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Serum procalcitonin and C-reactive protein kinetics as indicators of treatment outcome in hospitalized patients with community-acquired pneumonia

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Background/aim: There has been growing interest in the use of serum procalcitonin (PCT) and C-reactive protein (CRP) in patients with community-acquired pneumonia (CAP). The aim of this study was to investigate whether an assessment of fever, leukocyte count, and serum CRP and PCT levels on admission and during follow-up (day 3) provides any information about the clinical outcome in hospitalized patients with CAP.

Materials and methods: Patients with a diagnosis of CAP who were admitted to and followed at four university hospitals were evaluated retrospectively using the Turkish Thoracic Society Pneumonia Database.

Results: A total of 103 hospitalized CAP patients (57 males, mean age: 61.5 ± 16.7 years) were enrolled in the study. Treatment failure (TF) was observed in 20 patients (19.4%). Pneumonia Severity Index scores, serum CRP levels, and PCT levels on admission were significantly higher in the TF group. There were significant decreases in CRP and PCT levels between admission day and day 3 in the treatment success group.

Conclusion: In patients with CAP, the body temperature and leukocyte count on admission do not predict outcome. Monitoring levels of CRP and PCT may be useful as a predictor of treatment outcome.

Key words: Procalcitonin, C-reactive protein, treatment, pneumonia

1. Introduction

Community-acquired pneumonia (CAP) continues to be a serious health problem worldwide, and disease course and outcome are highly variable. Recent population-based data showed an overall mortality rate of 13% in patients hospitalized with CAP, and this number rose to more than 35% in patients with severe CAP (1).

Most patients admitted for CAP respond satisfactorily to treatment, but approximately 15% develop treatment failure. Medical records have shown that death from CAP occurs primarily in patients with therapeutic failure (2).

Assessment of disease severity and prediction of outcome are prerequisites for adequate allocation of healthcare resources and therapeutic options in the management of CAP. The Pneumonia Severity Index (PSI) and the CURB-65 scores have only been approved for the prediction of mortality and their ability to predict other CAP-associated adverse outcomes has not yet been accepted. Both scoring systems have limitations for clinical use, including lack of practicability and only moderate sensitivity and specificity (3). To overcome these limitations, there is growing interest in the potential usefulness of biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) in the management of CAP (4–6).

We hypothesized that lack of improvement in CRP and PCT levels in response to antibiotic treatment would predict treatment failure. If correct, then biological markers could be useful to supplement prognostic scoring systems and clinical parameters in order to identify patients who have a greater probability of becoming sicker and who would thus require closer monitoring.

According to the current guidelines, the response to antibiotic treatment is primarily assessed with the improvement in signs and symptoms, including body temperature, following 3 days of treatment (7). Thus, we

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have also aimed to investigate whether the measurement of CRP and PCT levels during follow-up would contribute to correct treatment in hospitalized patients with CAP.

2. Materials and methods

In this study, patients with a CAP diagnosis were admitted to and followed at four university hospitals between 2010 and 2013 and retrospectively evaluated using the Turkish Thoracic Society Pneumonia Database. This database is an internet-based registry in which participating centers record the data of all adult patients with CAP. The database includes information on clinical, laboratory, radiographic, and treatment and outcome-related findings. The database currently contains data about 1050 patients. All patient case files (n = 103) include data on demographic features, clinical findings, and CURB-65 and PSI scores on admission, and body temperature, white blood cell (WBC) count, and PCT and CRP values on admission (D0) and on day 3 (D3) were also included in this study. PCT analysis was conducted using a chemiluminescence immunoassay with a PCT kit (Siemens, USA) on a Centaur XP device (Siemens, USA). CPR analysis was conducted using an immunoturbidimetry immunoassay with a CRP kit (Beckman Coulter, USA) on a AU5800 analyzer (Beckman Coulter, USA).

Patients with nosocomial pneumonia and with immunosuppression were not registered in the database.

Treatment failure (TF) was defined as persistence or reappearance of fever (>37.8 °C) and radiographic progression (a 50% or more increase in the extent of infiltrates), including pleural effusion and/or empyema, or worsening of the clinical condition, which would necessitate a change in antibiotic treatment or death. Treatment success (TS) was defined as improvement or resolution of all symptoms and clinical and radiographic signs of pneumonia between days 10 and 15 without the appearance of new signs and/or symptoms and with no need to change antibiotic therapy.

Data were collected about patient demographics, symptoms and signs, and laboratory and radiographic findings. CURB-65 and PSI scores on admission, body temperature, leukocyte count, and PCT and CRP values on D0 and D3 were recorded. Comparisons were then made between patients with TS and TF.

Written informed consent was obtained from every patient before registration to the database. The study was approved by the local ethics committee.

2.1. Statistical analysis

Statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation unless stated otherwise. Comparisons between groups were performed using a t-test or the Mann–Whitney U test. A chi-square test was used to make comparisons between categorical variables. Receiver-operating characteristic (ROC) curves were drawn for the CRP and PCT levels, body temperature, and WBC counts on D0 and D3. The area under the curve (AUC) for each of these parameters was calculated for prediction of treatment failure. The sensitivity and specificity values were calculated from the resulting models. The significance level was accepted as a $P < 0.05$.

3. Results

A total of 103 hospitalized CAP patients (57 males, mean age: 61.5 ± 16.7 years) were included in the study. Treatment failure was documented in 20 patients (19.4%). The initial CURB-65 and PSI scores were 2.2 ± 1.0 and 101.8 ± 36.4, respectively. There were no significant differences in age, sex, comorbidities, or CURB-65 scores at the presentation stage between the TS and TF groups. PSI scores, on the other hand, were significantly higher in the TF group (Table 1).

3.1. Body temperature and biomarkers on admission

On admission, there were no differences in fever and leukocyte counts between the two groups. No cutoff value for baseline fever or leukocyte count was found that would

Table 1. Baseline characteristics of patients with TS and TF.

	TS group (n = 83)	TF group (n = 20)	P-value
Age, years	60.3 ± 16.8	66.5 ± 15.7	0.143
Sex, male, n (%)	49 (59.0)	8 (40.0)	0.099
Comorbidities, n (%)	65 (78.3)	15 (75.0)	0.478
CURB-65 score	2.2 ± 1.0	2.5 ± 0.9	0.149
PSI score	94.6 ± 33.2	131.4 ± 34.2	<0.001

PSI: Pneumonia Severity Index.

predict treatment outcome. However, serum CRP levels and PCT levels on admission were significantly higher in the TF group (17.0 ± 12.1 vs. 26.2 ± 13.5 mg/dL and 3.6 ± 7.8 vs. 17.1 ± 26.0 ng/mL) (Figures 1 and 2). A baseline CRP level of >15.0 mg/dL was found to predict TF with a sensitivity and specificity of 50.6% and 77.8% (OR: 3.59). Similarly, a baseline PCT level of >1 ng/mL had a sensitivity of 56.5% and a specificity of 78.6% (OR: 4.77) (Table 2).

3.2. Body temperature and biomarkers on D3

Fever and leukocyte counts on D3 were significantly higher in patients in whom treatment failed (Figures 3 and 4). A body temperature of >37.0 °C on D3 was found to predict TF with a sensitivity and specificity of 69.4% and 65.0%. A WBC level of >12,500/mm^3 on D3 had a sensitivity of 72.4% and a specificity of 75.0% (Table 2).

There were significant decreases in body temperature, leukocyte count, and CRP and PCT levels between admission and D3 in the TS group, but not in the TF group (Figures 1–4).

A decrease in the CRP level by less than 60% on D3 predicted TF with a sensitivity and specificity of 38.9% and 88.2%. Similarly, a decrease in the PCT level by less than 60% on D3 had a sensitivity of 34.1% and a specificity of 91.7% in predicting TF (Table 2). When areas below the ROC curves for all of these parameters were examined, the

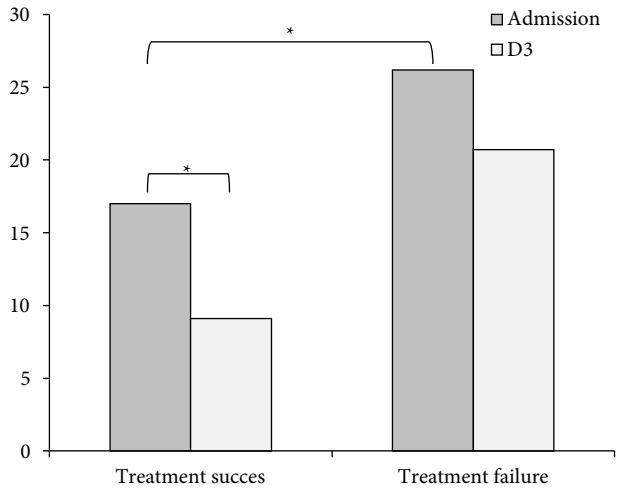


Figure 1. Changes in CRP levels in patients with treatment success and failure. CRP values on the y-axis are expressed in mg/dL. *P < 0.05.

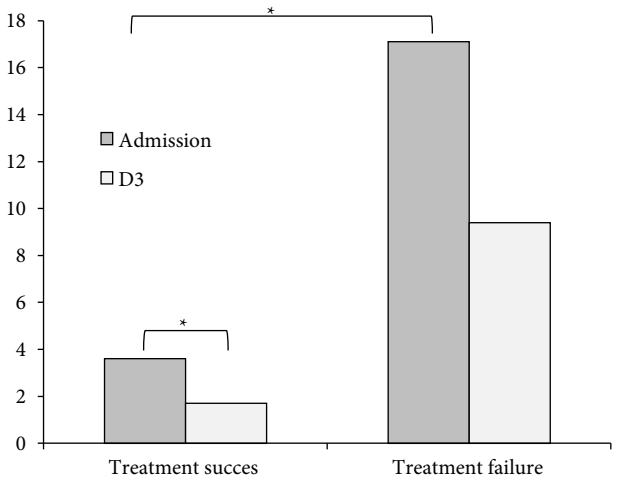


Figure 2. Changes in PCT levels in patients with treatment success and failure. PCT values on the y-axis are expressed in ng/mL. *P < 0.05.

Table 2. Sensitivity and specificity values for PSI, CRP, PCT, fever, and WBC count for predicting treatment failure.

	Sensitivity (%)	Specificity (%)	OR (CI)	P-value
PSI > 120	76.8	75.0	9.95 (3.20–30.94)	<0.001
CRP > 15.0 mg/dL (D0)	50.6	77.8	3.59 (1.09–11.90)	0.026
PCT > 1 ng/mL (D0)	56.5	78.6	4.77 (1.17–19.40)	0.021
Fever (°C) > 37 (D3)	69.4	65.0	4.22 (1.48–12.02)	0.006
WBC > 12,500/mm^3 (D3)	72.4	75.0	7.86 (2.54–24.33)	<0.001
CRP > 10 mg/dL (D3)	63.0	77.8	5.96 (1.78–19.97)	0.002
PCT > 0.5 ng/mL (D3)	57.5	76.5	4.40 (1.31–14.81)	0.011
Less than a 60% decrease in CRP level (D3)	38.9	88.2	3.63 (1.08–12.21)	0.027
Less than a 60% decrease in PCT level (D3)	34.1	91.7	9.17 (1.09–77.24)	0.017

PSI: Pneumonia Severity Index, CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood cells.

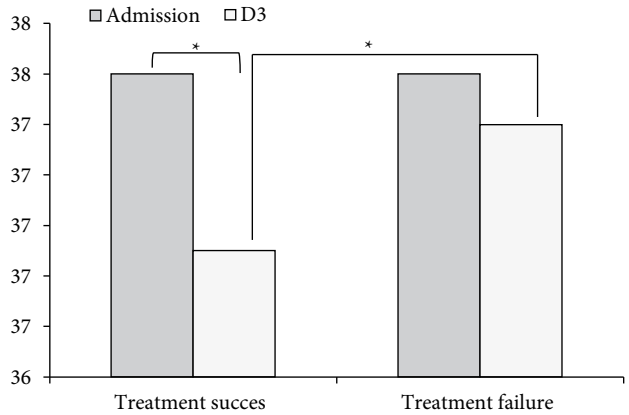


Figure 3. Changes in fever levels in patients with treatment success and failure. Fever values on the y-axis are expressed in °C . *P < 0.05.

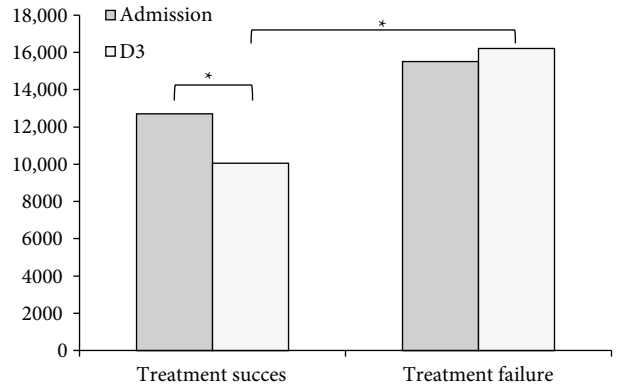


Figure 4. Changes in leukocyte levels in patients with treatment success and failure. Leukocyte values on the y-axis are expressed in mm^3. *P < 0.05.

parameters that best predicted treatment failure were the PSI scores, CRP and PCT levels on admission, and CRP and PCT levels and WBC count on D3 (Table 3).

4. Discussion

This study aimed to determine whether CRP and PCT levels on admission and during follow-up predict treatment response, and whether they would perform better in comparison to the traditionally used body temperature and leukocyte counts in CAP. We have found that the serum CRP and PCT levels at admiddion, not fever and leukocyte counts, were associated with treatment failure. The most effective parameters predicting treatment failure were the PSI score and the PCT level on admission and, following this, WBC, CRP, and PCT levels on D3.

Treatment failure develops in approximately 15% of hospitalized CAP patients, and almost 6% manifest rapidly progressive pneumonia (2). Fever and leukocyte counts have traditionally been used in the assessment of the course of infections and for the response to antibiotic treatment. However, in a study examining the prognosis in 53 consecutive patients with CAP, the body temperature and WBC on D0 and D3 showed no differences between survivors and nonsurvivors (8). On the other hand, initially increased and persistently elevated levels of biomarkers have been shown to identify patients at risk of treatment failure, and these markers can help clinicians better treat their patients (9). In another study, Lacoma et al. aimed to investigate whether PCT and CRP levels on admission and during the clinical course would be useful

Table 3. Area under the curve (AUC) values for PSI, fever, WBC, CRP, and PCT in predicting TF.

	AUC (CI)	P-value
PSI (admission)	0.793 (0.664–0.921)	0.001
Fever (°C) (admission)	0.479 (0.335–0.622)	0.770
WBC/mm^3 (admission)	0.628 (0.486–0.770)	0.076
CRP (admission)	0.706 (0.567–0845)	0.007
PCT (admission)	0.770 (0.627–0.914)	0.002
Fever (°C) (D3)	0.686 (0.537–0.834)	0.011
WBC/mm^3 (D3)	0.778 (0.639–0.917)	<0.001
CRP (D3)	0.761 (0.627–0.895)	0.001
PCT (D3)	0.800 (0.685–0.916)	<0.001

PSI: Pneumonia Severity Index, CRP: C-reactive protein,
PCT: procalcitonin, WBC: white blood cells.

in the management of patients with CAP. The levels of PCT and CRP on admission were found to be higher in patients who developed complications and in those who died (10). Similarly, in a prospective study of 453 patients with CAP, treatment failure was observed in 84 patients (18%) and was found to be associated with PCT and CRP levels on D1 and D3 (11). Ramirez et al. investigated the role of inflammatory biomarkers in the identification of patients who needed intensive care unit admission. They concluded that patients with severe CAP who had low levels of PCT could be safely admitted to the wards (12). Other studies (8,13–15) also investigated the value of monitoring CRP and/or PCT levels and showed that lack of improvement in these biomarkers predicted an unfavorable outcome.

This study has demonstrated that in patients with treatment failure, serum CRP and PCT levels on admission were significantly higher and remained high during the first 3 days of treatment. Body temperature and leukocyte count on admission do not predict treatment failure, but body temperature and leukocyte counts after 3 days of antibiotic treatment appear to be useful in detecting patients who have failed treatment.

Identification of patients with CAP who are more likely to experience treatment failure is important as this is associated with higher mortality rates (2). Prognostic scales such as the PSI have been validated for clinical use in CAP. However, the PSI has limitations for clinical use, particularly regarding practicability. This study also showed that the PSI is a good determinant of prognosis, but that the monitoring of leukocyte count and CRP and PCT levels during the first 3 days of antibiotic treatment provides similar information to the clinician regarding the risk of treatment failure.

In clinical practice, physicians caring for CAP patients would prefer to use a cutoff level for CRP and PCT that would define a high-risk group. In the study conducted by Ramires et al. (12), the cutoff levels for baseline CRP and PCT for predicting admission to the intensive care unit were found to be 26.0 mg/dL and 0.35 ng/mL, respectively. In another study, a baseline PCT level of >1 ng/mL was found to be associated with the development of adverse events in CAP patients (16). Together with the findings of this study, there appears to be agreement about cutoff levels of 1525 mg/dL and 1 ng /mL for CRP and PCT, respectively.

Two other studies reported that decreases in CRP levels by 50% (8) and 60% (15) compared with admission levels had significant sensitivity and moderate specificity. In addition, a more pronounced decline in CRP levels on D3 was associated with a high likelihood of having received incorrect empiric antibiotic treatment (15). Schuetz et al. showed that when analyzing relative changes in PCT concentrations between admission and D3, D5, and D7, nonsurvivors had a small relative increase on D3, while survivors had a significant decrease from admission to D3 (16). In another study, CRP was found to be a better predictor of clinical outcome than body temperature and leukocyte counts, both on admission and at follow-up (8). This study confirmed and extended these observations because it showed that in patients with treatment success, the CRP and PCT levels were lower on admission and decreased to lower levels on D3, in contrast to the patients in whom the treatment failed. These two biomarkers, together with the leukocyte count on D3, appeared to be better predictors of treatment failure than body temperature.

Several limitations need to be addressed. First, outpatients with CAP were not included in this study, simply because those patients were not as closely followed and their CRP and PCT levels were not regularly monitored; therefore, our results cannot be extrapolated for this population. Second, there were a relatively small number of patients included in the study. This was mainly due to the fact that only patients with complete data in the registry were included. Monitoring and recording of biomarkers in the database was left at the discretion of the attending physicians, and a large majority of the patients lacked the relevant data. The population in this study, however, appears to be similar to the remaining patients in the database in terms of age, sex, severity of pneumonia, and outcome. Thus, we assume that these findings could be valid for all hospitalized CAP patients. Third, we were not able to analyze whether there was an association between the biomarker levels and the causative pathogens since a pathogen was identified in only 15% of the study population. Nucleic acid and antigen detection tests are not routinely used in the participating centers, and these findings reflect real life. However, it would have been desirable to conduct subgroup analyses for patients with CAP on bacteria, atypical bacteria, and virus levels

In conclusion, we have observed that patients with treatment failure showed a more marked inflammatory response at presentation, and that this proinflammatory state failed to improve 72 h after treatment. In addition, the CRP and PCT levels on admission and on the following 3 days of antibiotic treatment, and the leukocyte count on D3, predicted the clinical outcome better than body temperature did.

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