Utility of Procalcitonin Concentration in the Evaluation of Patients with Malignant Diseases and Elevated C-Reactive Protein Plasma Concentrations

Silke Schüttrumpf, Lutz Binder, Thorsten Hagemann, Dinko Berkovic, Lorenz Trümper, and Claudia Binder

Departments of Hematology/Oncology and Clinical Chemistry, University of Göttingen, Göttingen, and Ev. Hospital Oberhausen, Oberhausen, Germany

Background. Elevated plasma concentrations of the C-reactive protein (CRP) are frequently found in patients with malignant diseases. Discrimination between infection and noninfectious acute-phase reactions is essential for therapeutic decisions.

Methods. Because increased procalcitonin (PCT) concentrations have been described predominantly in patients with a systemic infection, PCT plasma concentrations were measured prospectively in 111 patients with a hematological condition with a CRP concentration >8 mg/L.

Results. Documented cases of infection were identified in 42 patients, 39 patients had unexplained fever, and 30 patients had no signs of infection. Twenty patients in the latter group were classified as having an elevated CRP concentration caused by a high tumor load (tumor group), and 8 had elevated concentrations that were drug related (drug group). Median CRP concentrations did not differ significantly between groups of patients with and without infection. PCT concentrations were higher in patients with an infection than in patients without an infection and were within the normal range in all patients in the drug and tumor groups. As shown by receiver operating characteristic analysis, PCT concentration was a significant discriminator between having and not having infection, having infection and being in the tumor group, and having infection and being in the drug group. In contrast, CRP concentration was only a predictor of being in the drug group, when the cut-off point was set at 85.1 mg/L, which limited its clinical applicability.

Conclusions. PCT concentration contributes significantly to the differential diagnosis for elevated CRP concentrations in patients with hematological conditions and facilitates therapeutic decisions.

C-reactive protein (CRP) is a sensitive marker of acute-phase reactions of various origin. Plasma concentrations are elevated in patients with bacterial and fungal infections [1], as well as in patients with active rheumatoid arthritis, Crohn disease, and myocardial infarction and patients who have undergone major surgery [2–5]. Thus, its discriminatory power between infectious and sterile inflammations is limited.

Inflammatory conditions are frequent in patients with malignant diseases. In many cases, systemic infections of bacterial, viral, and fungal origin have been documented. In a considerable number of patients, however, the cause of the inflammation remains unclear. Unexplained fever is common, especially in patients with neutropenia.

Acute-phase reactions may also be caused by administration of drugs and blood products, as well as by the malignancy itself. Especially in patients with bulky solid organ cancer or advanced lymphoma, high tumor-cell turnover and spontaneous tumor lysis can lead to systemic inflammation, mimicking severe infection.

Because infections in these patients are often life threatening, a reliable marker to specify the origin of the inflammation is urgently needed. Procalcitonin (PCT) concentration is a promising candidate.
produced as part of the systemic response to circulating endotoxins and cytokines during bacterial and fungal infections [6, 7]. Plasma concentrations have been shown to correlate with the severity of the infection [8, 9]. Concentrations are significantly higher in patients with a systemic bacterial infection than in patients with a localized bacterial or viral infection [10, 11]. PCT concentration has been demonstrated to discriminate between septic complications and noninfectious, inflammatory reactions in critically ill patients, as well as between transplant rejection and infection in organ recipients [11, 12]. Elevated PCT concentrations have also been detected in patients with hemato-oncological conditions with neutropenia and infection [13–20]. However, there are still few data regarding whether PCT concentration can be used to identify patients in this population with tumor- or drug-induced, acute-phase reactions. Recently, we showed that PCT concentration can be used to discriminate between fever of infectious and noninfectious origin in these patients [21].

To further investigate the value of PCT concentration for the differential diagnosis of CRP elevations in this population, PCT plasma concentrations were determined prospectively in 111 patients with leukemia, lymphoma, and various solid organ tumors presenting with CRP concentrations above the normal range (>8 mg/L). Receiver operating characteristic (ROC) analysis was used to evaluate the suitability of using both parameters as discriminators of inflammations of different origin.

**PATIENTS AND METHODS**

**Patients.** A total of 111 consecutive patients (table 1) of the Department of Hematology/Oncology at the University of Göttingen (Göttingen, Germany) were prospectively enrolled in an observational study after providing informed consent. Inclusion criteria were having a diagnosis of a malignant disease and a CRP plasma concentration >8 mg/L.

Microbiological analyses were performed on blood samples, urine specimens, nasopharyngeal swab specimens, and specimens from other body regions that were suggestive of infection. All patients underwent chest radiography and/or high-resolution CT scanning. Abdominal ultrasound was performed to exclude hepatolienal candidiasis, abscesses, and other infectious causes. Patients were also checked for clinical and laboratory evidence of viral infections.

The diagnosis of microbiologically proven infection was determined on detection of an infectious agent in cultures of blood or other body fluids. A clinically defined infection was diagnosed when there was a clinically evident source of infection. Radiographic detection of pulmonary infiltrates lead to the diagnosis of pneumonia.

Fever in the absence of both clinical and microbiological evidence of infection and without association with either high tumor load or drug administration was classified as being an
Table 3. *P* values for the differences in median procalcitonin (PCT) and C-reactive protein (CRP) concentrations in patients with and patients without leukopenia.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>PCT concentration</th>
<th>CRP concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>.737</td>
<td>.470</td>
</tr>
<tr>
<td>Infection group</td>
<td>.031<em>b</em></td>
<td>.371</td>
</tr>
<tr>
<td>Unexplained fever group</td>
<td>.106</td>
<td>.110</td>
</tr>
<tr>
<td>Noninfection group</td>
<td>.153</td>
<td>.325</td>
</tr>
</tbody>
</table>

*a* Leukocyte count $\geq$ 1 cell/nL vs. leukocyte count $<1$ cell/nL.

*b* Statistically significant (Mann-Whitney *U* test).

unexplained fever. Because all of these patients promptly responded to antimicrobial and/or antifungal therapy, an unidentified infectious cause was suspected in these cases. Therefore, patients with unexplained fever were included in the infection cohort for some analyses.

The noninfection group was identified by exclusion diagnosis and the clinical course. If fever occurred, either it had to be resistant to antimicrobial and/or antifungal treatment or it had to resolve spontaneously. Clinical and microbiological signs of infection had to be absent. Drug reactions were assumed to have occurred when transient body temperature elevations occurred in close temporal association with the administration of drugs or blood products. Tumor-associated sterile inflammations were diagnosed in patients with a high tumor load or lymphoma with B symptoms.

**Analytical methods.** PCT concentration was measured with a monoclonal immunoluminometric assay (Lumitest PCT; Brahms Diagnostica GmbH), in accordance with the manufacturer’s instructions; concentrations $\leq$ 0.5 μg/L were considered to be normal. CRP concentration was determined by immunoturbidimetry (Rolf Greiner Biochemica); concentrations $\leq$ 8 mg/L were considered to be normal.

**Statistical methods.** Differences were analyzed using the Mann-Whitney *U* test (Statistica for Windows; StatSoft). *P* values $<.05$ were considered to be statistically significant. ROC curve analysis software, version 9.0.1 (Statistical Program for Social Science), was used to answer the question of how accurate PCT and CRP concentrations are when used to identify diseased patients. In a ROC curve, the true-positive rate (sensitivity) is plotted against the false-positive rate (1 - specificity), with the area under the curve being proportional to the probability of a correct discrimination.

**RESULTS**

**Characteristics of the study population.** Documented infections were detected in 42 of the 111 included patients. Ten of the patients with documented infections presented with bacteremia (7 patients had gram-negative bacterial infection, and 3 had gram-positive bacterial infection). Thirty-nine patients had unexplained fever. Underlying diseases were evenly distributed.

In 30 of 111 patients, elevations in CRP concentration were drug related or tumor associated. The drug group consisted of 8 patients with leukemia and 1 patient with non-Hodgkin lymphoma. They developed fever during or shortly after administration of cytosine arabinoside and all-trans retinoic acid. The tumor group consisted of 8 patients with advanced solid-organ tumors and 14 patients with bulky, non-Hodgkin lymphoma or with relapsed cases of leukemia with a high tumor load.

![Figure 1](image-url)

**Figure 1.** Differences in procalcitonin (PCT) plasma concentration (A) and C-reactive protein (CRP) plasma concentration (B) in the various subgroups. Data are given as box plots, in which the box encompasses the median value as well as the interquartile range (25th–75th percentiles). Minimum and maximum values are shown as bars. In places where there are statistically significant differences, as determined by the Mann-Whitney *U* test, *P* values are indicated.
**PCT and CRP concentrations in the different subgroups.**
PCT concentrations were high among patients with infections, especially among patients with pneumonia, bacteremia, or a clinically defined infection (table 2, figure 1A and B), whereas patients in the noninfection group mostly had concentrations that were within the normal range. In the tumor group, 2 patients had high PCT concentrations (19.9 and 85.0 μg/L). Both patients experienced massive tumor lysis and cytokine release following therapy with monoclonal antibodies and were, therefore, excluded from additional evaluations. Median PCT concentrations differed significantly between all groups and subgroups (figure 1A). Median CRP concentrations were significantly lower in the drug group than in the infection group. The other differences were not statistically significant (figure 1B).

Although CRP concentrations did not differ significantly between patients with leukocyte concentrations <1000 cells/μL and patients with leukocyte concentrations ≥1000 cells/μL, PCT concentrations were higher among patients without leukopenia, compared with patients with leukopenia (table 3). This finding was statistically significant for patients with infection, especially for patients with bacteremia, pneumonia, or a clinically defined infection.

**ROC analysis.** ROC analysis yielded a large area under the curve for PCT concentrations for the infection group versus those for the noninfection group, for PCT concentrations for the infection group versus those for the tumor group, and for PCT concentrations for the infection group versus those for the drug group (figure 2A–C and table 4), demonstrating that PCT concentration was a significant discriminator for all of these cases. By applying the cut-off point of 0.5 μg/L, as the manufacturer recommends, using PCT concentration enabled us to identify patients without infection with 100% specificity. The optimal cut-off point suggested by ROC analysis was 0.2 μg/L, yielding a higher sensitivity but a lower specificity.

CRP concentration did not have enough statistical power to discriminate between most of the above-named subgroups, with

---

**Table 4. Receiver operating characteristic analysis of the different subgroups.**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Area under the curve</th>
<th>SE</th>
<th>95% CI</th>
<th>Cut-off point</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection group vs. noninfection group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT concentration</td>
<td>0.852</td>
<td>0.036</td>
<td>0.771–0.913</td>
<td>0.2 μg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.0</td>
<td>82.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 μg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58.0</td>
<td>100.0</td>
</tr>
<tr>
<td>CRP concentration</td>
<td>0.571</td>
<td>0.061</td>
<td>0.473–0.666</td>
<td>52.2 mg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95.1</td>
<td>25.0</td>
</tr>
<tr>
<td>Infection group vs. drug group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT concentration</td>
<td>0.850</td>
<td>0.054</td>
<td>0.759–0.917</td>
<td>0.2 μg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.0</td>
<td>82.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 μg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58.0</td>
<td>100.0</td>
</tr>
<tr>
<td>CRP concentration</td>
<td>0.900</td>
<td>0.040</td>
<td>0.818–0.953</td>
<td>85.1 mg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Infection group vs. tumor group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT concentration</td>
<td>0.853</td>
<td>0.039</td>
<td>0.768–0.915</td>
<td>0.2 μg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.0</td>
<td>85.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 μg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58.0</td>
<td>90.9</td>
</tr>
<tr>
<td>CRP concentration</td>
<td>0.560</td>
<td>0.074</td>
<td>0.458–0.659</td>
<td>136.0 mg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46.9</td>
<td>75.0</td>
</tr>
</tbody>
</table>

**NOTE.** CRP, C-reactive protein; PCT, procalcitonin.

<sup>a</sup> Optimal cut-off point calculated using receiver operating characteristics analysis.
<sup>b</sup> Cut-off point recommended by the manufacturer.
the exception of discriminating between the infection group and the drug group. It enabled us to identify the drug group, with results comparable to results of the area under the curve for PCT concentration, sensitivity, and specificity. However, this was achievable only when we used a cut-off point far greater than the usual upper limit of the normal range (table 4).

**DISCUSSION**

Differentiation between inflammatory conditions caused by high tumor load, malignant cell lysis, or drug administration and inflammatory conditions of infectious origin is a challenging question regarding patients with a hemato-oncological condition. Rapid identification of the underlying causes is crucial, because the resulting therapeutic consequences are different and may even be mutually exclusive.

CRP concentration is known as a sensitive marker of inflammation, although its value is restricted by a limited specificity. Because abnormal CRP concentrations were part of the inclusion criteria, all patients in the present study had CRP concentrations above the normal range. High CRP concentrations were observed in patients with infection, especially in patients with bacteremia, pneumonia, or a clinically defined infection, as well as in patients in the tumor group. These results are in line with other authors’ general observations of critically ill patients [22, 23] and of special populations with hemato-oncological diseases [24–27].

There was no significant difference between the median CRP concentration of patients with infection and the median CRP concentration of patients without infection. ROC analysis confirmed that CRP concentration did not represent a suitable parameter to discriminate between these conditions.

The only subpopulation that could be identified with sufficient sensitivity and specificity was the drug group. The mathematically defined optimal cut-off point of 85.1 mg/L allowed exclusion of infections at lower concentrations with a specificity of 100%. However, regarding all subgroups, there was a broad overlap of CRP concentrations, and levels of up to 85.1 mg/L were frequently measured. Thus, the higher cut-off point seems to be of more statistical than clinical interest. Among nonselected patients with a lower prevalence of drug- or tumor-related acute-phase reactions, the value of individual CRP concentration for therapeutic decision making is limited.

Similar to CRP concentration, the highest PCT concentrations could be determined for patients with a documented infection. These findings are in accordance with the literature regarding unselected populations [9–11, 28, 29] and patients with a malignant disease [13–16, 25].

The main question of the study—whether PCT concentration would enable us to identify patients in the overall population whose elevated CRP concentrations were not caused by infection—was answered with surprising clarity. In contrast to median CRP concentrations, median PCT concentrations differed significantly between all subpopulations, with higher values being found in infection groups and their respective subgroups. Plasma concentrations in the noninfection cohort were ≤0.5 μg/L.

There are few data on the subject in the literature. Penel et al. [27] evaluated a cohort of febrile patients with head and neck cancer. Similar to our results, PCT concentrations were significantly higher among patients with an infection than among patients with paraneoplastic fever. In a retrospective analysis of 245 cases of fever in 155 patients with solid organ cancer [30], Penel and colleagues described a tendency of higher PCT concentrations among patients with infection, although this finding was not statistically significant. Nevertheless, when using 2 ng/mL as an arbitrary cut-off point, higher PCT concentrations were found in 19 of 95 patients with an infection, compared with only 2 of 39 with paraneoplastic fever. CRP concentrations were not significantly different between the 2 groups.

As we could show by ROC analysis, PCT concentration was a significant discriminator between patients with infection and patients without infection. It enabled us to exclude patients with infection and to identify patients with tumor- or drug-related elevations in CRP concentration with high discriminatory power and excellent specificity. A recent meta-analysis of data from patients hospitalized for suspected infection confirms these findings [31].

The question of whether PCT concentrations are influenced by leukopenia remains difficult to answer. Significantly lower concentrations in patients with leukopenia were found only in the cohort with documented infection. However, because the group was small and the number of severe infections may not have been evenly distributed between the populations, the significance of the results should not be overestimated. The same reasons may account for the conflicting reports in the literature, which describe lower concentrations in patients with neutropenia [18, 21, 32, 33] and patients with no interdependency [14–17].

In conclusion, the present results demonstrate that PCT concentration is a valuable additional parameter for the differential diagnosis for elevated plasma CRP concentrations in patients with malignant diseases. In the context of symptoms and clinical course, it contributes significantly to the exclusion of patients with infection. It facilitates the identification of patients with drug-induced and paraneoplastic elevations in CRP concentration, in whom the delay of chemotherapy because of suspected infection is unnecessary and potentially hazardous.

**Acknowledgments**

*Potential conflicts of interest.* All authors: no conflicts.
References


