms (cough, sputum, asthma attacks, etc.), activity limitations (climbing, dressing, games, household, etc.) and the disease effect (insecurity, anxiety, pain, disappointment, etc.). Scores of SGRQ range from 0 to 100 and lower SGRQ scores indicate more effectiveness of the SOPD treatment. The calculation of SGRQ scores was based on the weighted average method and each question of SGRQ was evaluated using results from previous research, experience and different statistical weighting approaches. If a specific question significantly affects life wellbeing of patients, then it will be assigned to a larger weight. Finally, scores from the three major parts were combined in order to obtain the final score. A score of 0 indicates that the disease does not have any effect on health status and life wellbeing of subjects whereas a score of 100 suggests that the disease have extremely significant impact on the life wellbeing of subjects. Moreover, SGRQ was answered with the following requirements: 1) All questions should be answered by patients themselves without any discussion with their families. 2) Doctors should not explain or interpret questions which are not understood by patients and patients should carefully answer all questions. 3) Physicians were responsible for checking all questions in order to make sure that all questions have been answered once patients completed their own SGRQ.

All questions of SGRQ were answered within 30 minutes and statistical software was used for score evaluations.

Grouping decision criteria

Patients with significantly reduced cough, less phlegm and fewer asthma symptoms were defined as the better group. Also, improved uri-

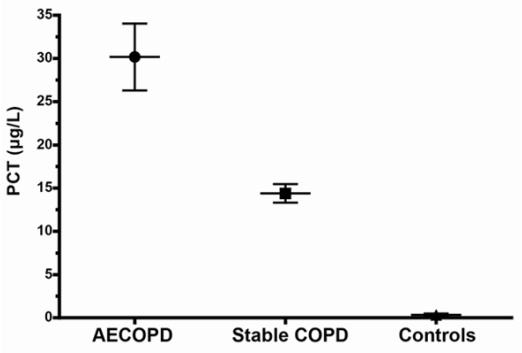

Figure 1. The expression level of PCT in the serum of individuals. AECOPD: patients with AECOPD. Stable COPD: COPD patients in stable stage. Controls: healthy people without COPD.

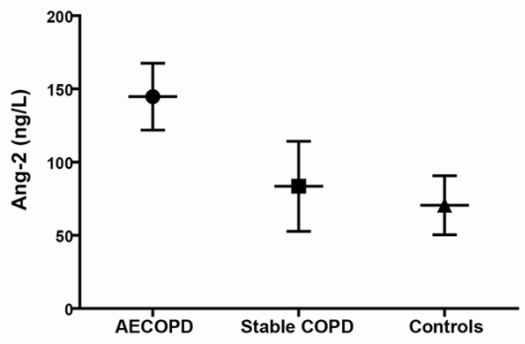

Figure 3. The expression level of Ang-2 in the serum of individuals. AECOPD: patients with AECOPD. Stable COPD: COPD patients in stable stage. Controls: healthy people without COPD.

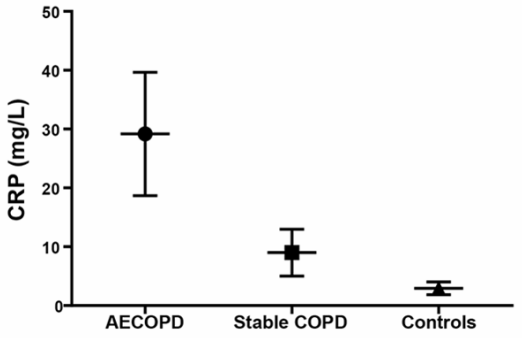

Figure 2. The expression level of CRP in the serum of individuals. AECOPD: patients with AECOPD. Stable COPD: COPD patients in stable stage. Controls: healthy people without COPD.

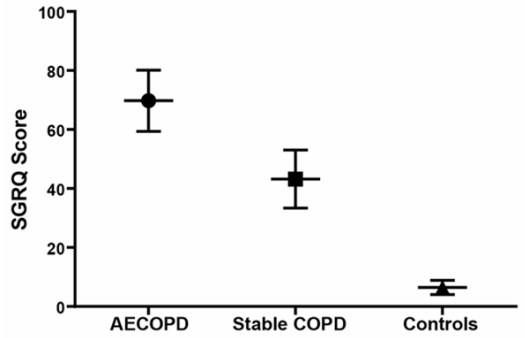

Figure 4. The SGRQ score of people in this study. AECOPD: patients with AECOPD. Stable COPD: COPD patients in stable stage. Controls: healthy people without COPD.

nalysis performance in the better group was reflected by reduced lung sound of patients. If cough, phlegm or asthma symptoms were not significantly reduced after treatment, then patients were included in the worse group in which subjects exhibited worse urinalysis which was characterized by insignificant reduction of lung sound.

Statistical analysis

SPSS19.0 statistical software was used for statistical analysis throughout the entire study. Counted data were expressed in the number of cases, while measurement data were expressed with mean ± standard deviation. Difference in continuous variables between two groups was evaluated using the t-test whereas difference in continuous variables among more than 2 groups was analyzed using the one-way analysis of variance (one-way ANOVA). Counted or categorical variables were analyzed using the chi-square test. Besides that, correlation analysis was carried out to determine whether or not there was a significant correlation between two continuous variables. Two-sided $P < 0.05$ provided evidence of statistical significance for all statistical tests.

Results

Demographic features of subjects in the AECOPD, stable SOPD and control group

As shown in **Table 1**, AECOPD group incorporated a total of 88 cases (55 males and 33 females) with an average age of 70.68±8.20 and a range between 50 and 90 years old. The stable COPD group included 40 patients (27 males and 13 females) with a mean age of 68.64±6.09 years and range between 50 and 90 years. Another 50 healthy subjects were

Table 3. The expression level of PCT, CRP and Ang-2 with SGRQ score of individuals in different groups after treatment

Index	Group	Day 1	Day 3	Day 7	P_{D3}-D1	P_{D7-D3}
PCT (μg/L)	Better (n = 61)	2.73±1.33	1.68±0.86	0.32±0.14	< 0.001*	< 0.001*
	Worse (n = 27)	2.73±1.34	4.78±3.21	6.87±5.13	0.035*	0.080
CRP (mg/L)	Better (n = 61)	13.79±6.96	9.31±4.01	3.21±1.71	< 0.001*	< 0.001*
	Worse (n = 27)	13.98±6.78	19.63±13.05	25.76±16.07	0.051	0.130
Ang-2 (ng/L)	Better (n = 61)	287.60±18.35	247.63±13.44	187.50±12.34	< 0.001*	< 0.001*
	Worse (n = 27)	287.60±18.46	344.8±20.61	468.60±25.47	< 0.001*	< 0.001*
SGRQ	Better (n = 61)	67.48±6.69	48.37±9.31	32.64±12.07	< 0.001*	< 0.001*
	Worse (n = 27)	67.48±6.73	114.87±18.20	135.79±20.91	< 0.001*	< 0.001*

*: $P < 0.05$.

included in the control group (23 males and 27 females) with a mean age of 67.88 ± 7.26 years and range between 50 and 90 years. As suggested by statistical analysis, there was no significant difference in age or sex among the AECOPD, stable COPD and control group ($P > 0.05$).

Association between pre-treatment expression of PCT/CRP/Ang-2 and life wellbeing status

As suggested by **Table 2**, PCT expression in AECODP patients was greatly higher than that of stable COPD patients ($P < 0.05$); while subjects in the control group exhibited a lower serum PCT level compared with AECOPD patients ($P < 0.05$) (**Figure 1**). Furthermore, CRP expression level of subjects in the control group was significantly lower than that of patients in the stable COPD group ($P < 0.05$). Stable COPD patients exhibited notably lower CRP expression level compared with AECOPD patients ($P < 0.05$) (**Figure 2**). In addition, subjects in the control group exhibited significantly lower Ang-2 expression level compared with patients in the AECOPD group ($P < 0.05$) and stable COPD patients exhibited lower Ang-2 expression level compared with AECOPD patients ($P < 0.05$) (**Table 2**). Also, Ang-2 expression in healthy individuals was significantly reduced compared with the stable COPD group ($P < 0.05$) (**Figure 3**). More importantly, subjects in the AECOPD group exhibited the highest SGRQ score in comparison to other two groups (all $P < 0.05$) and stable COPD patients had significantly higher SGRQ scores compared with healthy individuals (**Figure 4**). The detailed evaluation of health status and life wellbeing of subjects by SGRQ was presented in **Table 2**.

Association between post-treatment expression of PCT/CRP/Ang-2 and life wellbeing status

PCT, CRP, Ang-2 expression levels and SGRQ scores in the better group (n = 61) were all decreased as the treatment time extended and these figures significantly differed on day 1, 3 and 7 ($P < 0.05$) (**Table 3**). By contrast, subjects in the worse group (n = 21) exhibited remarkable increase in various effectiveness and health status indicators as time of treatment extended. Moreover, there was no significant difference in PCT and CRP expressions between different days during the treatment period ($P > 0.05$) whereas differences in Ang-2 and SGRQ among day 1, 3 and 7 over the treatment period appeared to be significant ($P < 0.05$).

Correlation analysis among PCT, CRP and Ang-2 expressions in patients with AECOPD

As suggested by correlation analysis among PCT, CRP and Ang-2 expression levels, serum level of CRP in patients with AECOPD was positively correlated with that of Ang-2 ($r = 0.619$, $P < 0.001$) (**Figure 5**); serum level of PCT was also positively correlated with that of Ang-2 ($r = 0.669$, $P < 0.001$) (**Figure 6**).

PCT, CRP and Ang-2 expressions were associated with life wellbeing of AECOPD patients

As shown in **Table 4**, the estimated correlation coefficient between PCT expression level and SGRQ score was 0.618 in AECOPD patients. In addition, the estimated correlation coefficient between CRP/Ang-2 expression level and SGRQ score was 0.641 and 0.641, respectively. Therefore, we concluded that PCT, CRP and

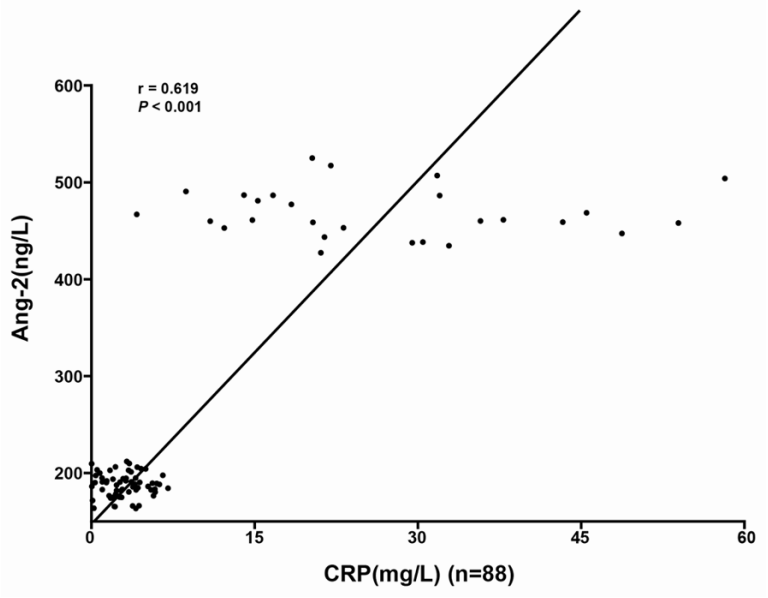

Figure 5. The correlation analysis of CPR and Ang-2 in AECOPD group after therapy.

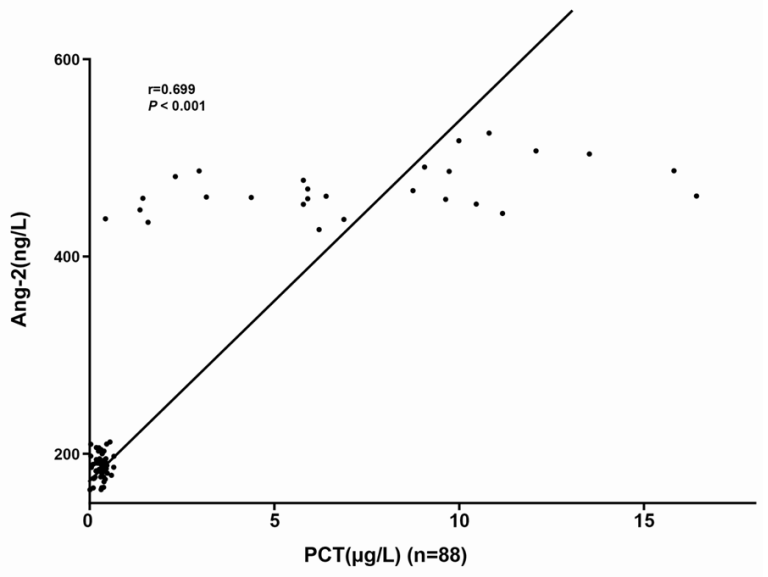

Figure 6. The correlation analysis of PCT and Ang-2 in AECOPD group after therapy.

Ang-2 expression levels were all positively associated with SGRQ scores ($P < 0.01$, respectively).

Discussion

Chronic obstructive pulmonary disease (COPD) possesses both high morbidity and mortality, especially when COPD is acutely exacerbated due to bacterial infections, viruses, tobacco consumption and air pollutants [16-18]. Hence, it is of great significance to find whether or not biomarkers can be used to indicate the severity of COPD and distinguish acute exacerbated COPD (AECOPD) from stable COPD so that early intervention can be introduced. CRP and PCT have been reported as normal biomarkers for COPD in formal studies [19, 20]. CRP, which is a widely used serum marker in diagnosing infectious diseases and monitoring sensitivities of antibiotics, has been found to be highly expressed in patients with AECOPD, especially in those who have purulent sputum and positive bacterial sputum cultures [21-24]. Recently, PCT has been prospectively studied in guiding antibiotic therapy as a biomarker in order to increase the sensitivity for diagnosing bacterial infections [25, 26]. Ang-2, which participates in some inflammatory diseases and mediating angiogenesis, has also been reported to be correlated with COPD exacerbations [27, 28]. Therefore, our objective was to verify whether CRP, PCT and Ang-2 could be considered as appropriate biomarkers for AECOPD and could be used to evaluate the severity of COPD.

Firstly, we detected CRP expressions in the control, stable COPD and AECOPD group and then we analyzed the correlation between CRP expression and SGRQ score in AECOPD patients. Results indicated that the expression level of CRP was the highest one in AECOPD patients among the three groups. Correlation analysis indicated that CRP expression level was closely related to the life wellbeing status of patients. AECOPD patients with high expression level of CRP exhibited poor life wellbeing status. As a result of this, CRP could be an

Table 4. The correlation analysis between SGRQ score with PCT, CRP and Ang-2 in AECOPD group

Group	PCT	CRP	ANG-2
SGRQ			
r value	0.618	0.641	0.527
P value	< 0.001*	< 0.001*	< 0.001*

*: $P < 0.05$.

appropriate biomarker of COPD and it may provide reliable information for distinguishing AECOPD from stable COPD. In accordance with our research, Bafadhel *et al.* and Lacoma *et al.* also demonstrated that CRP serum levels were closely related to the severity of COPD [17, 20]. As suggested by Brightling *et al.*, CRP could serve as biomarkers for guiding personalized corticosteroid and antibiotic treatment for AECOPD patients [16]. Similarly, Bafadhel *et al.* formulated a threshold level of CRP (> 48 mg/L) which can be used to tailor antibiotic treatments [20]. However, CRP was related to bacterial presence and it could not be used in distinguishing virus-associated AECOPD from others, which is a recognized limitation in applying CRP as a biomarker [19, 29].

Comparison of PCT expression levels among different groups and analysis of the correlation between PCT and SGRQ scores enabled us to discover that PCT had a similar role in estimating the severity of COPD and it may as one of the biomarkers for acute exacerbated COPD and these results were consistent with studies conducted by Bafadhel *et al*. and Lacoma *et al.* [17, 20]. They both identified a correlation ship between CRP and PCT, indicating that both CRP and PCT could assist in diagnosing AECOPD, evaluating the short-term prognostic outcomes of AECOPD patients, and guiding antibiotic treatments for AECOPD patients. However, some researchers argued that PCT was not able to reflect bacterial infections and only a moderate correlation between CRP and bacterial infections was observed, indicating that PCT was not a sensitive biomarker of AECOPD [19, 28, 30]. This inconsistency might be caused by different PCT detection approaches which might result in different sensitivity for diagnosing AECOPD.

Furthermore, we found that Ang-2 was also an appropriate biomarker of AECOPD and could be used in estimating the severity of COPD. As suggested by Cho *et al.* and Nikolakopoulou *et al.*, AECOPD patients exhibited a much higher serum Ang-2 level [27, 28]. Moreover, they both demonstrated that CRP expression was correlated with serum Ang-2 level and this correlation was verified by our study. By analyzing the correlation among PCT/CRP/Ang-2 expression levels in patients with AECOPD, we also showed that PCT expression was positively correlated with Ang-2 expression. Therefore, CRP, PCT and Ang-2 may have similar roles in distinguishing AECOPD from stable-stage AECOPD. Furthermore, we examined changes in these molecules in AECOPD patients after treatments were applied over a period of time in order to find out whether or not these changes were related to health and life wellbeing status of patients.

By comparing PCT, CRP, and Ang-2 expression levels in AECOPD patients who were effectively treated (better group) and those who were with ineffectively treated (worse group), we found that PCT, CRP, and Ang-2 expression levels in the better group were gradually decreased as treatment time extended, while Ang-2, PCT, and CRP expression level were increased in the worse group. All of these results indicated that changes in serum PCT and CRP levels, especially Ang-2 levels, could be used to evaluate the therapeutic effect of treatment on AECOPD patients. Similarly, Cho *et al.* and Nikolakopoulou *et al.* also demonstrated that serum Ang-2 levels of AECOPD patients was decreased when patients started to recover from AECOPD [27, 28]. Hence, monitoring serum Ang-2 levels, together with PCT and CRP levels during the course of therapy for AECOPD patients, might reflect informative changes in clinical conditions of AECOPD patients.

This pioneer study revealed the role of PCT, CRP together with Ang-2 in determining COPD severity, AECOPD diagnosis and therapeutic effects of treatment on AECOPD. However, our study contains some limitations. Firstly, the sample size of our study was relatively small and we only selected patients who were from the north-west of China and therefore more studies are still in demand. Additionally, several factors including judgment of doctors may have potential impact on assessing the effectiveness of AECOPD treatments and hence a more

objective evaluation approach should be designed to address this issue. In conclusion, PCT, CRP and Ang-2 have been demonstrated to be appropriate biomarkers for acute exacerbated COPD. Meanwhile, they could be used to evaluate the severity of COPD and the efficacy of AECOPD treatments.

Disclosure of conflict of interest

None.

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