Clinical Research Report

Procalcitonin may not be a differential diagnostic marker for bacterial infection in febrile patients with chronic gouty arthritis

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Abstract
Objective: This study aimed to examine the diagnostic value of serum procalcitonin (PCT) levels for identifying bacterial infection in febrile patients with chronic gouty arthritis.
Methods: Sixty-six febrile patients with chronic gouty arthritis were divided into non-bacterial infection (n = 45) and bacterial infection groups (n = 21). PCT levels were measured by an immunoassay. Other laboratory parameters, including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBCs), and the neutrophil ratio were extracted from medical records. Receiver-operating characteristic curves were used to evaluate diagnostic values and accuracy.
Results: Serum PCT levels, the ESR, CRP levels, WBC count, and neutrophil ratio were not different between the groups. To assess the ability of PCT to discriminate bacterial infection in febrile patients with chronic gouty arthritis (cut-off value: 0.5 ng/mL), the sensitivity and specificity of PCT were 22.2% and 61.5%, respectively. The area under the curve (AUC) of serum PCT levels was 0.526. The AUCs of related inflammatory indicators were 0.530 for the ESR, 0.635 for CRP, 0.577 for the WBC count, and 0.712 for the neutrophil ratio.
Conclusion: Serum PCT levels may not be a good biomarker for bacterial infection in febrile patients with chronic gouty arthritis.

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Introduction

Clinical manifestation of gouty arthritis (GA) is a metabolic disorder and shows an inflammatory response to deposition of monosodium urate crystals in joints, bones, and various tissues. GA generally presents as acute and chronic arthritis, which affects the first metatarsal joint, followed by other multiple joints, tophi, urolithiasis, and renal disease. Patients with GA show inflammatory clinical symptoms, joint swelling, and stiffness over inflamed joints, and even systemic fever during a period of an acute attack. Findings of leukocytosis and an increase in the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels in GA are similar to those of infectious diseases. Although a positive bacterial culture is commonly regarded as the gold standard in diagnosing infections, it is time-consuming and has a low positive rate. Therefore, finding an effective method to promptly identify bacterial infection in febrile patients with chronic GA is important.

Procalcitonin (PCT) is the precursor of calcitonin, which is secreted by C cells of the thyroid gland and produced by hydrolysis of specific proteins in cells. In systemic inflammation, particularly in bacterial infections, PCT is released from various forms of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1), indirectly and directly from microbial toxin. PCT levels rapidly increase in the first 2 to 4 hours after infection and then reach peak levels in serum within 6 to 24 hours. PCT levels then decrease as infection is controlled (normal condition: < 0.05 ng/mL). Therefore, PCT is generally regarded as a helpful biomarker in detecting bacterial infections. Most previous studies have shown that inflammatory markers for infectious arthritis, such as serum PCT, are significantly elevated. A previous study reported that PCT levels in serum and synovial fluid are a sensitive biomarker for differentiating septic arthritis from non-infectious arthritis, such as rheumatoid arthritis, osteoarthritis, and GA.

However, no studies have demonstrated whether PCT levels can show bacterial infection in patients with chronic GA who experience an acute attack. Therefore, this study aimed to evaluate the ability of PCT to diagnosis bacterial infection and guide prompt antibiotic therapy in febrile patients with chronic GA.

Materials and methods

Patients

This was a single-center, retrospective, observational study. All of the included patients were diagnosed with chronic tophaceous gout and fever (axillary temperature > 37.4°C) and were admitted between November 2011 and January 2014 at the Department of Rheumatology and Immunology, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital in Chengdu, China. The protocol for this investigation was approved by Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital Ethics Committee. This research was conducted in compliance with the Helsinki Agreement.
Written informed consent was obtained from each participant.

Patients with chronic GA and tophi were diagnosed in accordance with the 1977 American College of Rheumatology criteria. According to the criteria of bacterial infection, patients with chronic GA were divided into two groups as follows: the bacterial infection group (n = 21) and the non-bacterial infection group (n = 45). Inclusion criteria of patients with bacterial infection were as follows: (1) patients showed symptoms of chronic GA; (2) a pathogen was detected, with positive results for sputum culture, blood culture, secretion, and joint fluid culture; and (3) bacterial infection was diagnosed. Exclusion criteria were as follows: (1) patients with non-bacterial infections; and (2) uncertain causes with fever.

Clinical and laboratory assessment

Clinical and laboratory data of patients with chronic GA were retrospectively collected from medical records at the time of sampling serum PCT levels, including measurement of CRP levels, the ESR, the white blood cell (WBC) count, and the neutrophil ratio. Serum PCT levels were measured by using a chemiluminescent enzyme immunoassay (VIDAS; BioMerieux SA, Marcy l’Etoile, France). PCT levels of 0.25 to 0.5 ng/mL were likely to be a bacterial infection and those ≥0.5 ng/mL were very likely to be a bacterial infection. Therefore, PCT levels ≥0.5 ng/mL were considered as a positive result according to Schuetz et al. The WBC count (>10.0 x 10^9/L as a positive result) and the neutrophil ratio (>70% as a positive result) were estimated by using the Automatic Blood Cell Analyzer (SYSMEX XE-2100; Sysmex, Kobe, Japan). CRP levels >8 mg/L were considered as positive and measured by the Nephelometer (Olympus AU5421 automatic biochemistry analyzer, Olympus, Tokyo, Japan). An ESR >20 mm/h was considered as positive by using Wintrobe’s method.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. The variables tested in the study are shown as descriptive statistics. We tested the normality of data distribution with the Kolmogorov–Smirnov test and the distribution of the data was considered normal. Significance testing was carried out using the Student’s t-test and one-way analysis of variance was used with the Bonferroni post hoc test. The ability of distinguishing between bacterial infection and non-bacterial infection was evaluated by using receiver-operating characteristic (ROC) analysis. ROC curves were analyzed by using MedCalc software version 12 (MedCalc, Ostend, Belgium), and the sensitivity and specificity values of the optimal cut-off point were also calculated. The area under the curve (AUC) was calculated to evaluate diagnostic accuracy. In all analyses, p < 0.05 was considered to be statistically significant. All statistical analysis was performed by using SPSS Statistics version 16 (SPSS Inc., Chicago, IL, USA).

Results

Patients’ characteristics

The demographic and clinical characteristics of the included patients are shown in Table 1. A total of 66 consecutive patients were studied. The mean ages of patients in the bacterial infection and non-bacterial infection groups were 60.2 ± 17.1 years and 56.2 ± 13.5 years, respectively. The mean disease duration of patients with tophaceous gout and bacterial infection was 14.8 ± 9.7 years and that in patients without infection was 12.4 ± 8.7 years. In patients with bacterial infection,
the most common type of infection was pulmonary infection, followed by skin soft tissue infection, and joint infection (Table 2). Patients in the bacterial infection group had a significantly higher rate of glucocorticoid use and more ruptured tophi than did patients in the non-bacterial infection group (both p < 0.05).

| Table 1. Demographic and laboratory characteristics of enrolled patients |
|-------------------------------------------------------------|
| **Parameters** | **Bacterial infection group (n = 21)** | **Non-bacterial infection group (n = 45)** |
| Age, mean ± SD (years) | 60.2 ± 17.1 | 56.2 ± 13.5 |
| Course of disease, mean ± SD (years) | 14.8 ± 9.7 | 12.4 ± 8.7 |
| Type of infection | Pulmonary | Joint | Skin soft tissue | Renal insufficiency | Hepatic failure | Glucocorticoid use | Ruptured tophi | Hypertension | Hyperlipidemia | Diabetes mellitus | Coronary heart disease |
| Streptococcus pneumoniae | 5 | 2 | 8 | 1 | 0 | 11 (52.4)* | 9 (42.9)* | 12 (57.1) | 1 (4.8) | 6 (28.6) | 2 (9.5) |
| Klebsiella pneumoniae | 2 | N/A | N/A | N/A | N/A | 7 (15.6) | 4 (8.9) | 24 (53.3) | 0 | 9 (20) | 1 (2.2) |
| Haemophilus influenzae | 1 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Streptococcus hemolyticus | 1 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Values are mean ± SD or n (%). Ruptured tophi refers to tophus, which is a symptom of chronic gouty arthritis. SD: standard deviation; N/A: not available. *p < 0.05 |

| Table 2. Clinical information of patients with bacterial infection |
|-------------------------------------------------------------|
| **Parameters** | **Type of infection** | **Type of bacteria** | **Patients (n)** | **Percentage** |
| Infection | Pulmonary infection | Streptococcus pneumoniae | 5 | 42.6 |
| Joint infection | Haemophilus influenzae | Streptococcus hemolyticus | 1 | 1.9 |
| Skin soft tissue infection | Staphylococcus aureus | 8 | 38.1 |
| Pulmonary combined skin Soft tissue infection | Klebsiella pneumoniae | 1 | 1.9 |
| Joint infection | Staphylococcus aureus | 2 | 9.5 |
| Arthritis infection | Streptococcus pneumoniae | 1 | 1.9 |
| Culture site | Department of Rheumatology and Immunology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital |
| Disease duration of infection | 7 to 10 days before admission |

Serum PCT levels and related inflammatory markers in patients in the bacterial infection and non-bacterial infection groups

Serum PCT levels and related indices of inflammation were measured in patients in the two groups. Patients in the bacterial
infection group had similar PCT levels to those in the non-bacterial infection group (Table 3). A total of 28.6% of patients in the bacterial group had PCT-positive results and 46.7% in the non-bacterial group had PCT-positive results. There were no significant differences in the ESR, WBC count, and the neutrophil ratio between the two groups. CRP levels tended to be higher in patients in the bacterial group than in those in the non-bacterial group (p = 0.05).

**Ability of PCT and related inflammatory markers to distinguish infection in febrile patients with chronic GA**

ROC curves of serum PCT levels and related inflammatory indicators were used for discriminating infection in febrile patients with chronic GA. With a cut-off value of 0.5 ng/mL, the sensitivity and specificity of serum PCT levels were the highest (22.2% and 61.5%, respectively) (Table 4). The positive likelihood ratio and negative likelihood ratio were 0.577 and 1.265, respectively. The AUC of PCT was 0.526 (95% confidence interval [CI], 0.399–0.650). The AUCs of related inflammatory indicators were 0.530 for ESR (95% CI, 0.403–0.654), 0.635 for CRP (95% CI, 0.508–0.751), 0.577 for the WBC count (95% CI, 0.449–0.697), and 0.712 for the neutrophil ratio (95% CI, 0.588–0.817) (Table 4, Figure 1). Figure 2 shows scatter plots for each biomarker (PCT, ESR, CRP, WBC count, and neutrophil ratio).

When serum PCT levels > 0.5 ng/mL were regarded as a positive result, the positive predictive value and negative predictive value in patients with chronic tophaceous gout were 21.2% and 62.9%, respectively. The positive predictive values of CRP, the ESR, the neutrophil ratio, and the WBC count were 31.3%, 35.6%, 35.2%, and 34.9%, respectively.

**Table 3.** Related inflammatory indices for detecting bacterial infection in patients with chronic gouty arthritis

| Parameters             | Bacterial infection group (n = 21) | Non-bacterial infection group (n = 45) | p value |
|------------------------|-----------------------------------|---------------------------------------|---------|
| **PCT (ng/mL)**        |                                   |                                       | 0.5     |
| Mean                   | 0.72 ± 1.10                       | 0.72 ± 0.81                           |         |
| Maximum                | 3.86                              | 3.48                                  |         |
| Positive rate, % (n)  | 28.6 (6/21)                       | 46.7 (21/45)                          |         |
| **ESR (mm/h)**         |                                   |                                       | 0.08    |
| Mean                   | 59.1 ± 32                         | 48.3 ± 28                             |         |
| Positive rate, % (n)  | 81 (17/21)                        | 75.6 (34/45)                          |         |
| **CRP (mg/L)**         |                                   |                                       | 0.05    |
| Mean                   | 124.32 ± 85                       | 91.1 ± 72.4                           |         |
| Positive rate, % (n)  | 95.2 (20/21)                      | 95.6 (43/45)                          |         |
| **WBC count (× 10⁹/L)**|                                   |                                       | 0.13    |
| Mean                   | 14.3 ± 5.61                       | 12.9 ± 4.2                            |         |
| Positive rate, % (n)  | 71.4 (15/21)                      | 62.2 (28/45)                          |         |
| **Neutrophil ratio (%)**|                                   |                                       | 0.08    |
| Mean                   | 84.8 ± 5.85                       | 82.3 ± 6.8                            |         |
| Positive rate, % (n)  | 100 (21/21)                       | 84.4 (38/45)                          |         |

Values are mean ± standard deviation or % (n). PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell; ESR: erythrocyte sedimentation rate.
Discussion

Many recent studies have reported that PCT is highly accurate in diagnosing bacterial infections, especially bacterial meningitis, septic shock, bacteremia, and pyelonephritis.13,14 PCT levels are closely related to the severity of infection and clinical prognosis, suggesting that PCT can be a sensitive indicator of early detection.15 Studies have shown that PCT can be used for differential diagnosis of non-infectious arthritis, such as rheumatoid arthritis, and other non-infectious arthritis and bacterial infections.16–18 However, no studies have examined the significance of PCT in clinical manifestation of gout, which is similar to clinical manifestations of bacterial infections and arthritis. To the best of our knowledge, there has been little research

| Biomarkers | AUC (95% CI) | Cut-off value | Sensitivity (%) | Specificity (%) |
|------------|--------------|---------------|----------------|-----------------|
| PCT, ng/mL | 0.526 (0.399–0.650) | 0.5 | 22.2 | 61.5 |
| ESR, mm/h  | 0.530 (0.403–0.654) | 20 | 90.4 | 22.2 |
| CRP, mg/L  | 0.635 (0.508–0.751) | 8 | 95.2 | 2.2 |
| WBC count, × 10⁹/L | 0.577 (0.449–0.697) | 10 | 71.4 | 37.8 |
| Neutrophils, % | 0.712 (0.588–0.817) | 0.70 | 100 | 15.6 |

AUC: area under the curve; PCT: procalcitonin; CI: confidence interval; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell.

Figure 1. Receiver-operating characteristic curves for PCT, the ESR, CRP, WBCs, and the percentage of neutrophils for diagnosis of infection in patients with chronic gouty arthritis.

PCT: procalcitonin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells.
on the utility of PCT to identify gout with bacterial infections and crystal arthritis. One of the reasons for this lack of research could be because the incidence of bacterial infections is relatively low. Another reason may be that gout with recurrent bacterial infections is rare, and thus it has not attracted sufficient attention. Therefore, using PCT as a biomarker to monitor infectious diseases by these features could be advantageous.

In patients with acute exacerbation of chronic GA, bacterial infections should be identified early. Many previous studies have demonstrated that PCT is a useful marker of bacterial infections in sepsis/septic shock, and this is more superior to conventional bacterial culture. Additionally, PCT appears to be a highly sensitive and specific marker in differentiation between septic and non-septic arthritis. In this study, we assessed whether PCT levels could be a reliable biomarker in differential diagnosis between patients with bacterial infection and those with non-bacterial infection with chronic GA. We found that serum PCT levels in patients in the bacterial infection group were not significantly higher than those in patients in the non-bacterial infection group (Table 3). Additionally, 21 of 45 patients in the non-bacterial infection group showed PCT-positive results, 12 of whom had chronic renal insufficiency, 2 had hepatic insufficiency, and 1 had renal transplantation. A previous study reported the isolated presence of calcitonin precursors in patients with benign liver diseases (such as hepatitis) or with hepatocellular carcinoma. Therefore, we believe that renal or hepatic insufficiency might influence PCT levels to some extent. Liu et al. reported that serum PCT levels were higher in patients with GA than in healthy controls without infection. This finding can be explained by various pro-inflammatory cytokines, such as IL-6, TNF-α, and particularly IL-1β, which have important roles in inflammation caused by an acute gout attack. However, an inflammatory response has also been reported in patients with autoimmune diseases, such as adult-onset Still’s disease, granulomatosis with...
polyangiitis (Wegener’s granulomatosis), and Good pasture’s syndrome. These autoimmune diseases often cause a sepsis-like high fever, which is called systemic inflammatory response syndrome. Some reports have indicated that massive production of inflammatory cytokines, such as TNF and IL-6, in such sepsis-like conditions may stimulate production of PCT. Additionally, a previous study suggested that PCT levels were not elevated in patients with local infections, such as wound infection or cellulitis. Therefore, patients with chronic GA who experience an acute attack with fever might have non-infectious systemic inflammatory response syndrome, and most of the inflammatory cytokines are released into the blood. However, larger studies are needed to prove this hypothesis.

Schuetz et al. suggested that a bacterial infection may be present when a PCT value is between 0.25 ng/mL and 0.5 ng/mL in patients. Furthermore, a cut-off level of PCT > 0.5 ng/mL suggested bacterial infection and needed immediate antibiotic therapy. Therefore, PCT levels ≥ 0.5 ng/mL were considered as a positive signal for investigating its diagnostic value in our study. We found a low sensitivity of 22.2% and a low specificity of 61.5% for differentiating bacterial infection in patients with chronic GA and fever with a cut-off PCT value of 0.5 ng/mL. Furthermore, the positive predictive value for chronic tophaceous gout was 21.2%. Therefore, we showed that PCT measurement may be not a highly specific marker for detecting bacterial infections in ROC curve analysis, which is inconsistent with previous studies. Additionally, glucocorticoids can elevate the WBC count, but the effects of glucocorticoids on PCT levels are unclear. In our study, 11 patients who used glucocorticoids were enrolled in the bacterial infection group and seven were in the non-bacterial infection group. However, almost half of the patients presented with elevated PCT levels in those who used glucocorticoids. Therefore, the effects of glucocorticoids on PCT levels should be investigated in the future.

Our study showed that there were no other significant differences in other conventional inflammatory markers, such as CRP levels, and the ESR, neutrophil ratio, and WBC count, between the two groups. The positive predictive value was also low for these variables (31.3%, 35.6%, 35.2% and 34.9%, respectively), which may have been due to the inflammatory reaction in gout. The WBC count may also have been related to the effects of glucocorticoids because the bacterial infection group had a significantly higher rate of glucocorticoid use than did the non-bacterial infection group.

Our study suggests that serum PCT levels may not be a good biomarker for bacterial infection in febrile patients with chronic GA. However, because the incidence of chronic GA is low, and the number of patients with chronic GA associated with fever is even fewer, the number of patients enrolled in this study was small. Further studies with a larger number of samples are required to verify our findings.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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