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The diagnostic values of C-reactive protein and procalcitonin in identifying systemic lupus erythematosus infection and disease activity

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Abstract

To explore the values of C-reactive protein (CRP) and procalcitonin (PCT) in identifying infection and disease activity in systemic lupus erythematosus (SLE) patients.

Patients with SLE and infection from April 2015 to January 2018 were included in this study. We compared the clinical characteristics and biomarkers between different groups and calculated the receiver operating characteristic curve, sensitivity, and specificity of the corresponding biomarkers. Logistic regression analysis was performed on the variables exhibiting significant differences in univariate analysis.

A total of 177 SLE patients were retrospectively analyzed. The patients were divided into noninfected-inactive group, noninfected-active group, infected-inactive group, and infected-active group. CRP level of infected-inactive group was significantly higher than noninfected-inactive group ($P < .05$), but not significantly in infected-active group than noninfected-active group ($P > .05$). Multivariate analysis showed that CRP (>24.0 mg/L) was the only independent risk factor for SLE infection (odds ratio, OR = 2.896, $P = .032$). PCT level of infected-active group was significantly higher than infected-inactive group ($P < .05$), but not significantly in noninfected-active group than noninfected-inactive group ($P > .05$). SLE active group had shorter disease course, lower infection rate, higher PCT level, and lower platelet count (PLT). Multivariate logistic analysis showed that PCT (>0.048 ng/mL) and PLT ($<150 \times 10^9$/L) were independent risk factors for SLE activity (OR = 3.498 and 4.391, $P = .011$ and 0.009), and disease course (>96 months) was independent protective factor (OR = 0.169, $P < .001$). The area under the curve of the logistic model was significantly larger than any single variable (all $P < .05$).

CRP is the only effective marker for diagnosing infection in SLE patients. Moreover, PCT helps predict SLE activity.

Abbreviations: AUC = area under the curve, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, hsCRP = high sensitivity C-reactive protein, N% = percentage of neutrophils, OR = odds ratio, PCT = procalcitonin, PLT = platelet count, ROC = receiver operating characteristic curve, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, WBC = white blood cell.

Keywords: biomarker, C-reactive protein, infection, procalcitonin, systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, characterized by a chronic autoimmune response to multiple autoantigens and involving multiple organs. With the development of medical technologies, the diagnosis and treatment of SLE have been significantly improved. So far, SLE treatment mainly relies on glucocorticoids and immunosuppressive drugs. Thus, the SLE disease itself and the immunosuppressive therapy increase the risks of infection, multiple organ dysfunction syndrome, and multiple organ failure syndrome. Moreover, infection is considered as a common complication of SLE and one of the leading causes of death.[1–5] Up to 50% of SLE patients experience major infections during the disease course, and 20% to 55% of them die.[6–8] The diagnosis of these patients is an important challenge because the initial clinical manifestation of SLE is very similar to the acute febrile phase of infection (e.g., sepsis). Infections often require anti-infective treatment and reducing the number or dose of immunosuppressive agents, while the active SLE requires enhanced immunosuppressive therapy. Given that treatments to infection and active SLE are completely opposite, making the correct early diagnosis is critical for determining the treatment strategy. In recent years, many studies have focused on investigating the biomarkers used for early diagnosis of infection and disease activity in SLE patients, which include C-reactive protein (CRP) and procalcitonin (PCT).[9–20]

CRP is an inflammatory biomarker, which is synthesized by the liver during the acute reaction phase in response to interleukin (IL)-6 regulation. CRP has been used to distinguish infection from

primary disease activity in SLE patients. In a meta-analysis involving 8 studies and 668 patients with rheumatic diseases,[20] the area under the curve (AUC) of using CRP to diagnose infection was 0.860, with the sensitivity of 82.4% and specificity of 66.55%, suggesting that CRP can be used to diagnose infection in patients with rheumatic diseases, and the sensitivity and specificity are good. However, other studies have reported that CRP level is elevated in many rheumatic diseases, including rheumatoid arthritis, vasculitis, and SLE, limiting the application of CRP in the diagnosis of bacterial infections in these diseases.[21,22]

PCT is usually produced by parafollicular C cells, which release PCT upon the stimulations from bacterial toxins and IL-1β. The PCT level of healthy people is less than 0.10 ng/mL and is only mildly elevated in some special cases, such as viral infection, local infection, or cancer. However, after bacterial infection, the PCT level can rapidly increase by hundreds to thousands of folds, and then quickly returns to the normal range after the infection is controlled, without being affected by renal function or glucocorticoid.[23,24] Therefore, PCT can be used to evaluate the progression of bacterial infection, assess the efficacy of antibacterial therapies,[25,26] and distinguish between infectious and noninfectious inflammations.[10] Moreover, the PCT level is correlated with the severity of bacterial infections.[13,15] There were studies using PCT to distinguish infection from disease activity in SLE patients, but the results were controversial.[13–15]

In this study, we examined the biomarker levels of infected and noninfected SLE patients and performed stratified analysis on these patients according to their disease activities. With these approaches, we hope to explore the diagnostic values of CRP and PCT in identifying SLE infection and disease activity, in order to improve the accuracy of diagnosis and treatment for SLE patients.

2. Methods

2.1. Patients

The SLE patients who were hospitalized at the Department of Rheumatology of the Third Affiliated Hospital of Soochow University from April 2015 to January 2018 were selected as the study subjects. All the patients were above 14 years old, and their diseases were diagnosed based on the American College of Rheumatology standard in 1997.[27] The study was approved by the Ethics Committee of our institute. All patients and their family members signed the informed consent form. Blood samples were collected within 24 hours after hospitalization to assess the following parameters: white blood cell (WBC, 4–10 × 10^9/L), percentage of neutrophils (N%, 40–75%), erythrocyte sedimentation rate (ESR), CRP, high sensitivity C-reactive protein, PCT, and platelet count (PLT). The Sysmex XN9000 (Japan) was used for blood routine examination, Roche cobas8000 (Indianapolis, IN, USA) was used to measure PCT (reference value: 0.021–0.500 ng/mL), and BECKMAN COULTER AU5800 (Brea, CA, USA) was used for CRP measurement (reference value: 0–10.0 mg/L). Blood culture was conducted with the BD BACTEC FX (Sparks, MD, USA) machine. All the blood samples were taken before antibiotic treatment. The disease activity of each patient was scored based on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[28]

2.2. Definition of infection

The diagnosis of infection is based on the positive results of pathogen culture, typical symptoms and signs, and the positive imaging results. The clinical symptoms of infection include body temperature >38°C or <36°C, sore throat, cough, expectoration, abdominal pain, diarrhea, frequent urination, urgent urination, dysuria, local suppuration, etc. When a patient was suspected to have an infection, he/she was recommended to receive imaging examinations such as ultrasound, X-ray, computed tomography, or magnetic resonance imaging. Before anti-infection treatment, specimens (such as sputum, urine, feces, blood, purulent secretions, drainage fluid, etc.) from the suspected infection sites were taken and cultured. Effective anti-infection treatment could also support the diagnosis of infection. Patients were divided into infected and noninfected groups depending on whether they were infected. Sepsis is defined by the presence of infection and systemic inflammatory response syndrome according to the standards of 2001.[29]

2.3. Measurement of SLE disease activity

The disease activity of each patient was scored based on SLEDAI with the following definition: 0 to 4: inactive, 5 to 9: mild, 10 to 14: moderate, ≥15: severe. The patients were divided into active and inactive groups depending on whether their disease is active; the patients with a SLEDAI ≥5 were put into active group.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 18.0 statistical software (Chicago, IL). The data following normal distribution were presented as mean ± SD, the data with non-normal distribution were presented as median P50 (P25, P75), and the counting data were expressed as number or percentage. t test was used to compare between 2 normally distributed groups, Mann–Whitney U test was used for the comparison between 2 non-normally distributed groups, Kruskal–Wallis H test was used for the comparison between multiple non-normally distributed groups, and the chi-squared test was used to compare the percentages. The receiver operating characteristic curve (ROC) and the AUC was used to compare the diagnostic performance of different parameters. MedCalc 15.2.2 software (MedCalc, Ostend, Belgium) was used to compare different diagnostic tests. The non-normally distributed data or grade data were analyzed with Spearman correlation. Correlation analysis of the 2 categorical variables was performed by logistic regression, and a logistic model was also built. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 177 SLE patients who were hospitalized at the Department of Rheumatology from April 2015 to January 2018 were included in the study. Among these patients, there were 11 males (6.2%) and 166 females (93.8%), with the ages ranging from 16 to 75 (43.4 ± 16.5) years old, and the disease course spanning from 4 days to 30 years.

Among the 177 SLE patients, 129 had infection (72.9%), of which, 87 had respiratory infection, 8 had digestive tract infection, 7 had skin and soft tissue infection, 6 had urinary tract infection, 5 had lymph node/tube infection, 3 had an oral infection, 1 had endocarditis, and 12 had mixed infections. Also, in infected patients, 9 patients had sepsis. The disease activity of each patient was scored by SLEDAI. According to the infection and SLEDAI score, the patients were divided into noninfected-inactive SLE (n = 14), noninfected-active SLE (n = 34), infected-inactive SLE (n = 61), and infected-active SLE (n = 68) (Table 1).

Table 1

The demographic and clinical characteristics of infected and noninfected systemic lupus erythematosus patients.

Characteristics	Noninfected-inactive SLE n = 14	Noninfected-active SLE n = 34	Infected-inactive SLE n = 61	Infected-active SLE n = 68	P
Age (years)	46.5 ± 16.2	38.2 ± 14.2	46.7 ± 17.1	42.6 ± 16.7	.089
<50	8 (57.1)	28 (82.4)	32 (52.5)	46 (67.6)	**.026**
≥50	6 (42.9)	6 (17.6)	29 (47.5)	22 (32.4)	
Gender (%)					
Male	1 (7.1)	2 (5.9)	4 (6.6)	4 (5.9)	1.000
Female	13 (92.9)	32 (94.1)	57 (93.4)	64 (94.1)	
Disease course (months)	120 (102, 228)	24 (1, 120)	120 (120, 156)	60 (48, 120)	**.001**
SLEDAI score	2 (1, 2)	8 (6, 10)	2 (1, 3)	6 (6, 10)	**<.001**
Fever (%)	10 (71.4)	31 (91.2)	51 (83.6)	61 (89.7)	.228
Laboratory parameters					
CRP (mg/L)	7.0 (4.5, 32.7)	11.7 (6.6, 39.2)	40.6 (12.2, 97.7)	16.1 (7.0, 36.8)	**.008**
PCT (ng/mL)	0.040 (0.030, 0.154)	0.086 (0.048, 0.262)	0.064 (0.043, 0.236)	0.092 (0.053, 0.897)	.052
ESR (mm/h)	25 (11, 56)	37 (15, 81)	44 (30, 67)	29 (18, 43)	.112
ESR/CRP	1.9 (0.9, 5.1)	1.9 (0.8, 5.3)	1.0 (0.5, 2.5)	1.8 (0.6, 3.0)	.413
hsCRP (mg/L)	8.14 (2.75, 10.82)	7.04 (0.50, 20.38)	21.10 (3.37, 78.16)	8.28 (1.16, 31.60)	.461
WBC (×10^9/L)	6.95 (5.53, 8.76)	4.79 (3.32, 10.4)	6.89 (4.85, 10.02)	4.93 (3.30, 8.14)	.162
N%	80.90 (56.55, 87.45)	81.30 (66.30, 86.80)	78.4 (66.2, 85.90)	80.60 (66.80, 86.00)	.880
PLT (×10^9/L)	180 (168, 212)	193 (130, 262)	176 (152, 215)	159 (111, 213)	**.021**

The data following normal distribution was presented as mean ± SD, the data with non-normal distribution were presented as median P50 (P25, P75).
CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, hsCRP = high sensitivity C-reactive protein, N% = neutrophil percentage, PCT = procalcitonin, PLT = platelet count, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, WBC = white blood cells.
Bold indicates P < .05.

The clinical characteristics and biomarker test results of 4 groups were as follows: no significant difference was found in gender or fever rate among 4 groups (P > .05); there was significant difference in age, disease course, SLEDAI score, CRP, and PLT (P < .05), but the other laboratory parameters did not show obvious change (P > .05) (Table 1).

3.2. The association between CRP Level and infection in SLE patients

The biomarker test results of noninfected-inactive vs. infected-inactive and noninfected-active vs. infected-active were shown in Figure 1. CRP level of infected-inactive group was significantly higher than noninfected-inactive group (P < .05), but not significantly in infected-active group than noninfected-active group (P > .05). Other laboratory parameters did not show obvious differences (P > .05). The 9 sepsis patients in the infected group had a mean CRP level of 41.4 (7.0, 167.0) mg/L, which was significantly higher than other infections (P < .05) (data not shown). Specifically, the highest PCT levels of 2 sepsis patients were 25.550 ng/mL and 56.830 ng/mL, respectively.

The ROC curve of SLE infection diagnosis was plotted in Figure 2 (AUC = 0.642, P = .003). The best cut-off value was 24.0 mg/L, with the corresponding sensitivity of 48.6% and specificity of 79.5%. The univariate and multivariate analyses of age (≥50 years), disease course, SLEDAI score, CRP (>24.0 mg/L), PCT, and ESR showed that CRP (>24.0 mg/L) was the only independent risk factor for infection in SLE patients (odds ratio, OR = 2.896, P = .032) (Table 2).

3.3. The association between PCT level and disease activity in SLE patients

The biomarker test results of noninfected-inactive vs. noninfected-active and infected-inactive vs. infected-active were

shown in Figure 3. PCT level of infected-active group was significantly higher than infected-inactive group (P < .05), but not significantly in noninfected-active group than noninfected-inactive group (P > .05). ESR and PLT level of infected-active group was significantly lower than infected-inactive group (P < .05), but not significantly in noninfected-active group than noninfected-inactive group (P > .05). Other laboratory parameters did not show obvious differences (P > .05).

Spearman correlation analysis found that PCT was positively correlated with SLEDAI, CRP, ESR, WBC, with the r = 0.173, 0.446, 0.200, 0.216, and P = .021, .000, .012, .004, respectively; PCT was slightly negatively correlated with PLT, with the r = −0.283 and P < .001.

The ROC curves of different variables predicting SLE activity (Fig. 4) showed that, there was no significant difference in AUC between disease course, PCT, and PLT (P > .05) (Table 3). The univariate and multivariate analyses on patient age (≥50 years), disease course (>96 months), PCT (>0.048 ng/mL), CRP, ESR, PLT (<150 × 10^9/L) showed that PCT (>0.048 ng/mL) and PLT (<150 × 10^9/L) were independent risk factors for SLE activity (OR = 3.498 and 4.391, P = .011 and .009), and disease course (>96 months) was independent protective factor for SLE activity (OR = 0.169, P < .001) (Table 4).

Based on the multivariate analysis results, the risk score for predicting SLE activity is calculated as Logit (P) = −1.777 × disease course (>96 months = 1; <96 months = 0) + 1.252 × PCT (>0.048 ng/mL = 1; <0.048 ng/mL = 0) + 1.480 × PLT (<150 × 10^9/L = 1; >150 × 10^9/L = 0).

The above logistic model was used to predict the ROC curve of SLE activity. Compared to disease course, PCT, and PLT, the AUC of the logistic model were significantly larger than any of the single variables by MedCalc software (all P < .05) (Fig. 4, Table 3).
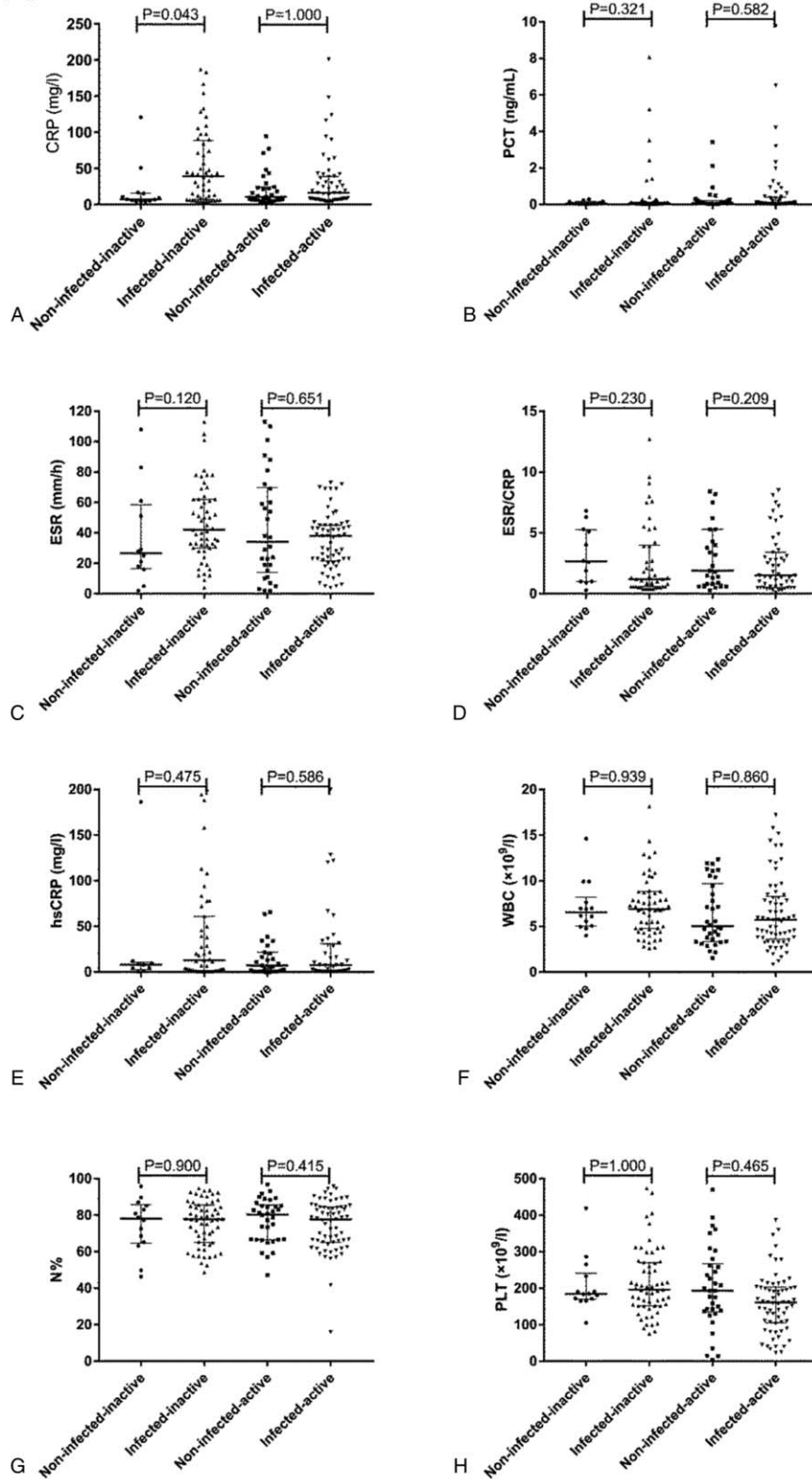
Figure 1. The biomarker test results of noninfected-inactive SLE vs. infected-inactive SLE and noninfected-active SLE vs. infected-active SLE. CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, hsCRP = high sensitivity C-reactive protein, PCT = procalcitonin, PLT = platelet count, SLE = systemic lupus erythematosus, WBC = white blood cell.
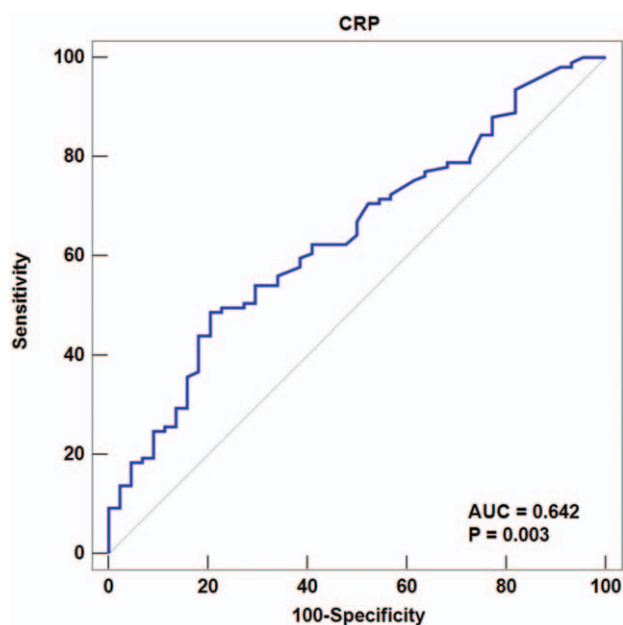
Figure 2. ROC curve of C-reactive protein in the diagnosis of infected SLE patients. AUC = area under the curve, CRP = C-reactive protein, ROC = receiver operating characteristic curve, SLE = systemic lupus erythematosus.

4. Discussion

The ideal biomarkers should be highly sensitive and specific and also associated with the severity and prognosis of the infection. Moreover, its usage should be easy, fast, and inexpensive. Traditional biomarkers are not very accurate in diagnosing infection and primary disease activity of SLE patients. For example, traditional biomarkers such as WBC, N%, ESR, etc., are highly susceptible to the effects of drugs, especially glucocorticoids.[14,30] Currently, the biomarker studies predicting infection and disease activities have been widely carried out in different populations. The candidates include CRP, PCT, delta neutrophil index, presepsin, ratio of neutrophil to lymphocyte, CD64, S100A8/A9, etc.[9,11,12,17,19,31] However, there is still no ideal biomarker available.

4.1. Serum CRP level is significantly elevated in infected patients

In our study, infected-inactive SLE had significantly elevated CRP level than noninfected-inactive SLE; this finding is consistent with

the previous studies.[12,13,20] The best cut-off value of CRP predicting SLE infection was 24.0 mg/L, which is close to previous studies; but the sensitivity is slightly lower.[15,19,32] This discrepancy may be related to the patient number, infection site, and the difference in pathogens. Gao et al[13] reported that CRP level was positively correlated with the severity of pulmonary infection: the high-risk group had significantly higher CRP than the low and moderate-risk groups; moreover, after anti-infection therapies, the serum CRP levels of SLE infection patients were greatly decreased ($P < .01$). In our study, the CRP levels of the 9 sepsis patients were significantly elevated, suggesting that severe infection might occur when CRP level is highly elevated.

Interestingly, from our study, PCT was not increased in infected SLE patients. Liu et al[11] and Lanoix et al[33] also found that PCT cannot diagnose infection. But in other reports,[13–15] PCT levels were significantly elevated in patients with SLE infection. This discrepancy may be caused by different pathogens and different infection sites. In our study, the infection was mainly at respiratory sites, and some of the respiratory infections were viral infections. However, PCT is mainly used to identify bacterial infections.[13,15] Moreover, our study was based on patients with local infections, and PCT is better at diagnosing systemic infections.[15] It also needs to be noted that the 2 sepsis patients in our study had significantly high PCT levels, suggesting that sepsis should be considered when PCT is significantly elevated.

4.2. The association between serum PCT levels and SLE activity

The most commonly used biomarkers for evaluating SLE activity are anti-dsDNA (double-stranded DNA) antibodies, complement (C3 and C4), ESR, PLT, 24 hours urinary protein, etc.; however, these markers are not specific and can be affected by the primary disease, glucocorticoids, immunosuppressants, etc.[34]

In this study, PCT levels were significantly elevated in active group compared to the inactive group, and it had a slightly positive correlation with SLEDAI ($r = 0.173$). This result is contradicted with the previous study showing that PCT had no correlation with SLE activity.[13–15] This discrepancy can be attributed to the different disease stages of different patient groups. Unfortunately, we did not dynamically monitor the PCT levels and further investigate the mechanisms. However, we also found that the sensitivity and specificity of PCT predicting disease activity were not ideal. The PLT level of active group was significantly reduced compared to inactive group, but its sensitivity was only 42.4%. Previous studies have reported that the use of multiple biomarkers could improve the accuracy of

Table 2

Univariate and multivariate analyses of the independent predictive variable for infection.

	Univariate analysis		Multivariate analysis	
Factors	OR (95% CI)	P	OR (95% CI)	P
Age (≥50 years)	1.962 (0.933, 4.122)	.075	1.631 (0.631, 4.217)	.313
Disease course (months)	1.002 (0.998, 1.006)	.392	1.000 (0.994, 1.006)	.938
SLEDAI score	0.937 (0.866, 1.013)	.103	0.983 (0.882, 1.095)	.755
CRP (>24.0 mg/L)	3.681 (1.616, 8.384)	.002	2.896 (1.097, 7.641)	.032
PCT	1.327 (0.863, 2.041)	.197	1.225 (0.768, 1.952)	.394
ESR	0.998 (0.985, 1.012)	.802	0.992 (0.975, 1.008)	.331
PLT	0.999 (0.995, 1.002)	.441	0.999 (0.995, 1.004)	.763

CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, OR = odds ratio, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.
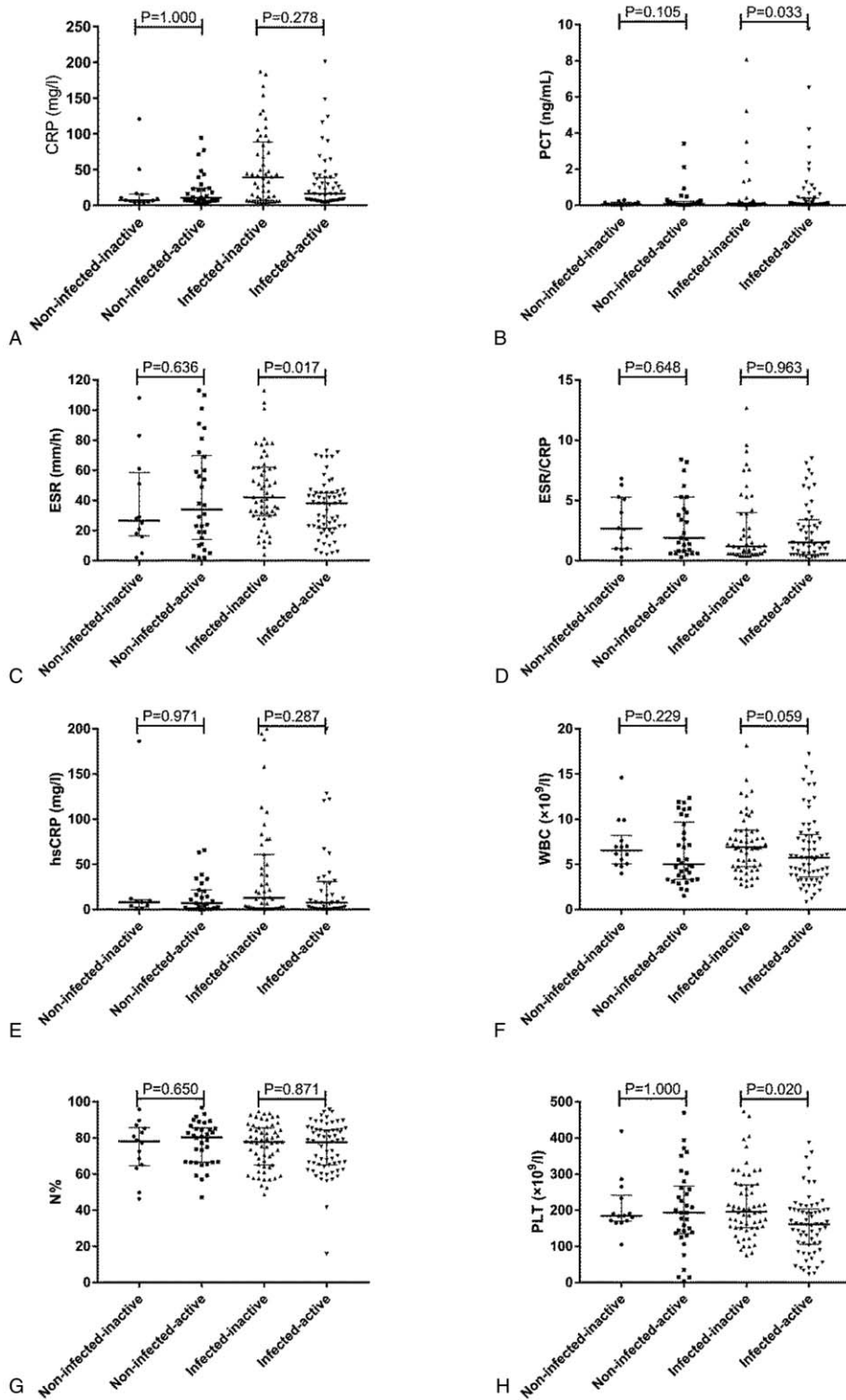
Figure 3. The biomarker test results of noninfected-inactive SLE vs. noninfected-active SLE and infected-inactive SLE vs. infected-active SLE. CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, hsCRP = high sensitivity C-reactive protein, PCT = procalcitonin, PLT = platelet count, SLE = systemic lupus erythematosus, WBC = white blood cell.
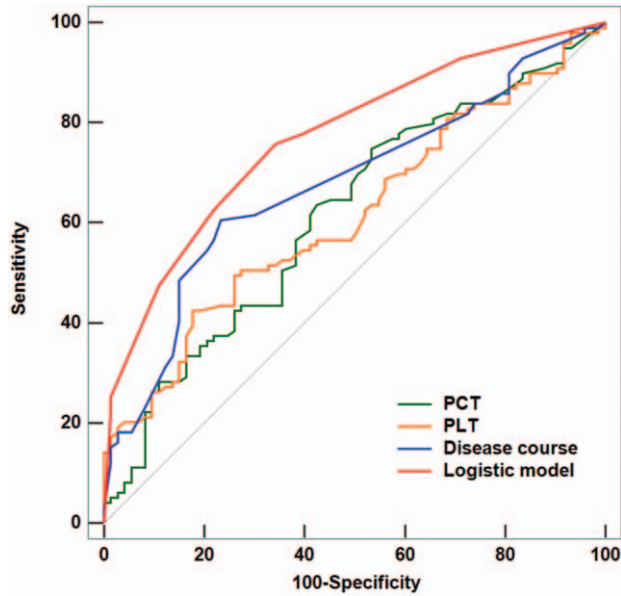
Figure 4. ROC curves of the logistic model, procalcitonin, platelet count, and disease course in the diagnosis of active SLE patients. PCT = procalcitonin, PLT = platelet count, ROC = receiver operating characteristic curve, SLE = systemic lupus erythematosus.

We also found that the older patients (≥50 years old) with longer disease course had lower primary disease activity. Considering the practical situations in the clinic, we think that in these patients, the primary disease usually has been well controlled after years or decades of treatment, thereby the primary disease activity is low.

There are also some limitations to our study. First, this study is a retrospective study; thereby it cannot continuously monitor the CRP and PCT levels to fully assess their diagnostic values, and also lacks the mechanistic investigation to understand how PCT is elevated in SLE patients. Secondly, some of the infected patients involved in this study did not receive pathogen examination, and their diagnosis was based on imaging results and symptoms, signs, so the diagnostic values of CRP and PCT in identifying viral, bacterial, and fungal infections could not be carefully evaluated. Third, the sample size in this study is relatively small, so its ability to detect differences between the 2 groups is low.

5. Conclusions

Taken together, our data suggest that CRP is the only effective marker for diagnosing infections in SLE patients, and sepsis should be considered when the PCT level is significantly elevated. Moreover, the combination of disease course, infection, PCT level, and PLT can better predict SLE activity, which helps to find the best timing for SLE treatment.

diagnosis. Echeverri et al[9] found that the combination of nCD64, PCT, and presepsin greatly improved the sensitivity and specificity of infection diagnosis. In our study, the logistic model combining disease course, PCT, and PLT was used to predict SLE activity, and its diagnostic efficacy was better than any of the single variables, suggesting that PCT can also be included in the SLE activity evaluation system.

Author contributions

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Formal analysis: Yuetao Wang, Xiaonan Shao.
Writing – original draft: Jing Wang, Rong Niu.

Table 3

The ability to predict systemic lupus erythematosus activity of different variables.

Factors	AUC	P	Cut-off	Sensitivity	Specificity	+LR	−LR
Disease course (months)	0.667	<.001	96	60.8	74.7	2.40	0.53
PCT (ng/mL)	0.614	.008	0.048	73.5	48.0	1.41	0.55
PLT (×10⁹/L)	0.615	.007	150	42.4	82.2	2.38	0.70
Logistic model	0.771*	<.001	0.4746	75.8	65.8	2.21	0.37

+LR = positive likelihood ratio, AUC = area under the curve, −LR = negative likelihood ratio, PCT = procalcitonin, PLT = platelet count.
* Compared to disease course, PCT and PLT, the AUC of the logistic model was significantly higher than any of the single variable (all $P < .05$).

Table 4

Univariate and multivariate analyses for the independent variables to predict active systemic lupus erythematosus.

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (≥50 years)	0.432 (0.231, 0.811)	.009	0.492 (0.176, 1.373)	.175
Disease course (>96 months)	0.219 (0.114, 0.421)	<.001	0.169 (0.065, 0.441)	<.001
PCT (>0.048 ng/mL)	2.564 (1.364, 4.821)	.003	3.498 (1.325, 9.233)	.011
CRP	0.990 (0.982, 0.998)	.012	0.991 (0.980, 1.002)	.102
ESR	0.989 (0.977, 1.002)	.090	0.995 (0.977, 1.014)	.597
PLT (<150 × 10⁹/L)	3.401 (1.655, 6.987)	.001	4.391 (1.449, 13.303)	.009

CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, OR = odds ratio, PCT = procalcitonin, PLT = platelet count.

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