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Original Article

Can serum procalcitonin and C-reactive protein as nosocomial infection markers in hospitalized patients without localizing signs?*

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Abstract

BACKGROUND: Early diagnosis of infection with the use of valuable markers leads to decreased mortality and morbidity. The aim of this study was to evaluate the value of procalcitonin (PCT) and C-reactive protein (CRP) for detecting nosocomial infection in hospitalized patients without localizing signs.

METHODS: We conducted a prospective observational study on 150 hospitalized patients with fever > 38ºC emerging 48-72 hours after their admission at Alzahra Hospital, Isfahan, Iran. The subjects did not have any localizing sign of infection. PCT and CRP values were determined using rapid tests and were compared with results of blood culture as the standard test. The sensitivity, specificity, positive and negative predictive values (PV) and likelihood ratios (LRs) were calculated for both PCT and CRP. Receiver operating characteristic (ROC) curves were also used to evaluate the diagnostic value of the PCT and CRP for detecting nosocomial infections. Finally, the areas under the resulting curves were compared.

RESULTS: PCT had a sensitivity of 57.1%, a specificity of 89.1%, a positive PV of 46.2%, and a negative PV of 92.7% while the corresponding percentages for CRP test were 76.2%, 48%, 19.3%, and 92.5%. PCT marker also had a higher positive LR and lower negative LR than did CRP marker. The observed areas under the ROC curves were 0.73 for CRP (95% CI, 0.63-0.82; p = 0.023) and 0.80 for PCT (95% CI, 0.68-0.91; p = 0.001). The optimal cut-off values (best diagnostic accuracy) were 39 mg/L for CRP and 7.5 ng/mL for PCT.

CONCLUSIONS: Determination of PCT and CRP is a valuable tool for identifying nosocomial infections. PCT showed better specificity, negative and positive PV. However CRP showed significantly better sensitivity compared with PCT. Therefore, these tests should be considered as part of initial work-up for patients with unknown source of infection.

KEYWORDS: Nosocomial Infection, Blood Culture, Procalcitonin, C-Reactive Protein.

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Nosocomial infections are one of the major causes of mortality and morbidity among hospitalized patients and represent a significant burden both for the patient and public health.[1] Untreated infections may result in serious complications leading to the over prescription of antibiotics, contributing to the antimicrobial resistance and increasing costs and adverse effects.[2] Early recognition of infection, as a cause of critical illness,[3] using high sensitivity infection markers with a negative predictive value is important in managing the patients and the outcomes they get.[4]

In most cases, a benign infection is diagnosed after receiving a complete history and performing a careful physical examination to reveal the site of infection. In rare instances, infection is manifested only by vague or nonspecific signs and symptoms.[5] Diagnosis of infection can be difficult, because positive bacte-

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riological samples may be late or absent, the clinical interpretation may be ambiguous, and traditional markers of infection may be unspecific. Other parameters such as procalcitonin (PCT) and C-reactive protein (CRP) have been considered to evaluate the infections in patients.[6] CRP is a typical acute-phase reactant that binds to several polysaccharides in bacteria, fungi, and parasites in presence of calcium.[7] PCT is a precursor protein of the hormone calcitonin with a molecular weight of approximately 13 kDa.[8] PCT is induced in the plasma of patients with severe bacterial or fungal infections or sepsis.[9] During systemic and severe infections, serum PCT concentrations increase to very high levels. PCT is more specific for detecting bacterial infection than other inflammatory markers, such as CRP and white blood cells, (WBC) because viral infections, autoimmune and allergic disorders do not induce PCT.[10] Serum PCT monitoring can help clinicians to manage nosocomial infections in patients.[11] There have been several studies evaluating the usefulness of quantitative PCT measurements for diagnosis of bacterial infections in patients with systemic inflammatory response syndrome (SIRS).[12] Recent investigations suggest that PCT may be a valuable addition to currently used markers for diagnosis of infection.[13] Moreover, it has been shown that PCT has a greater diagnostic value than CRP and WBC,[10] and this supports the need of evaluating PCT as a marker for infection and to compare it to CRP, which is currently the most used marker for this purpose. Therefore, this study aimed to investigate the diagnostic and prognostic value of PCT and CRP for detecting nosocomial infection in hospitalized patients without localizing signs.

Methods

In order to determine whether PCT and CRP can be used as markers for nosocomial infection in hospitalized patients without localizing signs, a prospective observational study was conducted from May 2008 to November 2009. This study was performed on 150 cases suspected to nosocomial infection identified based on SIRS criteria in internal medicine and surgery wards of Alzahra Hospital, Isfahan, Iran. We enrolled cases who had oral temperature > 38°C emerging 48-72 hours after their admission with no localizing sign of infection in their history or at physical examination. Exclusion criteria were administration of antibiotic therapy during the past two days and a fever lasting longer than seven days. Subjects with known immunodeficiency or cases whose fever had a specific reason except nosocomial infection were also excluded. The study protocol was approved by the Ethics Committee of Department of Infectious Diseases at Alzahra Hospital. In addition, informed consents were obtained from all patients. Patients were examined by an infectious diseases chief resident who took a complete history, performed a physical examination, recorded the degree and duration of the fever, and evaluated all patients to find any site of infection. Ethylenediaminetetraacetic acid (EDTA) blood samples were drawn from the patients and stored for culture, PCT and CRP examination. Blood culture (on sheep blood agar) was performed as a standard test for comparison between PCT and CRP in terms of their sensitivity, specificity, and negative/positive predictive values and likelihood ratios (LRs) for the detection of nosocomial infection. CRP values were determined in 50 µL samples of EDTA-blood using a rapid (15-minute) immunometric method (Nyococard CRP) (range of results < 40; 40-80; 80-100; and > 100 mg/L). Serum PCT levels were measured using a rapid semi-quantitative immunochromatographic test (Brahms PCT-Q; Brahms Diagnostica, Berlin, Germany) in 20 minutes (range of results < 0.5; 0.5-2; 2-10; and > 10 ng/mL).

The Fisher's exact test was used to compare demographic characteristics and laboratory values of the subjects. The sensitivity, specificity, negative and positive predictive values (PVs), and likelihood ratios (LRs) were also calculated for both PCT and CRP. The diagnosis accuracy of serum PCT and CRP for the diagnosis of nosocomial infection was expressed as the area under the corresponding receiver

operating characteristic curve (AUROCC) and the respective areas under the curves were calculated with 95% confidence intervals (CIs). Data was analyzed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA).

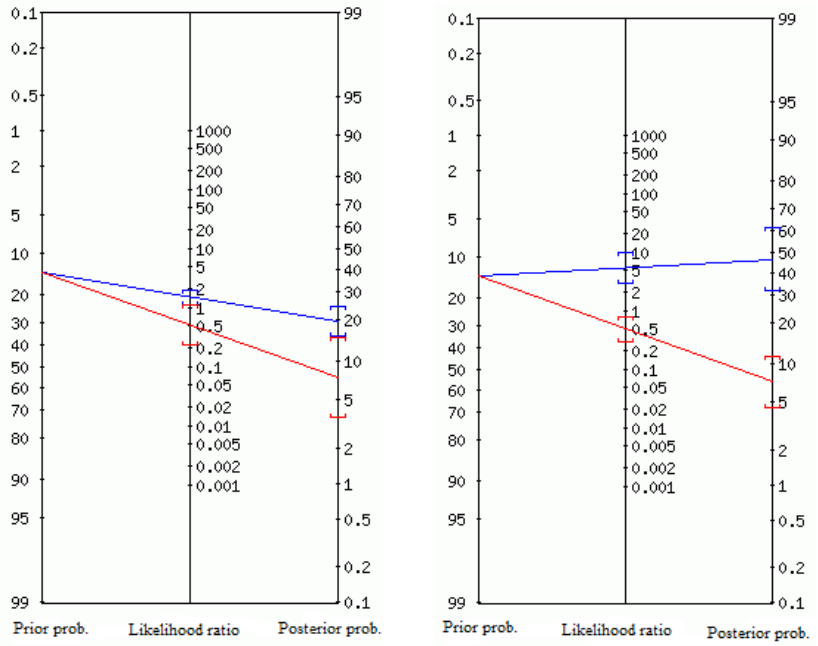
Results

We studied 150 patients including 107 (71.3%) males and 43 (28.7%) females. The mean age was 38 ± 17.2 years (range: 13-85). Patients hospitalized in internal medicine and surgical wards constituted 54.7% and 45.3% of all subjects, respectively. Overall, 129 blood cultures (86%) were negative and 21 (14%) were positive. Seventy five subjects (50%) had a serum PCT level below the detection limit of the test (PCT < 0.5 ng/mL), 8 (5.3%) had a PCT level between 0.5-2 ng/mL, 60 (40%) had a PCT level between 2.1-10 ng/mL, and in 7 (4.7 %) patients PCT was more than 10 ng/mL. Among the 21 subjects with positive blood cultures, 18 cases (85.7%) had a PCT higher than the normal range (PCT > 0.5 ng/mL) and 3 cases had a PCT concentration below the limit of detection of the test (PCT < 0.5 ng/mL) (one had occult pneumococcal bacteremia and the other two cases had pyelonephritis).

In our study, PCT had a sensitivity of 57.1%, a specificity of 89.1%, a positive PV of 46.2%, and a negative PV of 92.7%. The corresponding values for CRP test were 76.2%, 48%, 19.3%, and 92.5%. Diagnostic performance of PCT versus CRP in nosocomial infection is presented in Table 1.

The LRs were better for PCT (positive LR, 5.26 [95% CI, 2.83–9.76]; negative LR, 0.48 [95% CI, 0.29–0.79]) than for CRP (positive LR, 1.46 [95% CI, 1.09–1.96]; negative LR, 0.49 [95% CI, 0.22–1.08]) (Table 1). For a better visual understanding, the pre-test probability, the LR for the specified range of values, and the probability of having a nosocomial infection after measuring PCT and CRP were plotted into two separate nomograms (Figure 1).

The receiver operating characteristic (ROC) curves for PCT and CRP in the diagnosis of nosocomial infection can be seen in Figure 2. The observed areas under the ROC curves were 0.73 for CRP (95% CI, 0.63-0.82; p = 0.023) and 0.80 for PCT (95% CI, 0.68-0.91; p = 0.001). The optimal cut-off value (best diagnostic accuracy) was 39 mg/L for CRP and 7.5 ng/mL for PCT (Figure 2).



Accuracy of CRP based on culture Accuracy of PCT based on culture

Figure 1. Nomograms for applying likelihood ratios calculated for C-reactive protein (CRP) (on the left) and procalcitonin (PCT) (on the right).

Table 1. Diagnostic accuracy of serum PCT and CRP for the diagnosis of nosocomial infection.

	PCT	CRP
AUC	0.80	0.73
Cut-off value	7.5	39
Sensitivity (%)	57.1%	76.2%
Specificity (%)	89.1%	48%
True positive (%)	46.2	19.3
False positive (%)	53.8%	80.7%
True negative (%)	92.7%	92.5%
False negative (%)	7.3%	7.5%
PPV (%)	46.2%	19.3%
NPV (%)	92.7%	92.5%
LR +	5.26	1.46
LR -	0.48	0.49

AUC: Area Under the Curve; PCT: procalcitonin; CRP: C-reactive protein; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio.

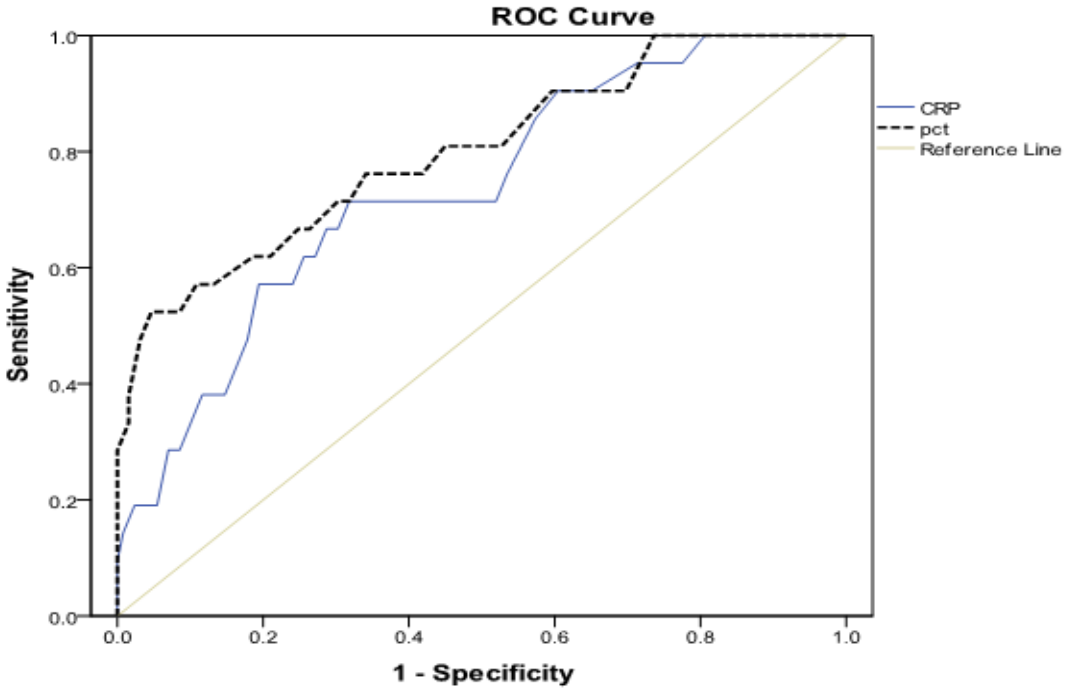


Figure 2. Receiver operating characteristics (ROC) curves comparing procalcitonin (PCT) and C-reactive protein (CRP) for detecting nosocomial infection. The area under the ROC curve was 0.73 for CRP (95% CI, 0.63-0.82; p = 0.023) and 0.80 for PCT (95% CI, 0.68-0.91; p = 0.001).

Discussion

The main purpose of the present study was to assess the value of PCT and CRP in identifying nosocomial infection among hospitalized patients without localizing signs. According to our study, PCT and CRP are valuable in diagnosis of nosocomial infections. Like our study, Becker et al. found that PCT can act as a marker of infection. In addition, the combination of PCT and CRP would provide the most useful information in diagnose of infection.[14] In this respect, there is recent interest in combining multiple markers to more effectively diagnose infection. Simon et al. reported that diagnostic accuracy of infection could be enhanced by combining PCT and CRP tests with clinical judgment.[15] In our study, PCT showed better specificity (89.1%), negative PV (92.7%), and positive PV (46.2%). However CRP showed significantly better sensitivity (76.2%). PCT

and CRP had comparable negative PVs for nosocomial infection of 92.7% and 92.5%, respectively. We propose an area under the curve of 0.80 ng/mL for PCT and 0.73 for CRP for diagnosis of nosocomial infection in patients. A meta-analysis was performed by Simon et al. to evaluate PCT and CRP for the diagnosis of bacterial infection in hospitalized patients. They concluded that the overall accuracy of PCT markers in differentiating bacterial infections from other non-infective causes of systemic inflammation was higher than that of CRP markers.[16] de Kruif MD et al. suggested that PCT biomarker adds significant diagnostic value to currently used markers of infection in terms of sensitivity and specificity. These data suggest that PCT may be a valuable addition to currently used markers of infection.[13] A study performed on 243 febrile patients in France, the PCT assay, with a 0.2 µg/L cut-off value, had a sensitivity of 77% and a specificity of 59% in diagnosing bacterial/parasitic infection.[17] Ugarte et al. reported CRP to be the best discriminate test due to its good specificity which made discrimination between infected and non-infected patients possible. They suggested that PCT should not replace CRP as a marker of infection in patients, but the combination of both markers can detect the infection with greater specificity.[18] Carol et al. showed that PCT is more sensitive than CRP in the diagnosis of infection (septicemia, meningitis and urinary tract infection).[19] Luzzani et al.described that PCT is a better marker of sepsis than CRP. Moreover, the course of PCT showed a closer correlation than that of CRP with the severity of infection.[20] Galetto-Lacour et al. concluded, having the same cost, PCT seemed to have a slight advantage over CRP because of its earlier increase after stimulation and a better sensitivity.[5] Another important finding in our study was that CRP test could also provide useful information. Its sensitivity and negative PV were 76.2% and 92.5%, respectively for a cut-off value of 39 mg/L. Pavcnik-Arnol et al. studied 66 patients with SIRS and reported a better accuracy of CRP compared with PCT for the diagnosis of bacterial sepsis.[21] Ertugrul et al. also suggested that CRP is currently the most widely used parameter to support the diagnosis of infection.[22]

In the present study, the use of PCT and CRP tests in predicting the occurrence of nosocomial infection was investigated. We believed that like any other typical clinical scenario, clinicians must decide if a kind of examination is necessary for hospitalized patients with nosocomial infection without localizing signs. Consequently, we agree with Hausfater that biological markers must be considered as diagnostic and prognostic tools that assist physicians in their clinical practice.[17]

Although these tests look promising, since this study has been performed in a specific setting on a relatively small number of cases and with a specific aim, more studies for determining the exact diagnostic accuracy of PCT and CRP are needed and should be undertaken to assess the additional value of these tests.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

FKh designed and conducted the research (including project conception, development of overall research plan, and study oversight). FA wrote the paper and made a major contribution and acted as a guarantor of all of the work. KD performed the research, collected the data, and provided essential materials, constructs, and databases. AMK analyzed the data.

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