Original Article

Application of procalcitonin, white blood cell count and neutrophil-to-lymphocyte ratio in the diagnosis of systemic lupus erythematosus with a bacterial infection

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease. This study aims to analyze the value of procalcitonin (PCT), white blood cell count (WBC), and neutrophil-to-lymphocyte ratio (NLR) in the differential diagnosis of SLE with a bacterial infection.

Methods: A total of 164 patients with SLE admitted to our hospital from January 2018 to December 2019 were selected as the research subjects. According to the results of bacterial culture, patients with SLE were divided into the bacterial infection group (46 cases) and the non-bacterial infection group (118 cases). Sixty healthy volunteers without the allergic disease, family history of tumors, or immunodeficiency in the same age group were selected as the control group during the same period. Fasting venous blood was collected in the morning to detect serum macrophage migration inhibitory factor (MIF), C-reactive protein (CRP), red blood cell distribution width (RDW), PCT, WBC, neutrophil count (NEUT) and lymphocyte count (LYMPH), and the NLR (NEUT/LYMPH) was calculated.

Results: CRP, PCT, WBC, and NLR levels were significantly higher in the bacterial infection group and the non-bacterial infection group than that in the control group, and which in the bacterial infection group is significantly higher than in the non-bacterial infection group ($P<0.05$). PCT, WBC and NLR were independent risk factors for SLE with bacterial infection ($P<0.05$). ROC curve analysis showed the areas under the curve of PCT, WBC, and NLR for the differential diagnosis of SLE with bacterial infection being 0.883, 0.669, and 0.624. Then, the sensitivities of 78.3%, 43.5%, and 69.6% were observed with the specificities of 98.3%, 91.5%, and 56.8%, respectively. The area under the curve of combined prediction was 0.919, with a sensitivity of 78.3%, and a specificity of 97.5%. These results showed that the value of the combined prediction was significantly higher than the single prediction of each indicator. And the levels of PCT, WBC, and NLR gradually decreased with the progress of treatment ($P<0.05$).

Conclusions: The combined detection of PCT, WBC, and NLR levels shows high sensitivity and specificity for SLE with a bacterial infection, which can be used for early auxiliary diagnosis of SLE with a bacterial infection.

Keywords: Procalcitonin (PCT); white blood cell count (WBC); neutrophil-to-lymphocyte ratio (NLR); systemic lupus erythematosus (SLE); bacterial infection

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs and multiple systems throughout the body, with common early signs and symptoms including fever, rash, pericarditis, arthritis, serous inflammation, and kidney damage (1). With the continuous development and progress of medical technology, the prognosis of SLE patients has been significantly improved, but the complications of SLE are still a severe problem in the clinic. Glucocorticoids and immunosuppressive agents are the primary drugs to treat SLE clinically. Although these agents can effectively alleviate the patient's disease, they may also increase the risk of bacterial infection to a certain extent (2). Because the disease causes immune dysfunction, using hormones, and immunosuppressive agents in the course of SLE treatment, patients are often in an immunosuppressive state. Patients with SLE are prone to progress to be sepsis after bacterial infection, one of the primary causes of death in SLE patients clinically (3). SLE at the early stage is often accompanied by fever and other symptoms, which is difficult to distinguish from fever caused by bacterial infection. Therefore, it is necessary to find laboratory indicators that can be used for early differential diagnosis to improve the prognosis of patients (4). Studies have confirmed that serum procalcitonin (PCT) level increases abnormally during bacterial infection but does not increase or only slightly increases during viral infection or non-inflammatory reactions (5). White blood cell count (WBC) and neutrophil-to-lymphocyte ratio (NLR) are commonly used indicators for diagnosis of bacterial infections clinically, which also has the advantages of straightforward retrieval from routine blood examination, convenient sampling, with mature detection methods, and rapid results (6,7). Currently, there is no study on the combination of PCT, WBC and NLR in the diagnosis of SLE. This study innovatively analyzed the value of PCT, WBC and NLR in the differential diagnosis of SLE combined with bacterial infection, aiming to provide more evidence for the clinical diagnosis and treatment of patients. We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1777).

Methods

General information

The ethics committee approved this study of Daqing Oilfield General Hospital, and we selected 164 patients with SLE who were admitted to our hospital from January 2018 to December 2019 as the research subjects. All the patients met the diagnostic criteria of SLE diagnosis and management (8). Patients with other autoimmune diseases, tumors, severe heart, lung, and kidney diseases, or those with viral, fungal, and tuberculosis infections were excluded. Among the enrolled patients, there were 48 males and 116 females, aged from 20 to 78 years, with an average of (44.85±10.26) years. The course of the disease was from 10 months to 15 years, with an average disease course (5.68±2.62) years old. Also, 60 healthy volunteers with no allergic diseases, no family history of tumor diseases, and no immune deficiencies in the same period and at the similar ages were selected as the control group, including 15 males and 45 females, aged 22 to 75 years old, with an average of (45.24±8.72) years old. The research subjects all voluntarily signed informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Grouping standards

Before antibiotic treatment, the SLE patient's blood, mid-section urine, sputum, and other specimens were collected for bacterial culture, and the results of bacterial culture were used as the "gold standard" for confirming infection. Patients with at least two positive results of bacterial cultures were divided into the bacterial infection group (patients with SLE combined with bacterial infection at stable and active stages were included), and the remaining patients were included in the non-bacterial infection group.

Observation indicators

The general data (such as sex, age, course of SLE) and laboratory indicators (including serum macrophage migration inhibitors (MIF), C-reactive protein (CRP), red blood cell distribution width (RDW) levels, PCT, WBC, neutrophil count (NEUT) and lymphocyte count (LYMPH) were compared among the 2 groups.

Before antibiotic treatment, 3 mL of venous blood in the fasting state in the morning was collected and then centrifuged at 3,000 g, 4 ℃ for 15 min. Automatic biochemical analyzer (MODEL: AU5800, purchased from Beckman Coulter) was used to detect MIF and CRP levels. The VIDAS automatic fluorescence immunoassay

Table 1 Comparison of general data of patients in the three groups

Group	Case	Man/woman	Age (years)	SLE course (years)
Bacterial infection group	46	10/36	46.85±8.56	6.20±3.10
Non-bacterial infection group	118	38/80	44.10±10.88	5.42±2.78
Control group	60	15/45	45.24±8.72	–
χ^2/F/t value		2.189	1.309	1.562
P value		0.335	0.272	0.120

SLE, systemic lupus erythematosus.

Table 2 Comparison of indicator levels in the three groups

Group	Case	MIF (ng/mL)	CRP (mg/L)	RDW (%)	PCT (ng/mL)	WBC (×10^9/L)	NLR
Bacterial infection group	46	2.01±0.26	28.01±4.17	15.02±2.13	2.58±1.85	8.95±2.48	3.59±1.93
Non-bacterial infection group	118	1.93±0.25	8.42±1.78	14.76±2.05	0.28±0.15	5.24±1.84	2.72±1.67
Control group	60	1.90±0.23	7.28±1.12	14.70±2.01	0.15±0.08	2.85±1.26	1.78±0.80
F value		2.727	1317.803	0.356	141.785	140.196	18.006
P value		0.068	<0.001	0.701	<0.001	<0.001	<0.001

MIF, migration inhibitory factor; CRP, C-reactive protein; RDW, red blood cell distribution width; PCT, procalcitonin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio.

instrument (Mérieux, France) was used to detect serum levels of RDW and PCT quantitatively. And the automatic blood cell analyzer (Optoelectronics, Japan) was used to detect the levels of WBC, NEUT, and LYMPH, and the NLR ratio (NEUT/LYMPH) was calculated.

Statistical analysis

All data were analyzed using the SPSS19.0 software (IBM, USA). Count data was expressed as case (%), and analyzed by Chi-squared test. The levels of PCT, WBC, and NLR were expressed as mean ± standard deviation and analyzed by the *t*-test. Logistic regression analysis was performed for multivariate analysis. The receiver operating characteristic (ROC) curve of research subjects was drawn to analyze the differential diagnosis value of PCT, WBC, and NLR in SLE with a bacterial infection. Results with P<0.05 were considered statistically significant.

Results

Comparison of general data

The results of bacterial culture showed that there were 46 cases of bacterial infection. And there was no significant difference in the general data, including gender, age, disease course of SLE patients in the three groups (P>0.05, *Table 1*).

Comparison of indicator levels in the three groups

There was no significant difference in MIF and RDW among the three groups (P>0.05). The levels of CRP, PCT, WBC, and NLR in the bacterial infection group and the non-bacterial infection group were significantly higher than those in the control group, and which were significantly higher in the bacterial infection group than in the non-bacterial infection group (P<0.05, *Table 2*).

Multivariate analysis for SLE combined with bacterial infection

Independent variables of multivariate analysis were selected as the above statistically significant variables, which could be directly input as they were all measurement data. The results showed that PCT, WBC and NLR were independent risk factors for SLE combined with bacterial infection (P< 0.05, *Table 3*).

Table 3 Multivariate analysis for SLE combined with bacterial infection

Indicator	Regression coefficient	SEM	Wald χ^2 value	P value	OR value	95% CI
CRP	1.005	1.219	0.098	0.073	2.146	0.835–4.279
PCT	1.119	1.854	0.348	0.006	2.637	1.124–5.071
WBC	1.150	1.892	0.363	0.004	2.843	1.302–5.748
NLR	1.225	1.993	0.412	<0.001	2.978	1.590–5.816

SLE, systemic lupus erythematosus; SEM, standard error of mean; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio.

Table 4 Analysis of PCT, WBC, NLR and their combination in the differential diagnosis of SLE patients combined with a bacterial infection

Indicator	AUC	95% CI	Youden index	Cut-off value	Sensitivity (%)	Specificity (%)
PCT	0.883	0.807–0.958	0.766	0.705	78.3	98.3
WBC	0.669	0.570–0.768	0.350	7.580	43.5	91.5
NLR	0.624	0.525–0.723	0.264	3.240	69.6	56.8
Combination	0.919	0.863–0.974	0.758	–	78.3	97.5

PCT, procalcitonin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; AUC, area under the curve.

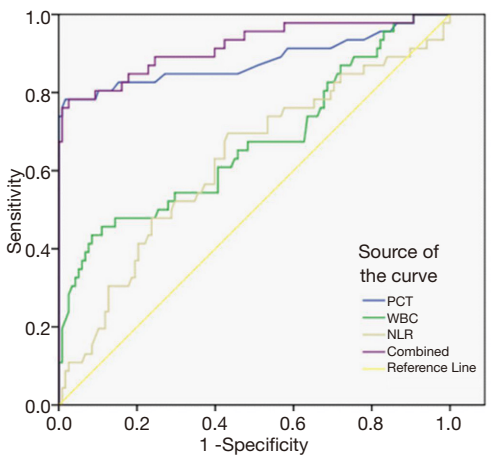

Figure 1 ROC curve of PCT, WBC, NLR and their combination in the differential diagnosis of SLE patients complicated with a bacterial infection. ROC, receiver operating characteristic; PCT, procalcitonin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; SLE, systemic lupus erythematosus.

Application value of PCT, WBC, NLR in the differential diagnosis of SLE with a bacterial infection

Results of ROC curve analysis showed that the area under the curve for differential diagnosis of SLE with bacterial infection was 0.883, 0.669, 0.624, respectively, with the sensitivities of 78.3%, 43.5%, 69.6% for PCT, WBC, and NLR, and the specificities of 98.3%, 91.5%, 56.8%, respectively. The area under the curve of the combined prediction was 0.919, with a sensitivity of 78.3%, and a specificity of 97.5%, showing that the combined prediction value was significantly higher than any of the single predictions (*Table 4*, *Figure 1*).

Changes in the levels of PCT, WBC and NLR in the bacterial infection group before and after treatment

The levels of PCT, WBC, and NLR gradually decreased with the progress of treatment, and the difference before and after treatment was statistically significant (P<0.05, *Table 5*).

Discussion

SLE is a common autoimmune disease. The etiology and mechanism of SLE are complex and have not yet been fully understood, mostly believed to be related to the imbalance of the patient's peripheral immune tolerance (9). SLE is a disease with an imbalance of the body's immune tolerance function, which can lead to the activation and proliferation of auto-reactive T lymphocytes and B lymphocytes of the immune system. And the neutrophils and macrophages promote the vicious circle of inflammatory injury (10). With

Table 5 Changes of PCT, WBC and NLR levels in the bacterial infection group before and after treatment

Time	PCT (ng/mL)	WBC ($\times 10^9$/L)	NLR
Before treatment	2.58±1.85	8.95±2.48	3.59±1.93
Treatment for 7 d	1.02±0.52	5.76±2.00	2.95±1.45
Discharged	0.30±0.08	3.90±1.44	2.20±0.78
F value	50.674	73.640	10.379
P value	<0.001	<0.001	<0.001

PCT, procalcitonin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio.

the improvement of diagnosis and treatment methods, the prognosis of SLE has been significantly improved, but the clinical manifestations of SLE are like a bacterial infection in many aspects. Patients with SLE are often in the status of immunosuppressing for the immune disorder caused by SLE itself, or by the hormones used during the treatment of the disease. Therefore, once there are bacterial infections in SLE patients, patients are more likely to progress to get sepsis, causing many deaths by infection and the no reduction of mortality of SLE (11). Combined bacterial infection has become a common reason for clinical death in SLE patients. Therefore, the differential diagnosis of SLE combined with bacterial infection has become a clinical problem that needs to be solved urgently.

In this study, we divided the SLE patients into bacterial infection group and non-bacterial infection group, according to the results of bacterial culture. It was found the levels of CRP, PCT, WBC and NLR in the bacterial infection group and non-bacterial infection group were significantly higher than those in the control group, and which was higher in the bacterial infection group than that in the non-bacterial infection group, suggesting that the levels of CRP, PCT, WBC and NLR are upregulated in patients with SLE. The increased level of these indicators in patients with bacterial infection is more significant than non-bacterial infection. Analysis of the reason shows that CRP expression level is generally increased in patients with infection and autoimmune diseases, which can reflect the inflammatory state of the body. PCT is the pro-peptide substance of serum calcitonin (CT), with no hormonal activity. Thyroid C cells secrete PCT in vivo. The level of PCT in the serum of healthy people is very low, while under the status of bacterial infection or sepsis, PCT can be synthesized in various tissues and organs, then many PTC will be released into the blood circulatory system. The body's status of immunosuppressing could not affect the increase of PCT concentration. Even if the patient is in an immunosuppressive state or has no visible clinical manifestations of SLE, the plasma PCT level will increase significantly. The WBC is the sum of nucleated cells, including neutrophils, lymphocytes, monocytes, and another karyocyte in peripheral blood. It is an essential line of defense for the body to resist the invasion of foreign bodies, including pathogenic microorganisms. In the clinic, various inflammatory reactions and infections could regulate the WBC level. Therefore, the diagnostic sensitivity and specificity are not high, and other serum inflammatory factors need to be combinedly used with the WBC to test the occurrence of infectious diseases (12). NLR is defined as the ratio of the inflammation activator NEUT and the inflammation regulator LYMPH. NLR is a reliable index of systemic inflammation, reflecting the balance between the two molecules. The higher the ratio, the higher the body's inflammatory response or stress response. Bacterial infection has a higher inflammation reaction or stress response in the body than viral infection, so NLR is better to reflect the infection status of the body than NEUT, and the increase of NLR often shows a bacterial infection. The detection of NLR cannot only reflect the disease at the cellular level but also show the patient's inflammatory response and immune status, further providing reference information for the clinical diagnosis and treatment of the disease (13,14). In this study, multi-factor analysis found that PCT, WBC and NLR were independent risk factors for SLE combined bacterial infection, indicating that the higher the level of PCT, WBC and NLR, the greater the risk of SLE associated bacterial infection. Further analysis of the ROC curve revealed that the sensitivity of CRP, PCT, WBC, and NLR in the differential diagnosis of SLE with bacterial infection was 78.3%, 43.5%, 69.6%, and the specificity was 98.3%, 91.5%, and 56.8%, respectively. Simultaneously, the predictive value of the combination of these three indicators was significantly higher than a single indicator alone; we observed a sensitivity of 78.3% and a specificity of 97.5%.

It can be concluded the combined detection of CRP, PCT, WBC, and NLR has good sensitivity and specificity for the diagnosis of SLE patients combined with a bacterial infection and can be used for early auxiliary diagnosis of this disease. And the levels of CRP, PCT, WBC, and NLR were gradually decreased with the treatment process.

However, the increase is almost no or not obvious when patients are with viral infections, tumors, and other diseases combined with fever. Therefore, several studies suggest that PCT could be used as a sensitive indicator for the early differential diagnosis of bacterial infections (15,16). The increase of PCT concentration is not affected by the immunosuppressive state of the body, and the plasma PCT concentration will be significantly increased even if the patient is in the immunosuppressive state or there is no obvious clinical manifestation. Therefore, PCT is also of good diagnostic value for patients with SLE complicated with bacterial infection and stable period without fever.

To sum up, although there are many studies on SLE combined with bacterial infections, opinions and conclusions are not uniform. The treatment of SLE is always with immunosuppressants and hormones, which are always double-edged swords for SLE patients. Therefore, clinicians should grasp the balance of the primary disease controlling and the infection risk. Indicators, including PCT, WBC, and NLR, may be used as monitoring indicators for the diagnosis and treatment of SLE patients combined with a bacterial infection. However, the sample size of this study is small, and it is a non-multicenter study, which has certain limitations. It still needs to be further demonstrated and improved in the next large-scale and multicenter study.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1777

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study of Daqing Oilfield General Hospital was approved by ethics committee. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Signed informed consent was taken from all patients.

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