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Role of C-reactive protein and procalcitonin in discriminating between infectious fever and tumor fever in non-neutropenic lung cancer patients

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Abstract

This study assessed whether C-reactive protein (CRP) and procalcitonin (PCT) levels can discriminate between infectious fever and tumor fever (TF) in non-neutropenic patients with nonsmall cell lung cancer (NSCLC).

This retrospective clinical study included 96 adults with NSCLC who were admitted to the Third Hospital of Hebei Medical University between July 2015 and July 2017. Febrile, non-neutropenic patients were enrolled. CRP and PCT levels, neutrophil count, and antimicrobial response were evaluated.

This study included 26 patients with TF, 49 with localized bacterial infection (LBI), and 21 with bloodstream infection (BSI). CRP levels in BSI were significantly higher than in TF ($P < .05$) and LBI ($P < .05$). No statistically significant difference was found between patients with TF and LBI ($P > .05$). PCT levels were significantly higher in BSI and LBI than in TF ($P < .05$). CRP and PCT levels in patients with stage IV disease were significantly higher than in those with stage II to III disease ($P < .05$). CRP and PCT levels declined significantly in patients with BSI who were responding to antimicrobials ($P < .05$).

Compared with CRP levels, PCT levels can discriminate between TF and infectious fever more accurately. PCT and CRP levels may predict different stages of lung cancer.

Abbreviations: AUC = area under the ROC curve, BSI = bloodstream infection, CRP = C-reactive protein, LBI = localized bacterial infection, NSCLC = nonsmall cell lung cancer, PCT = procalcitonin, ROC = receiver operating characteristic curve, TF = tumor fever.

Keywords: bacterial infection, C-reactive protein, non-neutropenic lung cancer, procalcitonin, tumor fever

1. Introduction

Patients with lung cancer are susceptible to bacterial infections due to their compromised systemic conditions. Most bacterial infections can be diagnosed easily and promptly on the basis of physical findings, blood tests, radiological imaging, and microbiological data. However, some patients present only with fever, without an elevated neutrophil count. In patients with lung cancer, fever may be caused by a bacterial infection or tumor fever (TF) without neutropenia. If bacterial infection is diagnosed immediately, antibiotics can be promptly administered. However, if the cause of fever cannot be accurately determined, antibiotics may be used inappropriately and ineffectively for patients with nonbacterial infections, which has several negative consequences, including the emergence of multidrug-resistant bacterial pathogens and drug-related adverse events. Furthermore, longer hospital stays, increase in patient mortality, and significant economic loss would result from antibiotic misuse.

C-reactive protein (CRP) and procalcitonin (PCT) have been reported to be important markers of bacterial infection in febrile neutropenic patients with cancer, with neutropenia being an important risk factor for infection.[1,2] However, to the best of our knowledge, no studies have investigated the role of CRP and PCT in differentiating between bacterial infections and TF in non-neutropenic patients with lung cancer. Thus, in the present study, we assessed the usefulness of measuring CRP and PCT levels in febrile, non-neutropenic patients with nonsmall cell lung cancer (NSCLC).

2. Materials and methods

2.1. Patients

We conducted a retrospective clinical observational study that included 96 adult patients admitted to the Third Hospital of Hebei Medical University between July 2015 and July 2017. This study has been approved by the Institutional Review Board of the Third Hospital of Hebei Medical University. Informed consent was not required for this retrospective study. Eligibility criteria were as follows: a diagnosis of NSCLC, axillary temperature

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>37.5°C, and the absence of neutropenia. The patients were classified into 3 groups, according to their electronic medical records:

1. TF group: Patients with no clinical, radiological, or microbiological evidence of infection.
2. Localized bacterial infection (LBI) group: Patients with symptoms and obvious clinical findings of LBI, including patients with pneumonia, acute tracheobronchitis, and urinary tract infections.
3. Bloodstream infection (BSI) group: Patients with positive blood cultures.

Defervescence within 96 hours of antimicrobial treatment was defined as a response to antimicrobials.

CRP and PCT were measured within 2 days of the onset of fever. Clinical data, including age, sex, lung cancer stage, comorbidities, CRP and PCT levels, neutrophil count, antimicrobial therapy, and response to antimicrobials, were collected from the patients' electronic medical records.

2.2. CRP and PCT measurements

The CRP level was determined by latex-enhanced immune turbidimetry using an automated system (Olympus America, Inc, Melville, NY). The reference value was <8 mg/L. The blood samples were centrifuged for 1 minute at 4000 RPM, and the supernatant was used to determine PCT concentration. The PCT level was measured using a PCT immunofluorescent assay. The PCT reference value was <0.5 ng/mL. All tests were carried out according to the manufacturer's instructions.

2.3. Statistical analysis

The statistical analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL). For non-normally distributed continuous data, nonparametric tests were applied. Kruskal–Wallis tests were first applied when comparing multiple groups. If a significant result was detected ($P < .05$), the Mann–Whitney U test was used for 2 independent samples. To evaluate CRP and PCT levels before and after therapy, the Wilcoxon rank-sum test was used for pairwise comparisons.

The receiver operating characteristic curve (ROC) was also calculated using SPSS software. The area under the ROC curve (AUC) was calculated to assess the diagnostic performance of CRP and PCT. The sensitivity, specificity, positive predictive value, and negative predictive value were obtained using the best cut-off values for CRP and PCT. Statistical significance was set at $P < .05$ for all analyses.

3. Results

3.1. Patient characteristics

A total of 96 patients were enrolled in the present study. The basic clinical characteristics of patients are summarized in Table 1. The median age was 66.5 years (range: 52–80 years) and 65 patients (67.7%) were male. There were 51 cases of lung squamous cell carcinoma, 42 cases of adenocarcinoma of lung, and 3 cases of large cell lung cancer. There were 26 febrile cases in the TF group, 49 cases in the LBI group, and 21 cases in the BSI group. There were no significant differences in the distribution of lung cancer types among the 3 groups and there were no cases of neutropenia. To evaluate the response to anti-infective treatment, we selected the patients in the BSI group who were administered anti-infective treatment for a minimum of 5 days. Of the 21 patients with septicemia in our study, 16 (76.2%) responded to anti-infective treatment and 5 (23.8%) did not.

Table 1

Patients' clinical characteristics.

Characteristics	TF group	LBI group	BSI group
Sex			
Male	18	32	15
Female	8	17	6
Age, y, median	68	64	68
Range	55–79	52–77	53–80
Histological type of lung cancer			
Lung squamous cell carcinoma	14	25	12
Adenocarcinoma of lung	11	23	8
Large cell lung cancer	1	1	1
PCT, median, ng/mL	0.28	0.67	7.50
CRP, median, mg/L	66.35	71.20	96.30
Neutrophil count, median ($10^3/\mu L$)	2.26	1.92	2.04

BSI = bloodstream infection, CRP = C-reactive protein, LBI = localized bacterial infection, PCT = procalcitonin, TF = tumor fever.

The profiles of infectious diseases in the LBI group are described in Table 2. Pneumonia was the most common infectious disease, followed by acute tracheobronchitis and urinary tract infection.

3.2. Levels of CRP and PCT in the TF group and infection groups

A comparison of CRP and PCT levels among the groups is presented in Fig. 1. CRP levels in the BSI group were significantly higher than in the TF and LBI groups ($P < .001$). However, there was no statistical difference in CRP levels between the TF and LBI groups ($P = .537$, Fig. 1A). The PCT levels in the BSI and LBI groups were significantly higher than in the TF group ($P < .001$, Fig. 1B).

3.3. Levels of CRP and PCT in the TF group according to the different stages of lung cancer

CRP and PCT levels were also compared by lung cancer stage. A comparison of patients with stage IV disease versus patients with stage II to III disease in the TF group is presented in Fig. 2. Eleven of the 26 patients (42.3%) had stage IV cancer and 15 (57.7%) had stage II to III cancer. Patients with stage IV lung cancer had significantly higher CRP and PCT levels than those with stage II to III lung cancer (CRP, $P = .012$; PCT, $P = .04$).

3.4. Patient response to antibiotics

Figure 3 shows the changes in CRP and PCT levels in response to anti-infective treatment in patients with BSI. The CRP and PCT

Table 2

Profile of localized infectious diseases.

Localized infectious diseases	LBI group
Pneumonia	39
Acute tracheobronchitis	7
Urinary tract infection	3

LBI = localized bacterial infection.

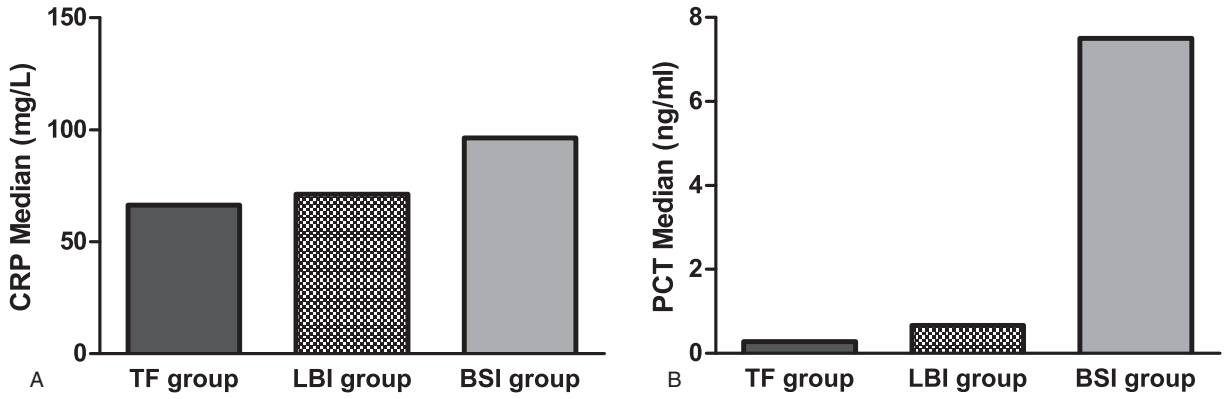

Figure 1. Comparative levels of C-reactive protein (CRP) and procalcitonin (PCT) in tumor fever (TF) group, localized bacterial infection (LBI) group, and bloodstream infection (BSI) group.

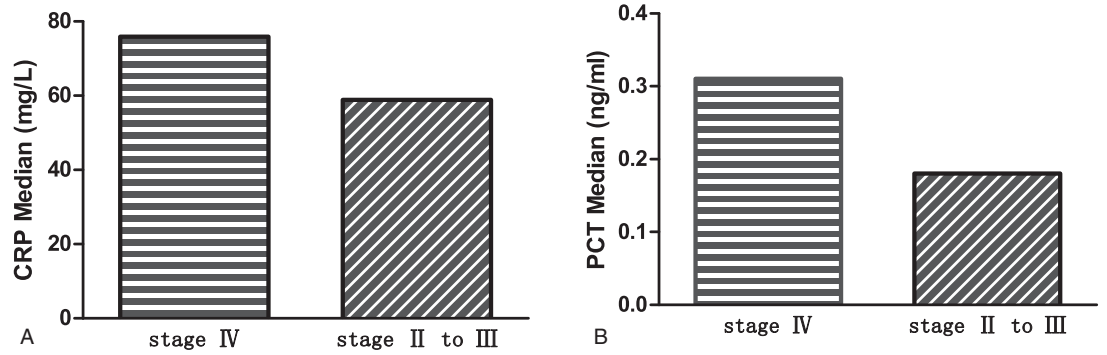

Figure 2. Comparative levels of C-reactive protein (CRP) and procalcitonin (PCT) in patients with stage IV and stage II to III in tumor fever group.

levels between days 5 and 7 following commencement of anti-infective treatment were significantly lower than those before therapy in patients with BSI who responded to treatment (CRP, $P=.002$; PCT, $P=.001$). CRP levels were lower at follow-up in patients who did not respond to treatment, although the difference was not significant (median CRP: 93.4 mg/L vs 98.4 mg/L, $P=.686$). PCT levels were increased at follow-up in patients who did not respond to treatment, although the difference was not significant (median PCT: 7.9 ng/mL vs 7.5 ng/mL, $P=.138$).

3.5. Diagnostic value of CRP and PCT levels

The discriminatory power of CRP and PCT levels for the prediction of infection was analyzed using the AUC, as shown in Figs. 4A to D. PCT levels had a greater discriminatory power between the TF group and LBI group (Figs. 4, A and B; AUC was 0.773 for PCT and 0.545 for CRP). The optimal cut-off value was 0.55 for PCT on the basis of ROC curve. At this cut-off level, the PCT test had a sensitivity of 73.5%, specificity of 92.3%, positive predictive value of 94.9%, and negative predictive value of 66.7%.

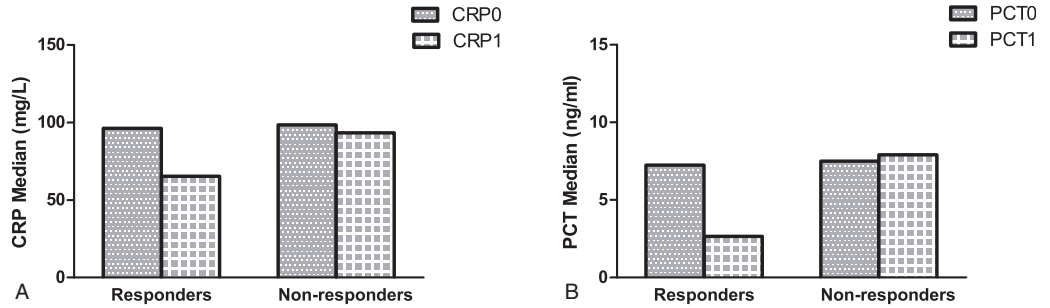

Figure 3. C-reactive protein (CRP) and procalcitonin (PCT) levels in patients with bloodstream infection according to response to anti-infective treatment.

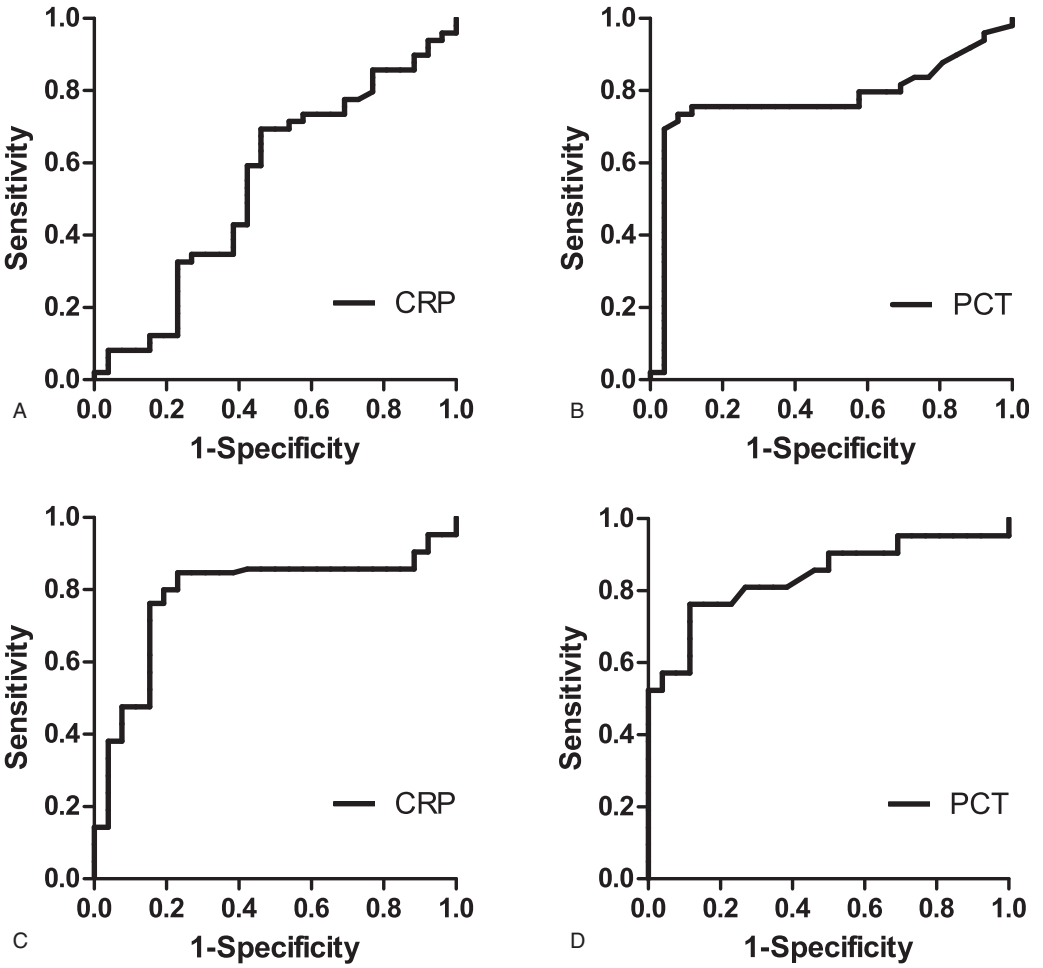

Figure 4. Comparisons of C-reactive protein (CRP) and procalcitonin (PCT) for prediction of infection using the area under the ROC curve between TF group and LBI group (A, B) and TF group and SBI group (C, D). BSI = bloodstream infection, LBI = localized bacterial infection, ROC = the receiver operating characteristic, TF = tumor fever.

PCT was also superior for discriminating between the TF and LBI groups (Figs. 4, C and D; AUC was 0.840 for PCT and 0.786 for CRP). The optimal cut-off value was 0.44 for PCT on the basis of the ROC curve. At this cut-off level, the PCT test had a sensitivity of 76.2%, specificity of 88.5%, positive predictive value of 84.2%, and negative predictive value of 82.1%.

4. Discussion

It is well recognized that infectious fever is the most common complication in patients with lung cancer. However, it is difficult to differentiate infectious fever from TF, so it can be challenging to make the decision to commence antibiotic treatment in patients with fever of unknown origin. In these cases, the identification of sensitive diagnostic biomarkers is crucial. CRP levels are increased in patients with lung cancer,[3] limiting the diagnostic specificity of this test.[4] Some studies[5,6] have suggested that PCT and CRP are elevated in febrile neutropenia and severe infection, and thus are useful biomarkers. PCT, a precursor of the hormone calcitonin, is composed of 116 amino acids and is normally secreted by neuroendocrine cells or C-cells of the thyroid. CRP is an acute-phase protein and is produced primarily by hepatocytes in the presence of infection. These are often used as biomarkers of infection in a range of diseases.[7–9] However, recent studies[10,11] have found that PCT levels were increased in patients with liver metastases or neuroendocrine component, raising doubts over the role of PCT as a definitive diagnostic tool for bacterial infection in patients with cancer.

Our data demonstrated that PCT levels were predictive of infectious fever and that CRP could discriminate between patients with BSI and those with TF. However, CRP levels were not significantly different between patients with LBI and those with TF. CRP and PCT levels may be biomarkers of advanced lung cancer. Our results also demonstrated that CRP and PCT levels at follow-up (between days 5 and 7) decreased. This may guide clinicians in choosing effective antibiotics and appropriate therapy duration.

Our results are consistent with those of a previous study,[12] in which the authors found that PCT levels were significantly higher in patients with infection than in other patients, although there were no differences in CRP levels between infectious and noninfectious hemato-oncology patients. PCT could be a predictor of bacterial infection, as PCT levels may be useful to identify the cause of fever in patients with NSCLC, and therefore help clinicians to make reasonable decisions regarding appropriate antibiotic therapy. Early detection of infection avoids treatment delays and enables appropriate use of antibiotics, thus reducing costs and improving the quality of life of patients. Blood

culture is the current gold standard for the diagnosis of BSI, although the process is time consuming. In contrast, PCT levels can be measured within 1 hour, which helps clinicians to make the correct diagnosis and promptly commence appropriate antibiotic therapy.

Patients with stage IV lung cancer have significantly higher CRP and PCT levels than those with stage II to III lung cancer, but the results are warranted in patients with no signs of infection. Our results are consistent with those of previous studies. Matzaraki et al[13] showed that PCT levels increased proportionately with cancer stages. Chaftari et al[14] found that PCT was useful in detecting the progression of cancer. In 1 retrospective study,[11] in which serum CRP and PCT levels were assayed in patients with lung cancer, CRP levels were associated with cancer stages. However, in that study, there was no correlation between PCT levels and cancer stages, PCT was only modestly associated with the number of metastatic sites. These inconsistent findings indicate that further studies are required involving patients with lung cancer with no signs of infection. The follow-up analysis of CRP and PCT levels in this study suggested that CRP and PCT were useful to guide effective antimicrobial stewardship in patients with infections and underlying lung cancer. This could promote rational antibiotic use, shorter therapy duration, decreased emergence of antibiotic resistance, reduced care costs, and improved quality of life of patients with lung cancer. PCT has recently been proposed for use to determine appropriate antimicrobial therapy in patients with infection.[15]

The present results indicate that PCT is more useful than CRP to discriminate between infectious fever and TF. We used sensitivity, specificity, positive predictive value, and negative predictive value to evaluate the diagnostic tests. We plotted the ROC curve and measured the AUC to determine diagnostic performance. The sensitivity, specificity, and the best cut-offs for clinical use are displayed on the ROC curve. AUC, as overall accuracy, was sometimes used to compare test performance; if the AUC is greater, the test will be better.

CRP and PCT are often used for the diagnosis of infectious diseases in clinical practice, their usefulness remains controversial. For example, the diagnostic accuracy of CRP and PCT for diagnosing bacterial infection as a cause of fever in one previous study[16] was poor, and another earlier study[17] found that PCT and CRP were not discriminators between infectious and noninfectious patients with NSCLC. However, some studies[18–20] have shown that PCT concentration is a better predictor than CRP concentration in the diagnosis of sepsis, and the results of our study also indicate that PCT is more useful than CRP to discriminate between infectious fever and TF. One study evaluated the use of serum CRP and PCT levels in children with cancer, with PCT found to be a better marker than CPR for excluding bloodstream infections (AUC was 0.751 for PCT and 0.638 for CRP).[21] Another study suggested that PCT was superior to CRP for predicting bacteremia in 92 patients with suspected sepsis (AUC was 0.876 for PCT and 0.602 for CRP).[22] Significant differences in PCT and CRP levels have also been observed between patients with positive and negative blood cultures (AUC was 0.720 for PCT and 0.558 for CRP), indicating that PCT was also superior to CRP for these patients.[23] The results of these studies were consistent with our findings.

Our study has a number of limitations. First, it was a retrospective study with a small number of patients. Secondly, the definition of septicemia may be incomplete because many factors affect culture sensitivity.[24] In addition, there might be false-negative blood culture results, because the single blood culture did not have adequate power to detect bloodstream infections. Prospective studies involving a larger sample size are required to corroborate our findings.

5. Conclusions

The results of our study indicate that PCT levels are a more useful parameter than CRP levels for discriminating between patients with TF and patients with infections. PCT and CRP levels may be predictors of advanced lung cancer, but the results are warranted in patients with no signs of infection. The decrease in CRP and PCT levels between days 5 and 7 following the commencement of anti-infective therapy can help clinicians determine appropriate antibiotic use and therapy duration, thus reducing the emergence of antibiotic resistance and medical costs.

Author contributions

GC was involved in the study design; ZZ was largely responsible for conducting the majority of the study and writing the manuscript; XL and YZ were involved in manuscript editing; YL and DW participated in its design and performed the statistical analysis; LL and TS were responsible for the collection of the clinical data.

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Methodology: Dongchang Wang.
Software: Yahua Li.
Writing – original draft: Zhifang Zhao.
Writing – review & editing: Xuze Li, Yunxia Zhao.

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