Original Article

The Diagnostic Utility of Procalcitonin for the Detection of Infection among Systemic Lupus Erythematosus Patients in a Tertiary Care Hospital

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Background: Clinical manifestations of infection in patients with systemic lupus erythematosus (SLE) are variable and involve significant diagnostic challenges. Delays in diagnosis and treatment strongly affect the clinical outcomes and mortality. The elevation of one's serum procalcitonin (PCT) level may be a diagnostic biomarker of infection in SLE.

Objective: To determine the diagnostic accuracy of PCT for bacterial and fungal infections in patients with SLE.

Materials and Methods: Samples of serum PCT were prospectively collected in all patients with SLE admitted to medical wards at Siriraj Hospital, a tertiary care center, between February 2011 and March 2012.

Results: One hundred twenty-four patients with SLE were enrolled. The mean age was 31.9±10.9 years. The median disease duration of SLE was five years. The Median Mexican SLE Disease-Activity Index Score was 8 (IQR 6 to 11.8). Ninety-five percent of patients had active SLE and 70% of them were treated with prednisolone of more than 15 mg/day or equivalent doses of other corticosteroids. The serum PCT levels of SLE patients with infection (n=39; median 0.52 ng/mL, IQR 0.15 to 1.49) were significantly increased, compared to those of SLE patients with no infection (n=85; median 0.09 ng/mL, IQR 0.04 to 0.16), p<0.001. The cut-off point of elevated serum PCT (0.5 ng/mL) for the diagnosis of bacterial or fungal infections in patients with SLE had sensitivity, specificity, positive predictive value, and negative predictive values of 51.3%, 95.3%, 83.3%, and 81%, respectively. The independent factors associated with elevated serum PCT levels of 0.5 ng/mL or more were the presence of a bacterial or fungal infection, a low hemoglobin level, and serum Cr of 2 mg/dL or more.

Conclusion: The elevation of one's serum PCT level may be a useful biomarker to detect bacterial and fungal infections in patients with SLE.

Keywords: Systemic lupus erythematosus; Procalcitonin; Sensitivity; Specificity; Infection; Sepsis; Flare

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Systemic lupus erythematosus (SLE) is a common multi-system autoimmune disease in Thailand. Despite recent advances in non-steroid therapy, infection remains one of the major causes of morbidity and mortality in SLE patients. Patients with highly active SLE disease are more susceptible to infection because of the intrinsic immunological abnormalities of lupus, immunosuppressive therapy, and the associated organ complications of the disease.

Disease flares occur with variable clinical manifestations such as fever, chills, or anemia, and may mimic infection, resulting in difficult differential diagnosis in the early stages of the disease. Furthermore, both situations can co-exist. Microbiological diagnosis is the gold standard for the diagnosis of infection, but a definitive result may take 24 hours or more. A rapid and accurate differential diagnosis is crucial for severely ill patients because the therapy of SLE flares and infection is in the opposite direction. Infection requires antibiotic therapy and the reduction of immunosuppressive drugs, whereas SLE flares require a higher dose of immunosuppressive drugs.

The clinical and conventional laboratory parameters of inflammation, including changes in body temperature, respiratory rate, tachycardia, leukocytosis, and an elevated erythrocyte-sedimentation rate are sensitive. However, their

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use is limited by the poor specificity regarding the diagnosis of infection, and may be affected by the underlying disease, treatment, or immunosuppressive drugs. Conventional SLE activity biomarkers, such as hypocomplementemia and anti-double-stranded-DNA antibodies are helpful, but not always reliable to distinguish between infection and active disease. In recent years, there have been significant efforts to determine several biological markers to differentiate disease flares from concurrent infections in febrile SLE patients, such as C-reactive protein (CRP), procalcitonin, complement C3, complement C4. neutrophil CD64 index, and presepsin[1-9].

CRP levels may be mildly to moderately elevated during SLE flares but are significantly elevated in patients with a bacterial infection. The CRP level may be a useful indicator of the presence of an infection in SLE patients. However, the range of CRP levels in patients with infection occasionally overlaps with those of patients with SLE flares[2-6].

Procalcitonin (PCT), a peptide precursor of calcitonin, consists of 116 amino acids and is physiologically secreted by the parafollicular C-cells of the thyroid. Generally, serum PCT levels are low, at less than 0.1 ng/mL, in healthy individuals and patients with viral infections, a localized bacterial infection, or inflammatory reactions of a non-infectious origin. PCT has been reported to increase rapidly in cases of systemic bacterial or fungal infections, malaria, severe burns, severe trauma, major surgery, and acute respiratory distress syndrome. The principal source of PCT seems to originate from parenchymal cells such as the liver, lungs, macrophages, pancreas, kidneys, adipocytes, or muscles. The function and elimination of PCT in infections remain unknown. PCT has a relatively short serum half-life of 22 to 35 hours, compared with CRP, which is 48 hours. Thus, PCT has been claimed to be a useful marker for diagnosing and monitoring systemic bacterial and fungal infections.

PCT has not been extensively studied in patients with SLE disease. Currently, the available studies are relatively small, in terms of sample size[3-7,10-15]. A systematic review by Serio et al in 2014 demonstrated the absence of a correlation between PCT levels and SLE disease activity (five studies, total n=221) and a significant benefit of PCT for the early differentiation between bacterial infection and SLE flares (seven studies, total n=457)[14]. In contrast, a meta-analysis by Liu et al in 2017, including 205 SLE-flare patients and 198 SLE patients with infection, revealed a conflicting result regarding the diagnostic utility of PCT[1]. The definitive cut-off for the differentiation between the two situations also remains controversial because their levels vary according to the severity of infection.

The purpose of the present study was to determine the usefulness of serum PCT for the diagnosis of non-viral infections and factors associated with PCT elevation among hospitalized patients with various degrees and treatments of SLE diseases.

Materials and Methods

Patient enrollment

A cross-sectional study was conducted from February, 2011 through March, 2012 in Siriraj Hospital, a 2,111-bed tertiary care university hospital in Bangkok, Thailand. All SLE patients with complete medical records hospitalized for any condition in the department of Internal Medicine were prospectively recruited for the study. The diagnosis of SLE was made 1) according to the American College of Rheumatology's revised criteria for the classification of SLE[16] or 2) from a renal biopsy. The patients were excluded if there were overlapping syndromes, incomplete clinical information, or unavailable specimens.

Clinical measurements

Clinical characteristics were collected from the medical records, including gender, age, body-mass index (BMI), criteria for SLE at diagnosis, the duration of SLE, the presence of underlying conditions, current medications, the source and causative organisms of infection, and the laboratory parameters, including the hemoglobin level, white blood cell count, serum creatinine, serum albumin, and serum total calcium.

SLE disease activity during recruitment was measured using the Mexican SLE disease-activity index (MEX-SLEDAI) score as remission with a score of 0 to 1, mild disease activity with a score of 2 to 5, moderate disease activity with a score of 6 to 9, severe disease activity with a score of 10 to 13, and very severe disease activity with a score of 14 or more[17,18].

The diagnosis of infection was evaluated by the infectious disease physicians and the rheumatologists using clinical symptoms, radiological findings, and microbiological tests. To evaluate the influence of infection on the PCT levels, the authors divided the infected patients into two subgroups based on their clinical infections, the authors' microbiological investigations, and their responses to empirical therapy. (i) A clinically significant infection subgroup involved febrile episodes with signs or symptoms of

an infection, and relevant causative pathogen were identified by gram stain, pathology, serology, culture, antigen, and molecular techniques or typical clinical, radiological, or laboratory evidence of infection, combined with significant improvement after the patient received appropriate antibiotics. (ii) A possible infection subgroup involved febrile episodes with or without signs or symptoms of a focal infection, negative microbiological investigations, and gradual improvement after receiving antibiotics.

PCT measurement

After informed consent was obtained, blood samplings of about 5 mL in a lithium-heparin tube were taken and sent to the laboratory department within 60 minutes. Serum samples were collected within 24 hours after study enrollment. The samples that were not processed immediately were frozen at –20°C. Serum concentrations of PCT were determined by using an Elecsys® BRAHMS PCT electrochemiluminescence immunoassay (Roche Diagnostics, Berlin, Germany) on the Cobas® e-analyzer according to the manufacturer's instructions. The limit of PCT detection was 0.02 ng/mL, and PCT levels less than 0.05 ng/mL were considered to be normal in the present study laboratory.

The present study protocol was approved by the Institutional Review Board of the authors' hospital (COA no. Si 673/2010), and informed consents were given from all subjects.

Statistical analysis

The statistical analysis was performed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to their homogeneity. Categorical variables were compared using the chi-squared test or the Fisher's exact test, as appropriated. The continuous variables were compared by the student t-test. Non-parametric tests were used when the application conditions were not applicable. Spearman's rank correlation coefficient was calculated to examine the correlation between the PCT levels and the selected variables. Statistical significance was defined as two-tailed with a p-value of less than 0.05. The PCT cut-off value to accurately diagnose infection in SLE patients was evaluated by the best combination of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LR), negative LR, and a receiver operating characteristic (ROC) analysis. Multivariable analysis using stepwise logistic regression identified factors independently associated with PCT level elevation. All significant univariate variables at p-value less than 0.05 that did not have a zero cell were included in the logistic model.

Results

Characteristics of SLE patients

One hundred thirty-four cases were enrolled during the 14-month study period. Ten patients were excluded due to specimen-collection errors (n=7) and incomplete medical records (n=3). Among 124 patients recruited for the present study, most participants were female (93.5%), and their mean age was 31.9±10.9 years. The median years since SLE diagnosis was five (IQR 1 to 10). The main criteria for SLE diagnosis included positive antinuclear antibody (80.6%), renal disorder (61.3%), arthritis (50.8%), positive anti-dsDNA (47.6%), and malar rash (44.4%). Most patients (70.2%) received more than 15 mg of prednisolone (or the equivalent) per day. Half of the patients (56.5%) received chloroquine or hydroxychloroquine. The demographic and clinical characteristics of the study patients are presented in Table 1.

Characteristics of infections

At the time of drawing blood for PCT measurement, 39 patients were found to have systemic bacterial or fungal infection and included 26 patients with clinically significant infection and 13 with possible infection. The other 85 patients had no evidence of infection. Twenty-one patients, including eight with clinically significant infection and 13 with a possible infection, were clinically suspected to have infection, but their cultures were not done or were negative. The most frequently documented infection was pneumonia, followed by bacteremia, gastrointestinal (GI) tract infection, urinary tract infection (UTI), and central nervous system (CNS) infection (Table 2). The causative microorganisms and PCT level are shown in Table 3. Almost all the patients in the infection group (97%) were receiving empirical antibiotics at the time of blood collection. In addition, 25 out of 39 infected patients had received antibiotics for more than 48 hours (median 3 days, IQR 2 to 5).

Comparison of SLE characteristics between the infection and non-infection group

In the present study, malar rash, neurologic disorder, clinical suspicion of infection, severe sepsis or septic shock, chloroquine or hydroxychloroquine

Table 1. Demographic and clinical characteristics of the SLE patients

Characteristics	All patients (n=124); n (%)	Infection group (n=39); n (%)	Non-infection group (n=85); n (%)	p-value
Sex: female	116 (93.5)	36 (92.3)	80 (94.1)	0.706
Age (year); mean±SD	31.9±10.9	33.3±12.4	31.3±10.2	0.342
BMI (kg/m^2); mean±SD	21.4±4.5	20.8±4.09	21.6±4.7	0.353
SLE criteria at diagnosis				
Malar rash	55 (44.4)	24 (61.5)	31 (36.5)	0.009
Discoid rash	26 (21.0)	9 (23.1)	17 (20.0)	0.696
Photosensitivity	15 (12.1)	5 (12.8)	10 (11.8)	1.000
Oral ulcers	34 (27.4)	15 (38.5)	19 (22.4)	0.062
Nonerosive arthritis	63 (50.8)	21 (53.8)	42 (49.4)	0.647
Serositis	14 (11.3)	6 (15.4)	8 (9.4)	0.366
Renal disorder	76 (61.3)	21 (53.8)	55 (64.7)	0.249
Neurologic disorder	16 (12.9)	9 (23.1)	7 (8.2)	0.022
Hematologic disorder				
• Hemolytic anemia	37 (29.8)	14 (35.9)	23 (27.1)	0.318
• Leukopenia	27 (21.8)	11 (28.2)	16 (18.8)	0.240
• Lymphopenia	20 (16.1)	8 (20.5)	12 (14.1)	0.369
• Thrombocytopenia	25 (20.2)	6 (15.4)	19 (22.4)	0.369
Positive antinuclear antibody	100 (80.6)	33 (84.6)	67 (78.8)	0.448
Immunologic disorder				
• Anti-dsDNA	59 (47.6)	23 (59.0)	36 (42.4)	0.085
• Anti-Sm	7 (5.6)	3 (7.7)	4 (4.7)	0.677
• Antiphospholipid antibodies	9 (7.3)	3 (7.7)	6 (7.1)	1.000
Other: vasculitis	13 (10.5)	5 (12.8)	8 (9.4)	0.545
Duration of SLE (year); median (IQR)	5 (1 to 10)	5 (1 to 10)	5 (0.9 to 10)	0.492
Other diagnosis	36 (29.0)	14 (35.9)	22 (25.9)	0.254
Hypertension	17 (13.7)	7 (17.9)	10 (11.8)	0.353
Avascular necrosis of hip joint	9 (7.3)	4 (10.3)	5 (5.9)	0.461
Thyroid disorder	5 (4.0)	1 (2.6)	4 (4.7)	1.000
Cerebrovascular disease	3 (2.4)	1 (2.6)	2 (2.4)	1.000
Chronic hepatitis B infection	3 (2.4)	1 (2.6)	2 (2.4)	1.000
Known HIV-positive	1 (0.8)	1 (2.6)	0 (0.0)	0.315
Pregnancy	1 (0.8)	1 (2.6)	0 (0.0)	0.315
Diabetes mellitus	1 (0.8)	0 (0.0)	1 (1.2)	1.000
Clinical diagnosis				
Active SLE*	118 (95.2)	35 (89.7)	83 (97.6)	0.077
• MEX-SLEDAI score; median (IQR)	8 (6 to 11.8)	9 (6 to 14)	8 (6 to 11)	0.833
Suspected infection	53 (42.7)	36 (92.3)	17 (20.0)	<0.001
• Severe sepsis/septic shock	3 (2.4)	3 (7.7)	0 (0.0)	0.029
Medications				
Current prednisolone (or equivalent) dosage ≥15 mg/day	87 (70.2)	21 (53.8)	66 (77.6)	0.007
Chloroquine or hydroxychloroquine	70 (56.5)	28 (71.8)	42 (49.4)	0.020
Cyclophosphamide	19 (15.3)	3 (7.7)	16 (18.8)	0.110
Azathioprine	19 (15.3)	2 (5.1)	17 (20.0)	0.033
Mycophenolate mofetil	6 (4.8)	2 (5.1)	4 (4.7)	1.000
Calcium supplementation	97 (78.2)	30 (76.9)	67 (78.8)	0.812
Receiving at least one antibiotics (ATB)	59 (47.6)	38 (97.4)	21 (24.7)	<0.001
Duration of antibiotic administration before blood collection (days); median (IQR)	0 (0 to 3)	3 (2 to 5)	0 (0 to 0)	<0.001
Laboratory parameters				
Procalcitonin level (ng/mL)				
• Median	0.116	0.523**	0.089	<0.001
• IQR	0.06 to 0.27	0.15 to 1.49	0.04 to 0.16	
• Range	0.02 to 32.97	0.05 to 32.97	0.02 to 1.15	
Hemoglobin level (g/dL); mean±SD	9.9±2.3	9.4±2.1	10.1±2.3	0.127
WBC count (/mm^3); median (IQR)	7,130 (4,378 to 10,595)	5,590 (4,100 to 10,580)	7,300 (4,570 to 10,675)	0.304
Serum creatinine level (mg/dL); median (IQR)	1.0 (0.7 to 1.6)	1.0 (0.7 to 1.9)	1.0 (0.7 to 1.5)	0.649
Serum creatinine level ≥2 mg/dL	21 (16.9)	9 (23.1)	12 (14.1)	0.217
Serum albumin level (g/dL); mean±SD	2.8±0.7	2.7±0.6	2.9±0.7	0.070
Serum calcium level (mg/dL)**; mean±SD	8.1±1.1	8.0± 1.5	8.2±0.7	0.538

BMI=body mass index; SLE=systemic lupus erythematosus; MEX-SLEDAI=Mexican SLE disease-activity index; WBC=white blood cell; SD=standard deviation; IQR=interquartile range

* MEX-SLEDAI Score ≥2, ** n=91

Table 2. Serum PCT levels in SLE patients with different sites of infections

Types of infections	No. of patients; n (%)	PCT level (ng/mL)	
		Median	Range
Pneumonia	14 (35.9)	0.26	0.05 to 19.92
Blood stream infection	7 (17.9)	0.64	0.09 to 6.10
GI tract infection	7 (17.9)	1.30	0.21 to 4.94
Urinary tract infection	6 (15.4)	0.90	0.09 to 33.00
CNS infection	6 (15.4)	0.20	0.07 to 0.73
Skin & soft tissue infection	5 (12.8)	0.99	0.21 to 19.92
Lymphadenitis	2 (5.1)	1.76	0.12 to 3.40
Prosthetic joint infection	1 (2.6)	0.21	0.21
Total	39 (100)*	0.52	0.05 to 33.00

PCT=procalcitonin; GI=gastrointestinal; CNS=central nervous system

* Nine patients had more than one source of infection

use, and antibiotic administration were more frequently observed in SLE with infection. However, current prednisolone therapy greater than 15 mg/day and azathioprine therapy were lower in SLE with infection than in SLE without infection (p=0.007 and 0.033, respectively). The lower dose of glucocorticoids among the infection group was possibly due to a high suspicion of sepsis. There were no significant differences in age, gender, BMI, disease duration, underlying disease, MEX-SLEDAI score, hemoglobin level, white blood cell (WBC) count, serum creatinine, serum albumin, or serum calcium between the infection and non-infection group.

Comparison of PCT values between the infection and non-infection group

PCT concentrations were elevated at or more than 0.5 ng/mL in 19.4% of total cases (24 of 124 patients), with a median of 0.12 ng/mL (IQR 0.06 to 0.27 ng/mL). The PCT levels were significantly elevated in SLE patients with infection, compared to those without infection (p<0.001). There was a very low and probably meaningless correlation between clinical disease activity (MEX-SLEDAI score) and serum PCT levels (r=0.188, p=0.037). In a subgroup analysis of infection, the PCT levels were

Table 3. Comparison of serum PCT levels in the clinically significant infection subgroup of SLE patients according to causative organisms (n=26)

Causative organisms	No. of patients; n (%)	PCT level (ng/mL); median
Gram-positive bacteria	5 (19.2)	0.21 (0.15 to 1.30)*
Staphylococcus aureus (MSSA)	2 (11.5)	0.21, 0.99
Coagulase negative staphylococcus	1 (3.8)	0.21
Streptococcus group D	1 (3.8)	1.30
Listeria monocytogenes	1 (3.8)	0.15
Gram-negative bacteria	5 (19.2)	2.67 (0.63 to 32.97)*
Escherichia coli + *Klebsiella pneumoniae*	1 (3.8)	1.28
Escherichia coli + *Acinetobacter baumannii*	1 (3.8)	0.63
Klebsiella pneumonia	1 (3.8)	32.97
Pseudomonas aeruginosa	1 (3.8)	2.67
Stenotrophomonas maltophilia	1 (3.8)	14.58
Other bacteria	1 (3.8)	0.65
Nocardia spp.	1 (3.8)	0.65
Mycobacterium infection	4 (15.4)	2.52 (0.09 to 19.92)*
Mycobacterium tuberculosis	3 (11.5)	0.10, 4.94, 19.92
Mycobacterium hemophilium	1 (3.8)	0.09
Mixed type of organisms	3 (11.5)	0.73 (0.64 to 6.1)*
Mycobacterium tuberculosis + *Cryptococcus neoforman*	1 (3.8)	0.73
Enterococcus faecium + *Candida tropicalis*	1 (3.8)	6.1
Staphylococcus aureus (MRSA) + *Acinetobacter baumannii*	1 (3.8)	0.64
Culture: not done or no growth	8 (30.8)	1.39 (0.05 to 3.4)*

PCT=procalcitonin; MSSA=methicillin-susceptible *Staphylococcus aureus*; MRSA=methicillin-resistant *Staphylococcus aureus*

* Median (range)

Table 4. Diagnostic performance of PCT for the prediction of systemic bacterial and fungal infections among SLE patients

PCT cut-off (ng/mL)	Diagnostic performance (95% CI)						
	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)	Positive LR	Negative LR	ROC area**
≥0.15	76.9 (60.7 to 88.9)	74.1 (63.5 to 83.0)	57.7 (43.2 to 71.3)	87.5 (77.6 to 94.1)	0.97 (1.99 to 4.43)	0.31 (0.17 to 0.56)	0.76 (0.67 to 0.84)
≥0.25	56.4 (39.6 to 72.2)	88.2 (79.4 to 94.2)	68.8 (50.0 to 83.9)	81.5 (72.1 to 88.9)	4.79 (2.52 to 9.13)	0.49 (0.34 to 0.71)	0.72 (0.64 to 0.81)
≥0.50	51.3 (34.8 to 67.6)	95.3 (88.4 to 98.7)	83.3 (62.6 to 95.3)	81.0 (71.9 to 88.2)	10.90 (3.99 to 29.75)	0.51 (0.37 to 0.71)	0.73 (0.65 to 0.82)

PCT=procalcitonin; LR=likelihood ratio; PPV=positive predictive value; NPV=negative predictive value; ROC=receiver operating characteristic; CI=confidence interval

* Prevalence of infection 31.5% (95% CI 23.4 to 40.4), ** ROC area was calculated as (sensitivity + specificity)/2

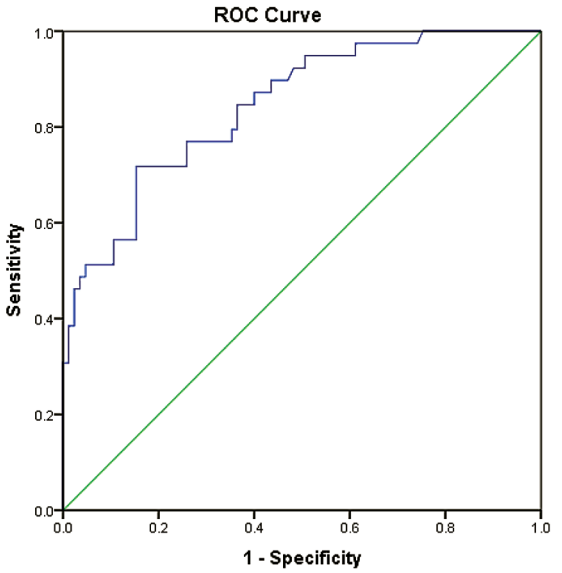

Figure 1. The receiver-operating-characteristic (ROC) curves of different cut-offs of serum PCT in SLE patients for the prediction of infection. The area under the curve (AUC) was 0.844 (95% CI 0.771 to 0.917; p<0.001).

more elevated in patients with clinically significant infection (n=26; median 0.86 ng/mL, IQR 0.44 to 3.13) than in patients with possible infection (n=13; median 0.15 ng/mL, IQR 0.11 to 0.21), p<0.001. All patients in the possible infection subgroup had a serum PCT level less than 0.5 ng/mL.

The cut-off value of PCT for the diagnosis of infection

In the ROC analysis of PCT, the area under the curve (AUC) was 0.844 (95% confidence interval [CI] 0.771 to 0.917; p<0.001) for diagnosing infection in SLE patients (Figure 1). The diagnostic performance of serum PCT at different cut-off values is presented in Table 4. A cut-off value of 0.5 ng/mL for PCT gave the best combination of sensitivity (51.3%), specificity (95.3%), positive predictive value (83.3%), negative predictive value (81.0%), positive LR (10.9), and negative LR (0.5). When the cut-off value was set at the lower value of 0.15 ng/mL, the sensitivity went up to 76.9%, but the positive predictive value and positive LR were significantly reduced to 57.7% and 0.97, respectively. For these reasons, the authors believed that the cut-off of 0.5 ng/mL was more clinically useful for SLE populations.

Five patients had overt infection, but their PCT levels were less than 0.5 ng/mL (Table 5). Three patients had bacterial infections, one had a *Mycobacterium hemophilum* infection, and one had invasive pulmonary aspergillosis. Four of those five patients had received appropriate antibiotics more than 48 hours prior to the PCT test.

In the present study, the authors found only four non-infected patients whose PCT level was above the cut-off level (0.58, 0.60, 0.66, and 1.15 ng/mL), and their detailed characteristics are listed in Table 6. None of these patients had evidence of systemic infection. All of them had a Mex-SLEDAI score at or higher than 6. Three patients had lupus nephritis and an elevated serum creatinine level (1.9, 5.4, and 6.6 mg/dL). One patient had oropharyngeal candidiasis.

Factors associated with PCT elevation

On multivariate analysis, the independent factors associated with PCT elevation of 0.5 ng/mL or more, were the presence of infection, a lower hemoglobin level, and serum Cr of 2 mg/dL or more (Table 7). There was a trend toward a higher PCT level in patients infected with gram-negative bacteria, compared with patients infected with other organisms, although this was not statistically significant (p=0.054), possibly due to the small sample size. Neither SLE disease activity nor immunosuppressive drugs had an impact on the PCT levels.

For all patients, in univariate analysis, there was no significant difference in their PCT level between renal and non-renal involvement of SLE (p=0.457) and the PCT level between hemolytic anemia and non-

Table 5. Characteristics of SLE patients with infection who had PCT level <0.5 ng/mL

Patients No.	Sex	Age (year)	Active organ involvement	MEX-SLEDAI score	Other diagnosis	Clinical infection	Fever*	Duration of appropriate antibiotic** (day)	PCT level (ng/mL)
1	F	29	Skin renal	10	-	Probable invasive pulmonary aspergillosis	+	1	0.04
2	F	38	-	0	HTN AVN of right hip	Disseminated *Mycobacterium hemophilum* infection	–	3	0.08
3	F	26	Skin	4	-	*Listeria monocytogenes* septicemia & meningitis	–	4	0.15
4	F	51	Skin CNS	10	HTN	MSSA tracheobronchitis	+	4	0.20
5	F	46	Skin	2	HTN AVN of both hips	Chronic PJI from coagulase negative *Staphylococcus*	–	4	0.21

MEX-SLEDAI=Mexican SLE disease-activity index; PCT=procalcitonin; F=female; CNS=central nervous system; HTN=hypertension; AVN=avascular necrosis; MSSA=methicillin-susceptible *Staphylococcus aureus*; PJI=prosthetic joint infection

* Within 24 hour of blood collection for PCT assay, ** Prior to blood collection for PCT assay

Table 6. Characteristics of SLE patients without infection who had PCT level ≥0.5 ng/mL

Patients No.	Sex	Age (year)	Active organ involvement	MEX-SLEDAI score	Other diagnosis	Serum creatinine (mg/dL)	PCT level (ng/mL)
1	F	35	Skin musculoskelental hematological CNS	6	Oropharyngeal candiasis	1.1	0.66
2	F	30	Renal	6	No	1.9	0.58
3	F	20	Renal cardiopulmonary	16	HTN ESRD on hemodialysis	5.4	0.60
4	F	64	Renal hematological	10	HTN chronic hepatitis B infection	6.6	1.15

MEX-SLEDAI=Mexican SLE disease-activity index; PCT=procalcitonin; F=female; CNS=central nervous system; HTN=hypertension; ESRD=end stage renal disease

hemolytic anemia of SLE (p=0.382). Furthermore, there was also no correlation between the PCT levels and the serum creatinine level (r=0.078, p=0.386) or between the PCT levels and hematocrit (r=–0.168, p=0.06).

As regards a subgroup analysis of non-infected patients (n=85), there was no significant difference in the PCT level between the renal and non-renal involvement of SLE (p=0.682), or between hemolytic anemia and non-hemolytic anemia of SLE (p=0.355). In contrast, there were a reasonable correlation between the serum PCT levels and the serum creatinine level (r=0.455, p<0.001), and there was a low correlation between serum PCT levels and hematocrit (r=–0.384, p<0.001).

These facts indicated that renal impairment and anemia per se, not the renal involvement or hemolytic anemia of SLE, used the principal origin of an increased plasma PCT.

Discussion

An early differentiation between infection and disease flares among febrile SLE patients is often very difficult. Microbiological investigations are quite time-consuming. Accurate and timely biomarkers for the detection of infection that are not affected by the SLE disease activity are clearly essential for the current management of SLE. In the present study, the authors performed a cross-sectional analysis to evaluate the clinical usefulness of serum PCT as a diagnostic marker for systemic bacterial and fungal infection in a relatively large number of SLE patients.

Consistent with the previous studies, the authors found that the PCT levels were elevated during bacterial, mycobacterial, and fungal infection. Those levels did not correlate well with SLE disease activity and were not influenced by systemic glucocorticoid or antimalarial therapy[1-7]. PCT may be a useful tool for clarifying the diagnosis in febrile SLE patients.

Our diagnostic cut-off figure of PCT at or above 0.5 ng/mL is consistent with most studies and standards for non-SLE patients[1,7]. The sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of non-viral infections were 51.3%, 95.3%, 83.3%, and 81%, respectively. The patients' characteristics may have contributed to the lower sensitivity of PCT obtained in the present study. First, the PCT levels correlate well with the severity of infection. Only 7.7% of infected patients had severe sepsis and septic shock

Table 7. Univariate and multivariable analysis of factors associated with PCT ≥0.5 ng/mL in SLE patients

Variable	Univariate analysis; n (%)				Multivariable analysis***	
	PCT ≥0.5 ng/mL (n=24)	PCT <0.5 ng/mL (n=100)	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex: female	23 (95.8)	93 (93)	1.73 (0.20 to 14.78)	1.000	...	...
Age (year); mean±SD	33.5±14.7	31.5±9.8	1.02 (0.98 to 1.06)	0.419	...	...
BMI (kg/m^2); mean±SD	21.2±4.7	21.4±4.5	0.99 (0.89 to 1.09)	0.785	...	...
Active SLE*	23 (95.8)	95 (95)	1.21 (0.14 to 10.87)	1.000	...	...
MEX-SLEDAI score; median (IQR)	9.5 (6 to 14)	8.0 (6 to 11)	1.07 (0.98 to 1.17)	0.220	...	...
Bacterial or fungal infection	20 (83.3)	19 (19)	21.32 (6.52 to 69.65)	<0.001	17.40 (3.91 to 77.41)	<0.001
Severe sepsis/septic shock	2 (8.3)	1 (1)	9.00 (0.78 to 103.72)	0.096	...	...
Causative organisms						
Gram positive bacteria	3 (12.5)	4 (4)	3.43 (0.71 to 16.47)	0.131	...	...
Gram negative bacteria	6 (25)	1 (1)	33.0 (3.75 to 290.69)	<0.001	16.10 (0.96 to 270.12)	0.054
Mycobacterium tuberculosis	3 (12.5)	2 (2)	7.00 (1.10 to 44.53)	0.049	3.30 (0.31 to 34.81)	0.321
Fungus (invasive)	2 (8.3)	0 (0)	NA	0.036	NA	NA
Other diagnosis						
Hypertension	4 (16.7)	13 (13)	1.34 (0.40 to 4.54)	0.741	...	...
Avascular necrosis of hip joint	2 (8.3)	7 (7)	1.21 (0.24 to 6.22)	0.685	...	...
Thyroid disorder	1 (4.2)	4 (4)	1.04 (0.11 to 9.78)	1.000	...	...
Cerebrovascular disease	1 (4.2)	2 (2)	2.13 (0.19 to 24.52)	0.479	...	...
Chronic hepatitis B infection	2 (8.3)	1 (1)	9.00 (0.78 to 103.72)	0.096	...	...
Known HIV-positive	1 (4.2)	0 (0)	NA	0.194	...	...
Pregnancy	0 (0.0)	1 (1)	NA	1.000	...	...
Diabetes mellitus	0 (0.0)	1 (1)	NA	1.000	...	...
Current medications						
Prednisolone (or equivalent) ≥15 mg/day	18 (75.0)	85 (85)	0.53 (0.18 to 1.55)	0.239	...	...
Chloroquine or hydroxychloroquine	17 (70.8)	53 (53)	2.15 (0.82 to5.65)	0.114	...	...
Cyclophosphamide	2 (8.3)	17 (17)	0.44 (0.10 to 2.07)	0.363	...	...
Azathioprine	2 (8.3)	17 (17)	0.44 (0.10 to 2.07)	0.363	...	...
Mycophenolate mofetil	3 (12.5)	3 (3)	4.62 (0.87 to 24.50)	0.086	...	...
Calcium supplementation	20 (83.3)	77 (77)	1.49 (0.46 to 4.81)	0.500	...	...
Laboratory parameters						
Hemoglobin level (g/dL); mean±SD	8.6±1.7	10.2±2.3	0.67 (0.52 to 0.87)	0.001	0.62 (0.44 to 0.88)	0.006
WBC count (/mm^3); median (IQR)	6,395 (3,835 to 10,850)	7,170 (4,615 to 10,565)	1.00 (1.00 to 1.00)	0.537	...	...
Serum creatinine level ≥2 mg/dL	9 (37.5)	12 (12)	4.40 (1.58 to 12.24)	0.006	8.52 (1.85 to 39.29)	0.006
Serum calcium level (mg/dL)**; mean±SD	7.9±1.4	8.2±1.0	0.76 (0.50 to 1.16)	0.199	...	...
Serum albumin level (g/dL); mean±SD	2.6±0.7	2.9±0.7	0.48 (0.24 to 0.96)	0.034	0.52 (0.17 to 1.58)	0.248

PCT=procalcitonin; BMI=body mass index; SLE=systemic lupus erythematosus; MEX-SLEDAI=Mexican SLE disease-activity index; WBC=white blood cell; SD=standard deviation; IQR=interquartile range; OR=odds ratio; CI=confidence interval

* Mex-SLEDAI score ≥2, ** n=91, *** All significant univariate variables (p<0.05) that did not have a zero cell were included in the multivariable analysis

during the blood collection. Second, the sensitivity of PCT is significantly reduced in patients that received appropriate antimicrobial therapy, in line with their clinical recovery. In the present study, more than half of the infected patients (64%) received antibiotics at least 48 hours before the blood collection. Third, the PCT levels are not elevated in non-invasive infection or chronic localized infection without systemic signs and symptoms. The present study included one patient each with tracheobronchitis and chronic prosthetic joint infection. Finally, a false negative on a PCT test can occur in the first few days in patients with invasive pulmonary aspergillosis. The present study also had one patient with early invasive pulmonary aspergillosis.

Although the sensitivity (51.3%) and negative

likelihood ratio (0.51) of PCT were not enough to be used as a rule-out diagnostic tool for systemic bacterial or fungal infections, the specificity (95.3%) and positive LR (10.9) of PCT was sufficiently high to be qualified as a rule-in diagnostic tool. In a population with a 50% prevalence (pretest probability) of systemic infection, a positive PCT test translates into a post-test probability of 91.6%, and a negative PCT test translates into a post-test probability of 33.8%. In other words, approximately one out of three patients with negative PCT test results may turn out to have an infection. Therefore, PCT for evaluating infectious complications in SLE patients must be interpreted cautiously. CRP is a more sensitive but less specific test than PCT. Combining the diagnostic value of CRP and PCT may further enhance the diagnostic accuracy. Therefore, the authors do not recommend the routine use of serum PCT to rule out infections in isolation. Instead, the authors suggest that medical decisions be based on the clinical findings, PCT test, and CRP level. In addition, the authors recommend the repeated measurements of PCT in the subsequent 24 to 48 hours of clinically suspected cases to further reduce the false-negative rate.

The PCT level may be elevated in the absence of infection among renal impaired patients[12-14]. The present study confirmed that serum creatinine level at or above 2 mg/dL was one of the independent factors associated with PCT elevation. Three of four patients in the non-infection group who had a falsely elevated PCT level had serum creatinine greater than 1.5 mg/dL (1.9, 5.4, and 6.6 mg/dL). The meta-analysis published in 2012 by Lu et al demonstrated that the accuracy of PCT testing of severely renal impaired patients was similar to the testing of patients with normal renal functions[19]. However, an observational study by Dumea et al showed that the PCT cut-off for the diagnosis of infection in patients with chronic kidney disease (CKD), end-stage renal disease (ESRD), and renal transplant should be 0.597 ng/mL[20]. In addition, a study by Lee et al demonstrated that the PCT cut-off for the diagnosis of bacterial infection in patients with ESRD should be 0.75 ng/mL[21]. Due to the limited number of subjects in the present study, the authors could not find an optimal PCT cut-off for renal impaired patients. So, the authors recommend using a higher cut-off value such as 0.6 ng/mL, to enhance the diagnostic accuracy in SLE patients with renal insufficiency. Further studies are required to evaluate the use of PCT as a diagnostic tool in this population.

The present study has strengths and weaknesses. On the positive side, the authors included all hospitalized SLE patients to reduce the number of selection biases. The authors did not exclude any patients with localized infections or renal impairment. Thus, the present study results provide more clinical implications for the physicians involved in the care of SLE patients. Regarding the limitations, first, the number of infected patients in the present study was small. However, more than half of them presented with SLE flares and had a moderate degree of SLE disease activity. Second, 64% of the blood samples were collected after 48 hours of empirical antimicrobial therapy, which may have affected the diagnostic accuracy of the PCT measurements.

Conclusion

A serum PCT level at or above 0.5 ng/mL has a poor sensitivity, but an acceptably high specificity in predicting bacterial or fungal infection among SLE patients. PCT levels are not influenced by either SLE disease activity or ongoing systemic glucocorticoid or antimalarial therapy. Elevated PCT levels strongly suggest a significant bacterial or fungal infection and should promptly investigate for potential sources. However, the serum PCT level may be falsely elevated in cases of renal insufficiency. Serum PCT levels may not be elevated in cases of localized, early, or partially treated infections. Consequently, serum PCT levels less than 0.5 ng/mL cannot rule out the possibility of infection. PCT measurement may be a useful biomarker in SLE patients for evaluating infections but must be interpreted cautiously.

What is already known on this topic?

Due to the limited sample size in most studies, the performance and cut-off point of serum PCT for the differentiation between SLE flares and infection varied.

What this study adds?

The cut-off point of elevated serum PCT at 0.5 ng/mL for the diagnosis of bacterial or fungal infections in patients with SLE had a sensitivity and specificity of 51.3% and 95.3%, respectively. The serum PCT level may be falsely elevated in cases of renal insufficiency. Serum PCT levels may be normal in cases of localized, early, or partially treated infections.

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Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

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