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Levels of Serum Procalcitonin and C-Reactive Protein for Evaluating Pulmonary Bacterial Infection in Patients with Lupus Erythematosus*

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Summary: The severity of systemic lupus erythematosus (SLE) patients with pulmonary bacterial infection varies widely. We investigated the significance of procalcitonin (PCT) and C-reactive protein (CRP) in evaluating the severity of pulmonary infection in SLE patients. This retrospective study contained a total of 117 patients (107 women and 10 men) with SLE from January 2010 to June 2011. Serum levels of PCT and CRP were measured by enzyme-linked immunosorbent assay. The severity of pulmonary bacterial infection (PBI) was evaluated using the pneumonia severity index (PSI). SLE patients with PBI, particularly those with bacterial isolates, had significantly higher levels of serum PCT and CRP than those without PBI. Serum PCT and CRP were not associated with SLE disease activity, but positively with the values of PSI in active SLE patients with PBI. Serum levels of PCT and CRP may be additional biomarkers in evaluating the severity of PBI in lupus patients.
Key words: systemic lupus erythematosus; procalcitonin; C-reactive protein; pulmonary infection

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with unpredictable course and periods of illness (called flares) alternating with remissions. SLE occurs 9 times more often in women than in men, affecting approximately 3.5 million females, and currently, the incidence of SLE remains increasing worldwide[1–3]. Clinically, SLE can cause inflammation and damage in all of the major organs[1]. Although there have been improvements in the medical management of SLE patients, SLE therapy currently depends on glucocorticoid and immunosuppressive drugs and others, which are associated with increased risks of infection, multiple organ dysfunction syndrome (MODS), and multiple organ failure syndrome (MOFS)[4]. SLE patients are sensitive to pulmonary infection, particularly caused by bacteria, virus, fungus; and SLE patients with severe infection and MODS usually have high morbidity and mortality. Therefore, early diagnosis and treatment to control microbial infection are crucial in the management of SLE patients, especially for those with pulmonary lesions.

Among the different types of microbes, bacterial infection is the most prevalent in SLE patients with pulmonary infection[5], and *Escherichia coli*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, and *Streptococcus pneumoniae* are common for pulmonary infection in SLE patients[6]. For the diagnosis of pulmonary bacterial infection (PBI) in SLE patients, isolation of bacteria is the gold standard. However, successful bacterial isolation remains challenging and time consuming. Given that those patients with severe PBI may progress to sepsis and MODS during the course and require immediate antibiotics treatment, other measures, such as white blood cell (WBC) counts, neutrophils, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), have been used for the early diagnosis of infection in SLE patients[7]. However, these measures do not differentiate SLE activity from bacterial infection in SLE patients[8].

Procalcitonin (PCT), the precursor of calcitonin, is normally secreted by parafollicular cells (C cells) of the thyroid and by neuroendocrine cells in the lungs and the intestine. Under the physiological condition, there is a very low level of serum PCT in healthy subjects[9]. Bacterial pulmonary and intestinal infection can stimulate the production of PCT, although the precise mechanisms are still unclear. There are a few reports on the diagnostic values of the levels of serum PCT in differentiating disease flare and bacterial infection in SLE patients[10–14]. It has been shown that serum PCT levels are used as an early diagnostic marker of bacteremia in patients with acute fever[11] and as an early predictor of patients with sepsis[13]. However, Lanoix *et al* reported that serum PCT levels do not differentiate infection from SLE flare in patients with SLE[10]. Therefore, the significance of PCT and CRP in SLE diagnosis, particularly in SLE patients with PBI, remains controversial.

In this study, we examined the levels of serum PCT and CRP in Chinese SLE patients with, or without, pulmonary infection. We also stratified the SLE patients according to the levels of clinical disease activities to explore the potential value of serum PCT and CRP levels in the diagnosis of pulmonary infection in SLE patients.

1 PATIENTS AND METHODS

1.1 Patients

The experimental protocol in this study was approved by the Ethics Committee of Zhengzhou University and written informed consent was obtained

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from individual patients. A total of 117 patients (107 women and 10 men) with SLE were recruited at the outpatient and inpatient services of the Department of Rheumatology, the First Affiliated Hospital, Zhengzhou University from January 2010 to June 2011 for this retrospective study. The patients were diagnosed as having SLE according to the revised criteria for the diagnosis of SLE from the American College of Rheumatology[15]. The exclusion criteria included: (1) other autoimmune diseases; (2) a history of burns, multiple traumas, surgery, onset of acute pancreatitis within the week post-recruitment; and (3) malignant tumors. The disease activities of individual patients were scored using the SLE disease activity index (SLEDAI)[16]. Patients with a SLEDAI score of 0–4 were defined as inactive SLE (n=35), 5–9 as mild active SLE (n=10), 10–14 as moderate active SLE (n=21), and >15 as severe active SLE (n=7). All patients with pulmonary infection had SLEDAI ≥5 (n=44). All patients were subjected to physical examination, and their demographic and clinical characteristics were recorded.

1.2 Clinical Sampling and Laboratory Tests

Three sputum and fasting venous blood samples were collected from SLE patients with suspected pulmonary infection immediately after admission and 14 days after treatment. Sputum and blood samples were subjected to bacterial culture. The blood specimens were routinely examined for WBC count, ESR, blood biochemistry, and arterial blood gas. The urinary specimens were collected for routine tests and bacterial culture. Individual SLE patients with fever or other suspected symptoms related to pulmonary infection were tested by chest X-ray and chest computed tomography (CT).

The diagnosis of pulmonary infection was made by all of the following: clinical symptoms, such as body temperature >38°C, cough with yellow or purulent sputum; abnormal chest X-ray and CT scanning. The severity of pulmonary infection was evaluated using the pneumonia severity index (PSI)[17]. Patients with a PSI score of <50 were considered as grade Ⅰ, 51–70 as grade Ⅱ, 71–90 as grade Ⅲ, 91–130 as grade Ⅳ, and a PSI score >130 as grade Ⅴ. Patients with grades Ⅰ–Ⅲ of PSI were classified as the low risk group, with grade Ⅵ of PSI as the moderate risk group, and those with grade Ⅴ of PSI as the high risk group.

Patients with pulmonary infection were treated with antibiotics and the treatment was adjusted later according to the isolates. In general, patients were treated with optimal antibiotics combined with voriconazole (0.2 g every 12 h on the day 1–2 and then 0.2 g per day; Pfizer, USA) or caspofungin (70 mg on day 1 and then 50 mg per day; Merck, USA). Patients with negative detection of sputum and blood bacteria were treated with beta-lactams (sulbactam and cefopcrazone intravenously, 3.0 g every 12 h; Pfizer, USA) or carbapenems (Imipenem and Cilastatin sodium intravenously, 0.5 g every 8 h; Merck, USA). In addition, these patients were treated with prophylactic medicines for the protection of gastric membrane, cough syrup, and anti-asthma if necessary.

The serum levels of PCT and CRP were measured by enzyme-linked immunosorbent assay (ELISA) using specific kits from RayBiotech (USA) and Invitrogen (USA), respectively, according to the manufacturers' instruction. The limitations of detection for serum PCT and CRP were 30 and 10 pg/mL, respectively[18].

1.3 Statistical Analysis

All statistical analyses were performed using SPSS ver. 18.0 (SPSS Inc., USA). Discrete variables are expressed as counts (percentage) and continuous variables as $x \pm s$, unless stated otherwise. Categorical data were analyzed by chi-square and Fisher exact tests, and continuous variables between groups were analyzed by Student's t-test. For non-normally distributed data, Wilcoxon test was used if only two groups were compared, and Kruskal-Wallis one-way analysis of variance (ANOVA) was used if more than two groups were compared. The relationship between two variables was analyzed by the Spearman rank correlation. A P value <0.05 was considered statistically significant.

2 RESULTS

2.1 Demographic and Clinical Characteristics of SLE Patients

The demographic and clinical characteristics of SLE patients are summarized in table 1. According to their clinical disease activity, there were 35 inactive, 38 active patients without obvious clinical symptoms and signs related to pulmonary infection, and 44 patients with clinical symptoms and signs related to a suspected pulmonary infection. There was no significant difference in the distribution of age and gender among these groups of patients. While there was only one patient with rash or anorexia in inactive SLE patients, and many active SLE patients or SLE patients accompanied with pulmonary infection displayed fever, skin rash, arthralgia, cough, anorexia, and chest distress and pain. In addition, the percentage of patients presenting with cough and chest distress was significantly higher in SLE patients with suspected pulmonary infection than active SLE patients without obviously clinical symptoms and signs related to pulmonary infection (P<0.05). As a result, inactive SLE patients just visited the outpatient service while all active patients and patients with pulmonary infection were hospitalized. The periods of hospital stay in the patients with pulmonary infection were significantly longer than those of active patients (P<0.05). Similarly, the number of peripheral venous blood WBCs and neutrophils in patients with pulmonary infection was greater than that in both inactive and active SLE patients without pulmonary infection (P<0.05). Interestingly, the levels of serum C4, but not C3, in active SLE patients without obvious pulmonary infection were significantly lower than those in the patients with suspected pulmonary infection (P<0.05). Among the patients with suspected pulmonary infection (n=44), there were 21 patients with positive bacterial isolates and the number of bacterial isolates is shown in table 2.

2.2 Significantly Higher Serum Levels of PCT and CRP in Patients with Pulmonary Infection

The levels of CRP have been used for evaluating systemic inflammation, and increased levels of serum CRP are associated with infection in SLE patients[13]. However, the value of serum PCT levels in differentiating SLE flare up and infection remains controver-

sial[10–13]. We examined the serum levels of CRP and PCT in different groups of patients immediately after admission or clinical visits (fig. 1). The levels of serum CRP and PCT in patients with pulmonary infection (36.63±23.94 mg/L and 3.59±3.58 ng/mL, respectively) were significantly higher than those in the inactive and active SLE patients without pulmonary infection (P<0.001). There was no significant difference in the levels of serum CRP and PCT between the inactive and active patients without pulmonary infection (CRP, 12.78±6.72 *vs.* 16.09±10.31 mg/L, P>0.05; PCT, 0.26±0.12 *vs.* 0.22±0.09 ng/mL, P>0.05). Hence, significantly higher levels of serum CRP and PCT existed in SLE patients with pulmonary infection.

Table 1 The demographic and clinical characteristics of patients

Characteristics	Inactive SLE (n=35)	Active SLE (n=38)	Active SLE with pulmonary infection (n=44)
Age (years)	26.86±4.43	28.26±4.75	27.0±4.15
Sex			
Male	4 (11.43%)	2 (5.26%)	4 (9.09%)
Female	31 (88.57)	36 (94.74%)	40 (90.91%)
Clinical symptoms			
Fever	0	22 (57.89%)	30 (68.18%)
Rash	1 (2.86%)	18 (47.37%)	12 (27.23%)
Arthralgia	0	20 (52.63%)	13 (29.55%)
Cough	0	1 (2.63%)	29 (65.91%)*
Anorexia	1 (2.86%)	6 (15.79%)	9 (20.45%)
Chest distress	0	15 (39.47%)	25 (56.82%)*
Chest pain	0	13 (34.21%)	18 (40.91%)
Hospital stay (days)	0	8.24±1.13	13.38±2.42*
Laboratory parameters			
WBCs ($\times10^9$/L)	5.69 (3.65–9.99)	6.96 (3.51–10.73)	12.7 (8.74–18.55)*
Neutrophils ($\times10^9$/L)	3.06 (1.20–5.75)	4.77 (2.08–9.68)	10.03 (6.45–16.10)*
C3	1.17 (0.83–1.59)	0.89 (0.79–0.99)	1.09 (0.90–1.59)
C4	0.27 (0.15–0.45)	0.11 (0.08–0.14)*	0.29 (0.17–0.44)

*P<0.05 *vs*. inactive SLE

Table 2 Stratification analysis of the levels of serum PCT and CRP

Sputum culture	n	PCT (ng/mL)	CRP (mg/L)
(+)	27	3.14 (0.98–19.86)*	37.40 (10.90–112.10)*
Klebsiella pneumoniae	6	5.18 (0.98–10.02)	50.50 (10.90–73.10)
Pseudomonas aeruginosa	8	2.88 (1.16–3.96)	28.20 (11.70–56.70)*
Acinetobacter baumannii	4	2.84 (2.08–11.30)	31.80 (21.80–102.80)
Staphylococcus aureus	3	10.90 (3.12–19.86)	58.90 (37.40–112.10)*
Aspergillus	4	5.82 (2.08–19.86)*	50.10 (21.80–112.10)*
Candida	2	3.35 (3.08–3.59)	39.20 (36.70–41.70)
(–)	23	2.11 (0.23–4.78)	25.90 (9.80–78.90)

*P<0.05 *vs*. the non-infected controls

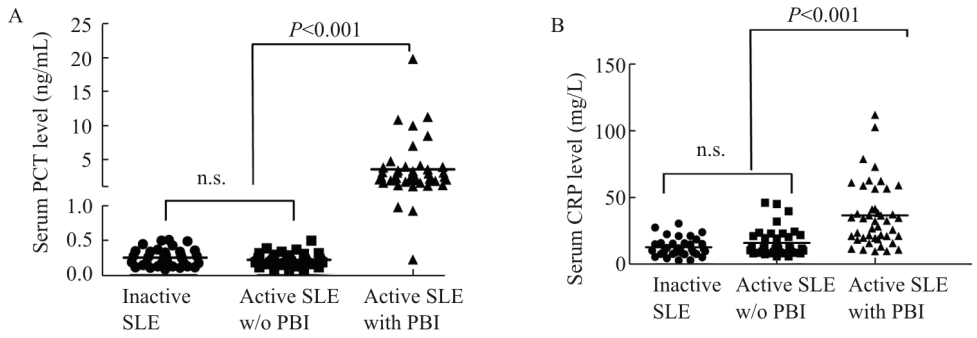

Fig. 1 Serum levels of PCT and CRP in the different groups of SLE patients

The levels of serum PCT and CRP in inactive (n=35), active (n=38), and active SLE patients with suspected pulmonary infection (n=44) were determined by ELISA. Data are expressed as the mean values of individual patients from three separate experiments. PBI: pulmonary bacterial infection; n.s.: no significance; w/o: with/without.

2.3 No Significant Association between Levels of Serum PCT and CRP and Disease Activity in Active SLE Patients without Pulmonary Infection

Previous studies indicate higher levels of serum PCT in active SLE patients with or without infection[12, 13]. However, we did not detect significantly higher levels of serum PCT in active SLE patients than those in inactive SLE patients. To further determine the potential value of serum levels of PCT and CRP in differentiating active SLE from patients with pulmonary infection, we classi-

fied active patients without pulmonary infection into mild, moderate, and severe groups and analyzed the levels of serum PCT and CRP. As shown in fig. 2, serum PCT levels were 0.23±0.07, 0.21±0.10, and 0.25±0.09 ng/mL in pulmonary infected patients with SLEDAI of 5–9, 10–14, and >15, respectively. Serum CRP levels were 20.17±12.94, 12.27±5.43, and 21.73±13.78 mg/L in pulmonary infected patients with SLEDAI of 5–9, 10–14, and >15, respectively. There was no significant difference in serum PCT and CRP levels among these three groups of patients with varying values of SLEDAI, indicating that the levels of serum PCT and CRP were not associated with SLE disease severities in patients without pulmonary infection (fig. 2A and 2B).

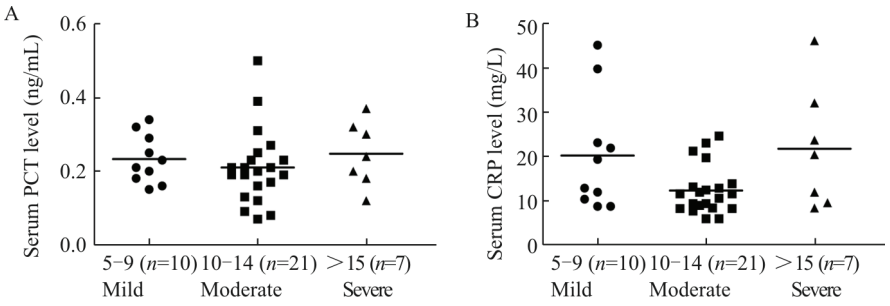

Fig. 2 Serum PCT and CRP levels in active SLE patients without pulmonary infection and with different disease severity
The patients with pulmonary infection were stratified, according to the severity of SLE, and the levels of serum PCT and CRP were compared among mild SLE (*n*=10), moderate SLE (*n*=17), and severe SLE (*n*=7). Data are expressed as the mean values of individual patients from three separate experiments. There was no significant difference among these groups of patients.

2.4 Association of Levels of Serum PCT and CRP and Severity of Pulmonary Infection in SLE Patients

Next, we analyzed the potential association of the levels of serum PCT and CRP with the severity of pulmonary infection in SLE patients. First, stratification analysis indicated the levels of serum PCT, but not CRP, in patients with positive sputum bacterial isolates, particularly those with *Staphylococcus aureus, Klebsiella pneumoniae, or Aspergillus,* were significantly higher than in those without positive sputum bacterial isolates ($P<0.05$, table 2). In addition, SLE patients in the high risk group (SI score >130) had significantly higher serum levels of PCT and CRP than those with a PSI score of <130 ($P<0.01$). There was no significant difference in the serum levels of PCT and CRP between SLE patients in low risk (PSI score <90) and moderate risk (PSI score 90–130) groups (fig. 3A and 3B). After treatment for two weeks with antibiotics, the levels of serum PCT and CRP in SLE patients with pulmonary infection were significantly decreased ($P<0.01$, fig. 4).

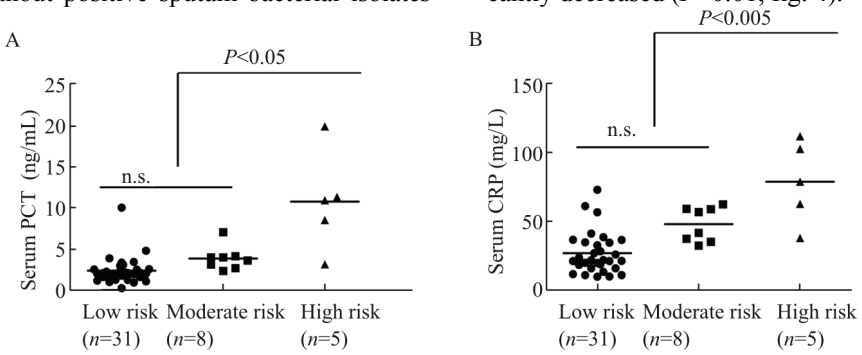

Fig. 3 Serum PCT and CRP levels in the different groups of SLE patients with pulmonary infection
The patients with pulmonary infection were stratified into the low risk (PSI score <90, *n*=31), moderate risk (PSI score 90–130, *n*=8), and high risk groups (PSI score >130, *n*=5). Data are expressed as the mean values of individual patients from three separate experiments. n.s: no significance;

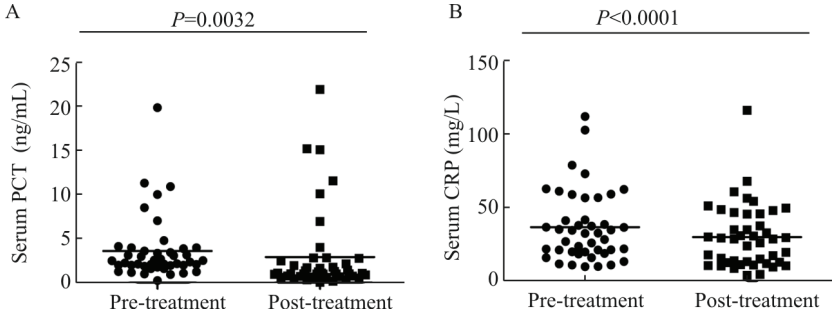

Fig. 4 Effect of antibacterial treatment on the serum levels of PCT and CRP in SLE patients with pulmonary infection
The levels of serum PCT and CRP in SLE patients with pulmonary infection were tested before and after treatment with antibiotics for two weeks. Data are expressed as the mean values of individual patients from three separate experiments.

3 DISCUSSION

Whether increased serum levels of PCT and CRP are associated with bacterial infection in SLE patients remains controversial[10, 19–22]. In this study, we found that the levels of serum PCT and CRP in active patients with pulmonary bacterial infection were significantly higher than those in inactive SLE patients and active SLE patients without obvious evidence of pulmonary infection. Furthermore, the levels of serum PCT in SLE patients with positive sputum isolates were also significantly higher than those without positive isolates. Although the levels of serum PCT and CRP were not associated with the values of SLEDAI in active patients with pulmonary infection, the levels of serum PCT and CRP were associated significantly with the values of PSI in this population. Thus, the levels of serum PCT and CRP may serve as biomarkers for evaluating the severity of pulmonary infection in SLE patients.

The significantly elevated levels of serum PCT and CRP in active SLE patients with pulmonary infection were consistent with previous observations[20, 23]. However, a previous study showed that the elevated serum PCT level was not associated with bacterial infection in SLE patients[10]. The discrepancy may be attributed to the different populations with different microbial infections as well as varying stages of infectious diseases. Indeed, we identified that 21 out of 44 SLE patients with pulmonary infection were infected with microbial pathogens (positive sputum specimens: 16 gram-negative bacteria, 5 gram-positive bacteria, and 6 fungi). Although there was no significant difference in the levels of serum PCT and CRP between those with gram-negative and gram-positive bacterial infections, the levels of serum PCT and CRP in those with positive sputum isolates were significantly higher than in the patients with negative isolates. These data suggest that elevated levels of serum PCT and CRP may reflect pulmonary infection in SLE patients. Interestingly, we observed one female patient with systemic infection of *Klebsiella pneumoniae* identified by three positive blood cultures who had a remarkably elevated serum PCT level (19.86 ng/mL), consistent with a previous report[11]. Given that the levels of serum PCT and CRP were positively associated with the severity of pulmonary infection in SLE patients, the high levels of serum PCT might arise from systemic infection in the patient. Alternatively, it is possible that some special bacterial infection may result in high levels of PCT production in SLE patients. Further investigation of how bacterial infection causes high levels of serum PCT and CRP in SLE patients is needed.

Notably, we measured the levels of serum PCT and CRP in patients with pulmonary infection following treatment with antibiotics. Thirty-nine out of 44 patients responded to antibiotics, accompanied by significantly reduced levels of serum PCT and CRP. In contrast, 5 patients with severe pulmonary infection (a PSI of Ⅴ) did not respond to the antibiotics and their serum PCT levels increased continually. Those patients died of severe pneumonia after 15 to 20 days of mechanical ventilation. These observations further suggest that we should pay more attention to those SLE patients with extremely higher levels of serum PCT and CRP. It also suggests that the levels of serum PCT and CRP may serve as biomarkers for evaluating the therapeutic responses of SLE patients to antibiotics and may be valuable factors for the prognosis of SLE patients with pulmonary infection[12–14, 24].

We recognized the limitations of current study. First, the sample size was small. Second, due to the retrospective nature of this study, there were no mechanistic studies on how microbial infection elevates the levels of serum PCT and CRP in active SLE patients with pulmonary infection. Therefore, further studies to validate these findings in a bigger population are warranted.

In conclusions, our data indicated significantly higher levels of serum PCT and CRP in active SLE patients with bacterial pulmonary infection. The levels of serum PCT and CRP may be additional biomarkers for evaluating the severity of pulmonary infection in active SLE patients and may be valuable for the prognosis of active SLE patients with pulmonary infection.

Conflict of Interest Statement

We declare that there are no conflicts of interest to this work.

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