

Association of acute phase reactants with prognostic scores in community acquired pneumonia

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Abstract

Objective: To investigate the association of C-reactive protein and procalcitonin with commonly used prognostic scoring systems, hospitalisation and mortality in cases of community-acquired pneumonia.

Methods: The prospective study was conducted from April 2014 to April 2015 at the emergency department of Marmara University Pendik Research and Training Hospital, Turkey, and comprised community-acquired pneumonia patients diagnosed according to the British Thoracic Society criteria. Prognosis was estimated using confusion, urea, respiratory rate, blood pressure and age >65 , Pneumonia Severity Index-Pneumonia Patient Outcome Research Team score, and severe community-acquired pneumonia scores. Data was analysed using MedCalc 15.8.

Results: Of the 203 patients assessed, community-acquired pneumonia was confirmed in 152(74.8%). Procalcitonin had moderate correlation with the three scales used ($p<0.001$), while C-reactive protein had weak correlation with them ($p<0.004$).

Conclusion: Both procalcitonin and C-reactive protein levels were found to be correlated with prognostic risk scores.

Keywords: Pneumonia, C reactive protein, procalcitonin, PSI, CURB-65, SCAP. (JPMA 71: 614; 2021)

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Introduction

Pneumonia is an important cause of morbidity and mortality worldwide despite the developments in antimicrobial treatment. It is common practice to administer empirical treatment directed at the most possible pathogens for pneumonia because identifying the aetiological microorganism is not generally possible.^{1,2} In this context, clinical and laboratory data may help in differential diagnosis, decision of hospitalisation, and estimation of prognosis.

C-reactive protein (CRP) is a polypeptide which is an important marker of inflammation, causes precipitation with C-polysaccharide on the cellular wall of pneumococcus and is responsible for activation of classical complement pathway and increased phagocytosis.³

Procalcitonin (PCT) is precursor of the hormone calcitonin. It was detected as a protein increasing in patients with sepsis and infection in the early 1990s. It has been accepted that PCT is specific to bacterial infections. Studies have revealed that bacterial endotoxin is the most potent stimulus for production of PCT. It mirrors the severity of infection and has emerged as the most studied

and promising blood biomarker for the risk stratification of patients.⁴

PCT and CRP are commonly used in patients with pneumonia to distinguish between viral and bacterial aetiology and to predict prognosis.⁵⁻⁸ Prospective studies from Turkey investigating the role of acute phase reactants in pneumonia are scarce.^{9,10} Whether PCT is an ideal index to predict the prognosis of pneumonia remains debatable, particularly in patients with different types and severities of pneumonia.⁴

The current study was planned to investigate the association of CRP and PCT with three prognostic scoring systems in patients with community-acquired pneumonia (CAP). These included pneumonia severity index (PSI), confusion, urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years (CURB-65) and severe community-acquired pneumonia (SCAP). It was also planned to investigate the association of acute-phase reactants with hospitalisation and mortality in such patients.

Patients and Methods

The prospective cohort study was conducted between April 2014 and April 2015 at the Emergency Department (ED) of Marmara University Pendik Research and Training Hospital, Turkey, and comprised patients admitted with a presumptive diagnosis of CAP.

Those included were patients of either gender aged >18

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years diagnosed with CAP according to the British Thoracic Society (BTS) criteria¹¹ and furnished informed consent. The exclusion criteria comprised pregnancy, diagnosis of nosocomial pneumonia, death before a definitive diagnosis, transfer to another hospital, and unwillingness to participate.

After approval from the institutional ethics review committee, the sample size was calculated in the light of previous studies^{12,13} with primary outcome effect size 0.3, type I error 0.05 and power 95%.

Data about hospitalisation and mortality was obtained from hospital records or the Turkish national death investigation system (available at the link: <https://obs.saglik.gov.tr/>).¹⁴ When the patient's survival status could not be determined, the patients were called up at the end of the first month of their hospital admission.

Data was collected using a study form consisting of demographics, history, physical examination, BTS-CAP criteria, CURB-65, PSI- Patient Outcomes Research Team (PORT), and SCAP by the attending physicians. The treatment and management of the patients were planned by the attending physicians and the study research team was not involved. The CRP and PCT levels were recorded along with other routine laboratory tests.

CURB-65 is a six-point scoring system (0-5) based on the presence of the following criteria: 1 point each for confusion, blood urea nitrogen (BUN) >20mg/dl, respiratory rate $\geq$ 30/min, systolic blood pressure (SBP) <90mmHg or diastolic (DBP) $\leq$ 60mmHg, and age >65 years.¹⁵ PSI consists of demographic features, co-morbid diseases, physical examination findings, and laboratory findings. The patients are categorised into five classes based on the total PSI score (class I-V).¹⁶ SCAP score comprises two major components in arterial potential of

hydrogen (pH) and SBP, and 6 minor components, namely, respiratory rate, ratio between arterial oxygen partial pressure (PaO₂) and fractional inspired oxygen (FiO₂) (P/F), BUN, confusion, age, and multilobar/bilateral infiltration on chest X-ray.¹⁷ The total score may be between 0-59 and score >10 is suggested to predict severe pneumonia. The study patients were separated into high (>10 points) and low ($\leq$ 10 points) risk groups.

Data was analysed using MedCalc 15.8. Data with normal distribution was presented as means $\pm$ standard deviation (SD) and that with skewed distribution was expressed as median and interquartile range (IQR) with 95% confidence intervals (CI). Categorical data was presented with frequencies and percentages and was compared between the groups using chi-square test. Continuous data was compared with student's t, analysis of variance (ANOVA), Mann Whitney U, or Kruskal Wallis tests, as applicable. Correlations between variables were analysed with Pearson or Spearman tests. The predictive values of continuous variables were determined using receiver operating characteristic (ROC) curves. The accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) of the groups to predict mortality and hospitalisation were calculated using cross-tabulation. Binary logistic regression analysis was performed to evaluate the association of risk scores, acute-phase reactants and clinically relevant factors with mortality. Because of the correlation between PCT and CRP levels, two separate regression models, one including CRP and the other including PCT, were used. A two-sided $p < 0.05$ value indicated statistical significance.

Results

Of the 203 patients assessed, CAP was confirmed in 152

Table-1: Comparison of categorical variables between outcome groups.

	Survived	Dead	p	Discharged	Hospitalized	p
Gender (% males)	66.4	62.5	0.8	65	66.3	0.9
Sputum production	95.4	94.5	0.6	96.7	94.6	0.7
Dyspnoea	96.1	91.7	0.3	93.3	96.7	0.4
Confusion	13.3	29.2	0.066	6.7	21.7	0.013
Cancer	24.2	37.5	0.2	26.7	26.1	1
Liver disease	2,3	8,3	0.2	3.3	3.3	1
Heart failure	12.5	25	0.12	11.7	16.3	0.5
CVD	7	16.7	0.13	10	7.6	0.8
CKD	9.4	20.8	0.15	8.3	13	0.4
CPD	32.8	16.7	0.15	38.3	25	0.1
Bilateral infiltration	32.8	58.3	0.022	26.7	43.5	0.04
Pleural effusion	15.6	41.7	0.009	11.7	25	0.06

CVD: Cerebrovascular disease, CKD: Chronic kidney disease, CPD: Chronic pulmonary disease.

*Significant differences are indicated with bold text.

Table-2: Comparison of continuous variables between outcome groups.

	Survived	Dead	p	Discharged	Hospitalized	p
Age (years)	66.6 ± 14.8	71.0 ± 12.9	0.15*	65.7 ± 14.4	68.4 ± 14.6	0.24*
Fever (°C)	38.1 ± 0.9	38.1 ± 1.1	0.8**	37.9 ± 0.8	38.2 ± 0.92	0.008**
MAP (mmHg)	92.6 ± 16.2	84.3 ± 17.7	0.068*	93.2 ± 14.5	89.9 ± 17.9	0.24**
Respiratory rate (min)	23.9 ± 6.4	30.7 ± 7.9	0.0002*	22.1 ± 5.5	26.9 ± 7.4	0.0001*
Heart rate (pulse/min)	108.5 ± 19.3	112.4 ± 19.3	0.4**	102.7 ± 18.0	113.4 ± 19.1	0.0007**
BUN (mg/dl)	25.2 ± 17.1	36.1 ± 16.2	0.0003**	22.6 ± 10.7	29.7 ± 20.2	0.03*
CRP (mg/l)	107.8 ± 80.0	187.3 ± 114.6	0.0009**	88.9 ± 63.7	140.9 ± 99.7	0.0014*
Glucose (mg/dl)	135.6 ± 49	164.1 ± 91.2	0.23*	129.7 ± 39.3	146.9 ± 67.2	0.08*
Haematocrit	35.0 ± 6.2	33.4 ± 6	0.3**	35.7 ± 5.6	34.1 ± 6.6	0.16**
Sodium (mEq/l)	133.8 ± 14.1	134.6 ± 4.8	0.4*	133.2 ± 13.5	134.4 ± 12.8	0.64*
pH	7.4 ± 0.1	7.4 ± 0.1	0.8*	7.43 ± 0.1	7.44 ± 0.1	0.34**
pO2 (mmHg)	60.8 ± 13.6	56.8 ± 13.8	0.1*	66.1 ± 14.7	56.4 ± 11.6	<0.0001*
Procalcitonin (ng/ml)	3.4 ± 12.5	8.2 ± 15.3	0.002*	0.4 ± 0.6	6.6 ± 16.3	<0.0001*

MAP: Mean arterial pressure, BUN: Blood urea nitrogen, CRP: C-reactive protein, PSI: Pneumonia severity index. pH: Potential of hydrogen, pO2: Pressure of Oxygen.

* Mann Whitney U test, ** Student t test. Significant differences are indicated with bold text.

Table-3: The association of prognostic scores and acute phase reactants with mortality.

Model 1	B	S.E.	Exp (B)	%95 Confidence interval		p*
				Lower	Upper	
Age	0.002	0.023	1.002	0.957	1.048	0.940
RR	0.085	0.045	1.089	0.997	1.190	0.058
SBP	-0.020	0.015	0.980	0.951	1.009	0.177
DBP	-0.006	0.022	0.994	0.952	1.039	0.799
BUN	-0.004	0.014	0.996	0.969	1.025	0.802
PSI	0.032	0.012	1.032	1.009	1.057	0.007
CURB-65	0.096	0.394	1.101	0.509	2.382	0.807
SCAP	-0.894	0.886	0.409	0.072	2.322	0.313
CRP	0.005	0.002	1.005	1.001	1.010	0.023
Constant	-5.959	2.306	0.003			0.010
Model 2						
Age	-0.004	0.022	0.996	0.954	1.039	0.837
RR	0.086	0.045	1.090	0.999	1.190	0.053
SBP	-0.021	0.015	0.979	0.951	1.008	0.153
DBP	-0.008	0.022	0.992	0.950	1.036	0.715
BUN	-0.006	0.016	0.994	0.964	1.026	0.724
PSI	0.035	0.012	1.036	1.012	1.060	0.003
CURB-65	0.079	0.388	1.082	0.506	2.315	0.840
SCAP	-0.872	0.851	0.418	0.079	2.215	0.305
Procalcitonin	0.012	0.019	1.012	0.976	1.049	0.530
Constant	-4.907	2.207	0.007			0.026

PSI: Pneumonia Severity Index; CURB-65: Confusion, urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years; SCAP: Severe community acquired pneumonia; CRP: C-reactive protein, RR: Respiratory rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. *Significant values are shown with bold text.

(74.8%). Cough, sputum production, and dyspnoea were found in 152(100%), 145(95.4%) and 145(95.4%) patients respectively. All of the patients had crackles and 24(15.8%) had confusion. Co-morbidities included chronic lung disease 46(30.3%), cancer 40(26.3%), heart failure 22(14.5%), chronic kidney disease 17(11.2%), cerebrovascular disease 13(8.6%), and liver disease 5(3.3%). All of the patients had infiltration and 56(36.8%)

had bilateral infiltration, while pleural effusion was found in 30(19.7%).

Only bilateral infiltration and pleural effusion were associated with death, while confusion and bilateral infiltration were associated with hospitalisation (Table-1). Respiratory rate, BUN, CRP, and PCT were higher in those who died compared to those who survived ($p < 0.05$).

Fever, respiratory rate, heart rate, BUN, CRP and PCT were higher and pressure of oxygen (pO₂) was lower in the hospitalised group compared to the discharged group (Table-2).

PCT, CRP and respiratory rate predicted both death and hospitalisation, while pO₂ and BUN predicted hospitalisation ($p < 0.05$). PCT level had moderate and positive association with PSI, CURB-65 and SCAP scores ($r = 0.39$, $p < 0.001$; $r = 0.3$, $p < 0.001$; and $r = 0.36$, $p < 0.001$; respectively). CRP level had weak and positive correlation with the PSI, CURB-65, and SCAP scores ($r = 0.2$, $p = 0.004$; $r = 0.13$, $p = 0.07$; and $r = 0.14$, $p = 0.04$; respectively).

The mean PSI score of those who died was significantly higher than that of those who survived (146.2 ± 45.7 vs. 102.8 ± 30.2 , $p = 0.0001$). Mortality in PSI groups I, II, III, IV and V were 0(0%), 1(6.2%), 3(10%), 3(4.7%), and 17(43.6%), respectively ($p < 0.0001$). There was a trend towards increased mean CRP and PCT in the higher PSI groups. The mean CRP levels in PSI groups I, II, III, IV and V were 90.6 ± 86.7 , 120.2 ± 74.2 , 78.3 ± 72.4 , 122.9 ± 81.1 and 150.8 ± 113 , respectively ($p = 0.01$). The mean PCT levels in PSI groups I, II, III, IV and V were 0.05 ± 0.02 , 3.5 ± 13.2 , 2.3 ± 10.2 , 2.3 ± 8.3 and 9.4 ± 19.3 , respectively ($p = 0.037$).

Mortality in CURB-65 groups 0, 1, 2, 3, 4 and 5 were 0(0%), 5(10.9%), 5(9.4%), 6(24%), 6(46.2%), and 2(100%) respectively ($p < 0.0001$). The mean CRP levels in the CURB-65 groups 0, 1, 2, 3, 4, and 5 were 149.9 ± 110.9 , 97.1 ± 76.3 , 123.4 ± 95.9 , 115.6 ± 69.7 , 172.1 ± 111.6 and 103.0 ± 124.5 , respectively ($p = 0.11$). The mean PCT levels in CURB-65 groups 0, 1, 2, 3, 4 and 5 were 0.4 ± 0.6 , 3.7 ± 12.2 , 4.2 ± 15.9 , 4.9 ± 11.1 , 7.4 ± 14.1 and 8.4 ± 9.5 , respectively ($p = 0.8$).

Mortality was significantly higher in the high SCAP group compared to the low SCAP group 7(30.2%) vs. 17(5.6%), ($p < 0.001$). The mean CRP level was significantly higher in the high-risk SCAP group compared to the low-risk SCAP group (149.7 ± 96.6 vs. 99.50 ± 80.45 , $p = 0.001$). The mean PCT levels were similar in high (3.78 ± 10.02) and low (4.45 ± 14.84) risk SCAP groups ($p = 0.8$).

Multivariate binary logistic regression analysis revealed that PSI score and the CRP level were independently associated with mortality, while in the model including PCT levels instead of CRP, only PSI score was independently associated with mortality (Table-3).

Discussion

In the present study, among the three prognostic scores assessed, only PSI had an independent association with mortality. CRP, but not PCT, was independently associated with mortality.

Menendez et al.¹⁸ reported a trend towards increased PCT levels in higher PSI and CURB-65 classes. However, there were similar CRP levels in PSI and CURB-65 classes.¹⁸ In line with this report, the PCT level was associated with the PSI class and the highest mean CRP and PCT levels were observed in the most severe PSI and CURB-65 classes in the present study. Contrary to their findings, the CRP level had an association with PSI and CURB-65 classes and the PCT level was not associated with the CURB-65 class in the present study.

The association between the SCAP score and CRP or PCT levels has been rarely investigated in patients with CAP. España et al.¹⁹ reported that the SCAP classification predicted pneumonia-related complications better than PSI and CURB-65 scores and PCT was better than CRP to predict pneumonia complications. In their study, adding PCT to the prognostic scores improved predictive ability. On the other hand, adding CRP improved the performance of only the PSI score.

In the present study, CRP, but not PCT, had an independent association with mortality. Several studies suggest an association between the CRP level and prognosis in CAP.²⁰⁻²² Most of these studies also suggest an association between PCT and mortality as well.^{21,22} However, in the present study, PCT was associated with mortality in univariate analysis, but multivariate regression analysis did not suggest an independent association. In one study,²³ CRP and PCT were associated with mortality in younger and older patients with CAP only in univariate analysis. However, in multivariate regression analysis, neither was independently associated with mortality.²³ The reason for the lack of independent association between PCT and mortality in the present study may be the presence of confounding factors, such as rheumatological conditions and malignancy. It may be speculated that such patients with co-morbidity may have more severe pneumonia because they are already immune-compromised.

The present study has several limitations. Firstly, the setting of this study was an ED of a university hospital and the frequency of patients with severe pneumonia was relatively high, therefore, the findings are not generalisable to every patient with CAP. Another limitation is inclusion of patients with cancer and rheumatological diseases both of which may influence CRP and PCT levels, therefore, these conditions could have affected the association between the scoring systems and acute-phase reactants. Third, some of the patients who were admitted to ED during the study period might have later been diagnosed with CAP, but they were not included. Fourth, nearly a quarter of the patients with a presumptive diagnosis of CAP were later diagnosed with other diseases, therefore we could not

reach the required sample size. Lastly, it is a cross-sectional study, so it is not possible to make strict conclusions about cause-effect relationship.

Conclusion

When used in conjunction with scoring systems, CRP and PCT levels may be helpful in estimation of prognosis in patients admitted to emergency units with CAP. CRP, but not PCT, level was found to be independently associated with mortality. PCT level had a stronger association with the prognostic risk scores than CRP. However, it should be kept in mind that both these tests have their own limitations and should only be components of a comprehensive assessment, especially in patients with comorbidities, such as rheumatological disorders and cancer.

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