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Proadrenomedullin determining clinical severity and analyzing prognostic value for pneumonia

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Abstract:

AIMS: In pneumonia patients, we need practical biomarkers that can contribute to the diagnosis, prognosis and the prediction of mortality, and that can direct therapy and treatment setting. In this study, the diagnostic importance and value to predict prognosis and mortality are investigated for plasma proadrenomedullin (proADM) levels in pneumonia patients.

MATERIALS AND METHODS: Sixty-three consecutive patients who had been diagnosed with pneumonia, as well as 54 volunteers as the control group, making 117 in total, enrolled in this study. The participants' ProADM, leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin levels were measured, and their pneumonia severity index (PSI) and CURB-65 scores were calculated.

RESULTS: Plasma proADM levels were higher in the controls. When we compare patients' proADM levels in the initiation, and after the treatment, patients' proADM levels were lower on the 7th day after the treatment. No significant supremacy was identified over the other markers. The ProADM levels were significantly correlated with PSI stages, but in deciding of the site of care, the distribution of proADM levels for the PSI and CURB-65 risk groups (as low and high risk) were statistically irrelevant. The mean proADM levels among the patients who developed complications were slightly higher than the others, but not to a statistically significant degree. A relationship was identified between the clinical severity scores and complications, and short-term mortality was 7.93%. The plasma proADM levels among the nonsurvivors were 0.7 nmol/L and 0.90 nmol/L in the survivors. Given these data, proADM failed to predict mortality while PSI and CURB-65 were superior predictors.

CONCLUSION: Using proADM levels alone to predict pneumonia prognosis and mortality and deciding upon a therapy setting makes no sense, although in consideration of previous studies, proADM would be useful as a supplementary contributor to clinical severity scores.

Keywords:

Biomarker, mid-regional- proadrenomedullin, pneumonia, proadrenomedullin

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Introduction

New research is conducted related to the diagnosis and follow-up of pneumonia,

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which is a major global health problem, with the aim to reduce incidence rates, treatment costs, and antibiotic resistance. Biomarkers, which have gained considerable popularity in recent years, are used in the diagnosis and severity of the disease, to measure

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responses to the treatment and in the evaluation of the prognosis. The use of biomarkers has been increasing every day, particularly in elderly patients and patients with comorbidities due to the nonspecificity of clinical symptoms, and the limitations of imaging methods and physiological measurements. Biomarkers show promise in the reduction of management errors, resistance formation, and cost in the propretreatment methods, as well as in traditional methods.

Adrenomedullin (ADM), which is a potent vasodilator peptide, could be synthesized from many tissues, such as the adrenal medulla, lungs, central nervous system, and vascular smooth muscle cells. Due to its similarity with calcitonin gene-related peptide, ADM is considered to be included in this gene family and vasodilates by increasing the cyclic adenosine monophosphate levels in vascular smooth muscle cells, and by releasing nitric oxide into endothelial cells.^[1] The significant stable mid-region part of the proadrenomedullin (ProADM), which is the precursor agent, is transformed into active ADM by being rapidly destroyed. The release of AMD, in which the normal plasma level is between 1 and 10 ng/L, increases in sepsis. ADM has bactericidal properties in which the plasma levels increase with hypoxia and inflammation,^[2] and it also increases the release of pro-inflammatory cytokines. Recent publications have found that plasma levels increase with the severity of pneumonia.^[3] Although there is scant research on this topic in our country, Turkey, plasma levels have been reported to be correlated with such clinical severity scoring systems as CURB-65^[4,5] and the pneumonia severity index (PSI).^[3,6-10]

CURB-65 and PSI scores are commonly used to evaluate pneumonia severity and the prediction of mortality. In these scoring systems, patient's routine clinical parameters, laboratory results, and clinical examination findings are required to be used, with PSI, in particular, and require 20 different parameters.

In this study, we aim to determine the importance of ProADM in the diagnosis of pneumonia and in the prediction of complications and mortality by measuring plasma ProADM levels of both the control group and the patients, who were diagnosed with pneumonia or who developed pneumonia during the hospitalization, on the 1st and 7th day of treatment. We aim further to research the role of ProADM in the evaluation of the severity and prognosis of pneumonia by comparing it with such clinical scorings as CURB-65 and PSI and classical biomarkers.

Materials and Methods

This is a prospective, single-center case-control study that was conducted between January 2016 and August

2016 after ethical approval was obtained from the Ethical Board of the Hospital (with a decision dated January 29, 2016, and numbered 1491-16-16/1539).

Patients who were consecutively admitted to the hospital with a diagnosis of pneumonia within the study period, patients to whom treatment was recommended, and patients who met the criteria were included in this study population. Patients who had at least one clinical finding, such as fever, cough, purulent sputum, and pleuritic chest pain, and with rales in auscultation, were diagnosed with pneumonia according to the ATS/ERS criteria,^[11,12] and the diagnosis was confirmed with the presence of a new infiltrate in radiological imaging. Of the 81 patients, eight were removed from this study after being included at the outset due to tuberculosis in one patient, malignancy in two patients, and other etiologic reasons in five patients. A further 10 patients who were admitted to the hospital and met the inclusion criteria were excluded from this study as they did not give consent, or whose controls were not done. Accordingly, a total of 117 patients were included in this study, and 63 were in the patient group, and 54 were in the control group. The control group consisted of patients who were admitted to the clinic with respiratory complaints or whose controls were carried out in the chest diseases clinic due to pulmonary disease history, radiological sequelae check, and tuberculosis screening, and who were not diagnosed with any disease following examinations and tests. Written consent for inclusion in this study was obtained from all patients and the members of the control group involved.

Follow-up and evaluation

Blood was drawn once from the control group and twice from the patients with pneumonia on the 1st and 7th days of hospitalization and treatment for the ProADM, procalcitonin (PCT), complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) tests. Detailed information on the anamnesis, habits, comorbidities, and empirical antibiotic therapy of the patients was recorded, and PSI and CURB-65 scores were calculated from the clinical and laboratory data.

The patients were also followed regarding complications. Respiratory failure due to hypoxemia, the development of a need for a mechanical ventilator, admission into intensive care, acute renal failure (1.5 times the increase in the baseline serum creatinine), shock (systolic blood pressure <90 mm/Hg and vasopressor requirement), nonresponse to empirical antibiotherapy, pleural effusion development, and newly developed cardiac complications (arrhythmia and myocardial infarction) were considered as poor clinical outcomes.^[6,13-18]

The remainder of the complete blood tubes that were taken for the CBC, ESR, and CRP was stored at -80°C in the hospital's biochemistry laboratory after plasma separation process and centrifugation at 1000 RPM for 15 min in accordance with the Elabscience Human ProADM and Human PCT enzyme-linked immunosorbent assay (ELISA) Kit leaflets for ProADM and PCT measurements.

Measurement of the plasma proadrenomedullin and procalcitonin levels

Plasma samples obtained for this study were taken from the -80°C refrigerator, and brought to room temperature, after which ProADM and PCT measurements were made in line with the (Elabscience Elisa, Wuhan, Hubei, China) kit procedures. The kit uses a sandwich ELISA method. The sensitivity for ProADM and PCT was 0.469 nmol/L and 0.018 $\mu\text{g}/\text{L}$, respectively.

Statistical analysis

The acquired descriptive data were expressed as frequency, percentage, standard deviation, median, and range. A Mann-Whitney-U-test was used to compare quantitative data to determine the differences between the two groups. For the determination of the time difference, a Wilcoxon test was used, and a receiver operating characteristic (ROC) analysis was applied to determine the cutoff point. A Spearman's rank correlation coefficient was used to determine any correlations. A correlation analysis was used to test the linear relationship between two variables, and to determine the degree of this relationship, if any. For the comparison of the cutoff data, a Chi-square test was used to determine the difference between the two groups.

Results

The mean age of the 63 patients included in this study was 51.97 ± 28.22 ; 46 (73.02%) were male and 17 (26.98%) were female. In the control group, there were 20 (37.04%) males and 34 (62.96%) females, with a mean age of 32.96 ± 10.44 . A statistically significant difference was identified in the age and sex distribution between the patient and the control groups, and the demographic characteristics of the participants had different distributions ($P < 0.05$).

A high smoking rate was observed among the respondents. Of the patients, 30 (47.61%) were active smokers, and 16 (25.39%) were ex-smokers. Congestive heart failure, chronic obstructive pulmonary disease, structural lung disease, chronic renal failure, chronic liver disease, cerebrovascular disease, malignancy, and diabetes mellitus were defined as comorbidities. In our study, 27 patients (42.85%) were found to have comorbidities. According to CURB 65, 36 patients

were included in the low-risk group (29 patients had 0 and seven patients had 1 point) with 0–1 points, and 27 patients were included in the medium-high risk group (13 patients had 2 points, eight patients had 3 points, and six patients had 4 points) with ≥ 2 points.

According to the PSI, 38 patients were included in the low-risk group with Stages I-II-III (27 patients were Stage I, two patients were Stage II, and nine patients were Stage III), and 25 patients were included in the high-risk group with Stages IV-V (10 patients were Stage IV, 15 patients were Stage V). The relatively high rate of patients in the low-risk group, based on their clinical severity scores, could be attributed to the young patient population in the hospital, administrative reasons and the inpatient treatment of the young adult patients.

Reproduction in the culture was observed in nine of the patients (six sputum and three blood), who began to undergo empirical antibiotherapy according to the national guidelines; and serology positivity was detected in five patients, one of whom had culture positivity.

In total, 14 patients were observed to develop complications. According to CURB-65, two patients were included in the low-risk group (Score 1), three were in the medium-risk group (Score 2), and nine were in the high-risk group. Of the patients who developed complications, three were in the PSI Stage III group, while the others were in the high-risk group (three patients were Stage IV and eight patients were Stage V).

Five of the patients died during hospitalization, and none of the discharged patients died within a month of discharge. According to the PSI data, all of the exitus patients were in the high-risk group, whereas two patients were in the medium-risk group with a score of 2 according to the CURB-65.

The white blood cells (WBCs), ESR, CRP, PCT, and ProADM levels of the patients were measured for comparison with the clinical scores regarding complication and mortality. The laboratory results of the control and patient groups taken on the 1st and 7th day of treatment are presented in Table 1.

As would be expected, a statistically significant difference was observed between the control group and the patient group in all biochemical markers ($P < 0.0001$). A statistically significant difference ($P < 0.0001$) was seen between the WBCs, CRP, PCT, and ProADM levels on the 1st and 7th day of the treatment of the patients [Figure 1], while no difference was observed in the ESR rates between the 1st and 7th days ($P = 0.201$).

When the pretreatment biomarkers and clinical severity scores of the patient group were compared, a statistically

Table 1: Comparison of the parameters of the control group and patients with pneumonia, obtained on the 1st and 7th day of admission

	Mean±SD			Test, P	
	Control	Patient		Control and patient day 1	Patient day 1 and day 7
		Day 1	Day 7		
WBCs (×10 ⁹ /μl)	7.2±1.73	13.05±6.86	8.79±3.51	<0.0001	<0.0001
ESR (mm/h)	13.44±10.49	58.32±32.65	55.25±32.65	<0.0001	0.201
CRP (mg/L)	3.13±1.59	151.58±113.6	48.92±70.72	<0.0001	<0.0001
PCT (μg/l)	0±0	0.71±1.03	0.14±0.38	<0.0001	<0.0001
ProADM (nmol/L)	0.07±0.05	0.89±0.51	0.43±0.37	<0.0001	<0.0001

C: Control, WBCs: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PCT: Procalcitonin, ProADM: Proadrenomedullin, SD: Standard deviation

Table 2: Analysis of the relationship between pretreatment biomarkers and clinical severity scores in the patient group

	ProADM	CURB-65	PSI score	PSI stage
ProADM				
<i>r</i>	1.00	0.255	0.334	0.313
<i>P</i>		0.04	0.01	0.01
CURB-65				
<i>r</i>	0.255	1.00	0.907	0.903
<i>P</i>	0.04		0.00	0.00
PSI score				
<i>r</i>	0.334	0.907	1.00	0.952
<i>P</i>	0.01	0.00		0.00
PSI stage				
<i>r</i>	0.313	0.903	0.952	1.00
<i>P</i>	0.01	0.00	0.00	
WBCs				
<i>r</i>	0.271	0.14	0.12	0.12
<i>P</i>	0.03	0.27	0.37	0.33
ESR				
<i>r</i>	0.535	0.20	0.19	0.15
<i>P</i>	0.00	0.12	0.13	0.23
CRP				
<i>r</i>	0.757	0.511	0.549	0.533
<i>P</i>	0.00	0.00	0.00	0.00
PCT				
<i>r</i>	0.532	0.636	0.671	0.673
<i>P</i>	0.00	0.00	0.00	0.00

WBCs: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive protein, PCT: Procalcitonin, ProADM: Proadrenomedullin, SD: Standard deviation, CURB-65: Confusion, blood urea nitrogen, respiratory rate, blood tension and age (65 and above), PSI: Pneumonia severity index

significant positive relationship was observed between ProADM and CURB-65, PSI score, PSI stage, WBCs, ESR, CRP, and PCT results [Table 2].

In the evaluation of the biomarkers according to the accepted severity scores for the prognosis, a positive correlation was observed in the ProADM, and its correlation coefficient was found to be lower than CRP and PCT.

When the distribution of the biochemical parameters was evaluated against the PSI stages, the distribution of the parameters, aside from WBCs and ESR, was found to be statistically significant ($P < 0.05$) [Table 3 and Figure 2]. In

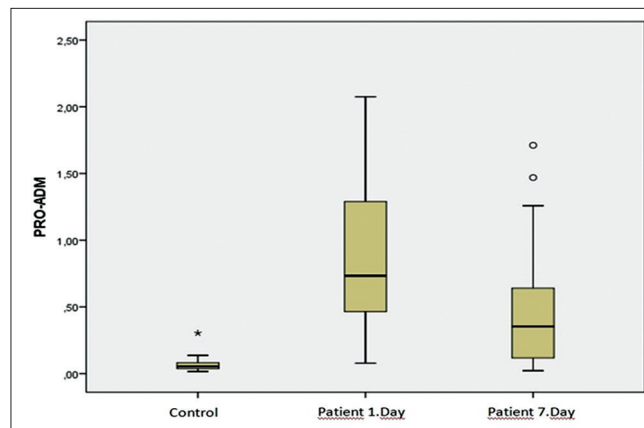


Figure 1: Comparison of proadrenomedullin levels of the control group and patients with pneumonia, obtained on the 1st and 7th day of admission

general, the more the stage increased, the more the level of ProADM increased. The difference between stages was found to be statistically significant ($P = 0.018$); however, the mean levels of Stage II and III were seen to be higher than those of Stage IV and V, which are considered as high risk.

When the ProADM levels were analyzed according to the CURB-65 and PSI risk groups, the distribution was found not to be statistically significant ($P = 0.08$, $P = 0.12$, respectively) [Table 4].

When the clinical severity scores and biomarkers were evaluated regarding complication development, the CURB-65 and PSI scores and PCT values were found to be statistically significant [Table 5] ($P < 0.05$). When the distribution of pretreatment biochemical variables of patients was examined regarding complication development, no significant outcome was obtained for WBCs, ESR, or CRP.

When the ROC analysis of the biomarkers was examined regarding complications [Figure 3], the area below the curve (AUC) was found to be 0.545 for ProADM and was below all other parameters, but significant only in PCT complication prediction ($P = 0.048$).

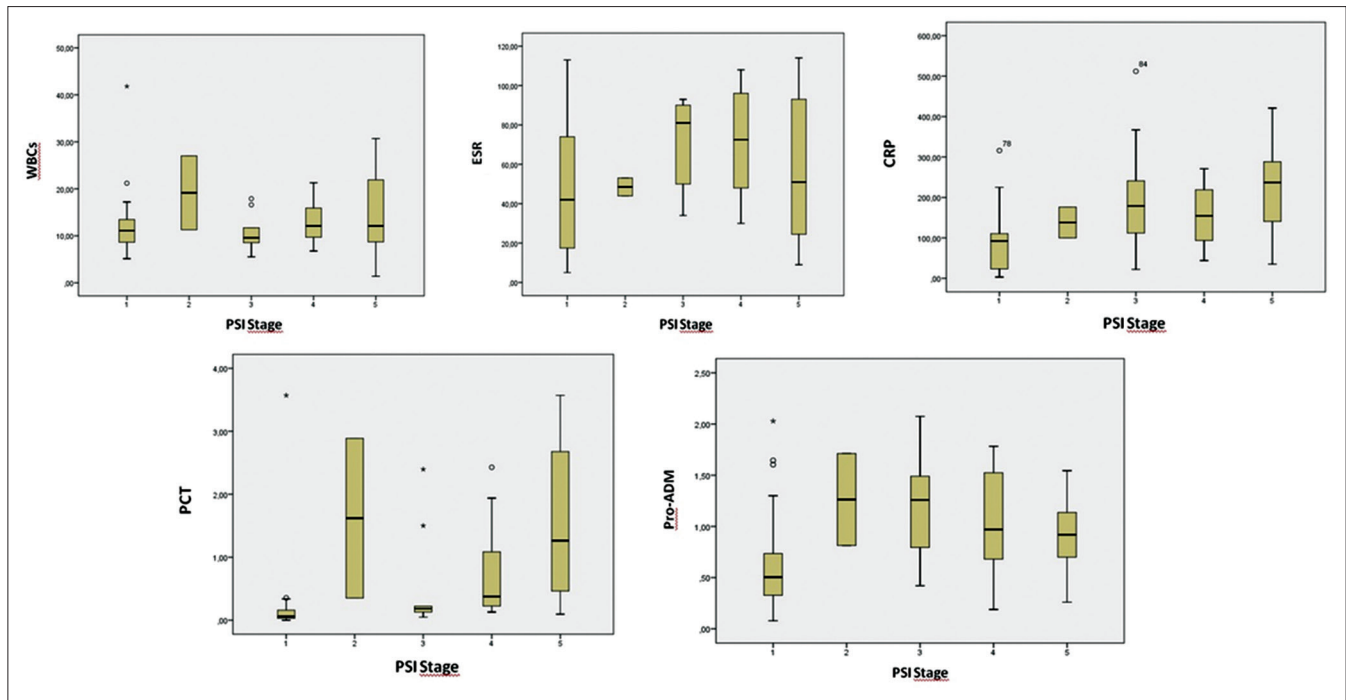


Figure 2: Distribution of biochemical parameters according to pneumonia severity index stages

Table 3: Distribution of the biochemical parameters according to pneumonia severity index stages

	PSI stage, Mean±SD					Test, P*
	1	2	3	4	5	
WBCs	12.34±6.9	19.15±11.1	10.83±4.2	12.83±4.4	15±8.64	0.509
ESR	50.33±33.74	48.5±6.36	68.33±24.41	72.3±26.8	58.67±38.19	0.409
CRP	88.03±76.82	138±53.74	210±148.94	157.19±72.39	229.01±116.12	0.001
PCT	0.22±0.68	1.62±1.79	0.54±0.83	0.77±0.81	1.54±1.22	0.000
ProADM	0.67±0.51	1.26±0.63	1.2±0.52	1.04±0.51	0.94±0.37	0.018

*Kruskal-Wallis Test. PSI: Pneumonia severity index, SD: Standard deviation, WBCs: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive protein, PCT: Procalcitonin, ProADM: Proadrenomedullin

Table 4: Distribution of proadrenomedullin levels according to pneumonia severity index and CURB-65 risk groups

	PSI, mean±SD		Test, P*
	Low risk (I-II-III)	High risk (IV-V)	
Pro-ADM	0.83±0.56	0.98±0.43	0.12
	CURB-65		Test, P*
	Low risk (0-1 points)	Medium-high risk (2 ≥ points)	
Pro-ADM	0.81±0.56	0.99±0.42	0.08

*Mann-Whitney U. ProADM: Proadrenomedullin, CURB-65: Confusion, blood urea nitrogen, respiratory rate, blood tension and age (65 and above), SD: Standard deviation, PSI: Pneumonia severity index

In the comparison of AUC with the PSI (AUC: 0.84) and CURB-65 (AUC: 0.87) scores, which were found to be significant in terms of complication development, the AUC was found to be 0.545 in the ROC analysis for ProADM, but was not superior to the scoring systems [Figure 4].

When the clinical severity scores and biomarkers were evaluated regarding mortality, the CURB-65 and PSI

scores were found to be statistically significant ($P = 0.012$, $P = 0.004$, respectively). When the mean values of the two groups were compared for all biomarkers, the difference was not statistically significant regarding mortality [Table 6]. In the ROC analysis, AUC was found to be 0.43 ($P = 0.60$) in the mortality prediction for ProADM and was not superior to other biomarkers [Figure 5].

In the comparison of AUC with the PSI (AUC: 0.87) and CURB-65 (AUC: 0.82) scores, which were found to be significant regarding mortality prediction, the AUC was found to be 0.43 in the ROC analysis for ProADM, and it was not superior to the scoring systems [Figure 6].

Discussion

In our comparative study of 63 pneumonia cases and 54 controls, the plasma ProADM levels of the patient group were found to be statistically and significantly higher ($P < 0.0001$), and a statistically significant decrease was observed in the plasma ProADM levels of the

Table 5: Comparison of biomarkers and scores according to complication status

	Complication, mean±SD		Test, P
	No	Yes	
WBCs	12.74±6.92	14.14±6.78	0.477
ESR	56.90±32.18	63.29±35.00	0.524
CRP	142.69±120.61	182.72±80.58	0.061
PCT	0.67±1.04	0.87±1.02	0.048
ProADM	0.87±0.54	0.93±0.44	0.608
CURB-65	0.86±1.19	2.79±1.05	0.000
PSI score	63.43±52.99	143.93±46.75	0.000
	n (%)	n (%)	P
PSI stage			
1	27 (55.1)	0.0	0.001
2	2 (4.1)	0.0	
3	6 (12.2)	3 (21.4)	
4	7 (14.3)	3 (21.4)	
5	7 (14.3)	8 (57.1)	
Culture			
No	47 (95.9)	7 (50.0)	0.0001
Yes	2 (4.1)	7 (50.0)	
Mortality			
No	49 (100.0)	9 (64.3)	0.0001
Yes	0.0	5 (35.7)	

PSI: Pneumonia severity index, SD: Standard deviation, WBCs: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive protein, PCT: Procalcitonin, ProADM: Proadrenomedullin, CURB-65: Confusion, blood urea nitrogen, respiratory rate, blood tension and age (65 and above)

patients with pneumonia, which were measured on the 1st and 1th day of treatment, ($P < 0.0001$). In a study by Pereira *et al.*,^[19] in which the kinetics of ProADM as an early predictor of response in cases of severe pneumonia and its importance in admission to the intensive care unit were evaluated, ProADM levels were found to be the same in both exitus and living patients. They considered mortality to be a poor marker but interpreted a reduction in ProADM levels within 48 h of antibiotherapy to be a good clinical marker, which suggests ProADM as a guide for short-term antibiotics use. In the present study, the high plasma ProADM levels in the patient group and their significant decrease after the antibiotherapy are consistent with Pereira *et al.*'s research findings.

Demographic differences were found between the control group and the patient group in our study although this was not considered an obstacle for the interpretation of the data, as it was known that there was no difference in terms of age and sex for the plasma ProADM levels.^[20]

In the present study, culture positivity was observed in the samples taken from nine patients, and the mean ProADM value of these patients was 0.72 nmol/L before the treatment, whereas the mean value of the other patients was 0.91 nmol/L. All patients whose cultures were found to be positive were in the high-risk group according to clinical severity scores. In a single-center study that involved 302 patients with

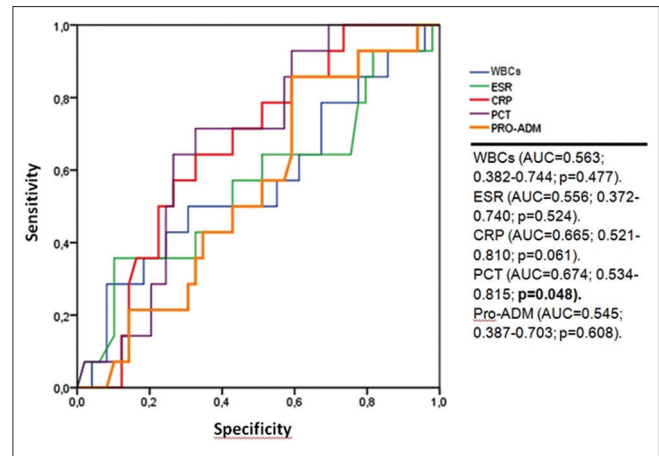


Figure 3: Comparison of biomarkers with receiver operating characteristic analysis regarding complication development

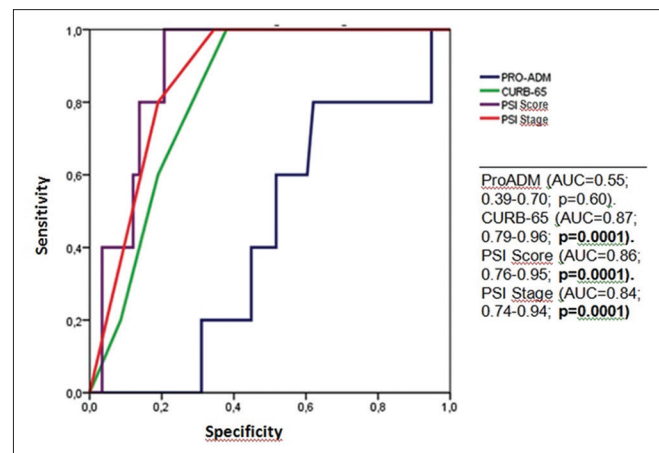


Figure 4: Comparison of proadrenomedullin with clinical severity scores regarding complication development (receiver operating characteristic analysis)

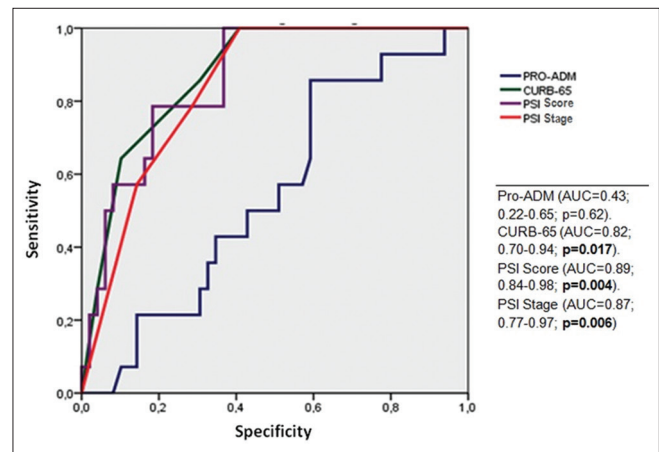


Figure 5: Comparison of proadrenomedullin with clinical severity scores regarding mortality (receiver operating characteristic analysis)

community-acquired pneumonia (CAP) who were admitted to the emergency services in Switzerland, ProADM levels were found to be increased in those who had culture positivity. In this study, comorbidities were

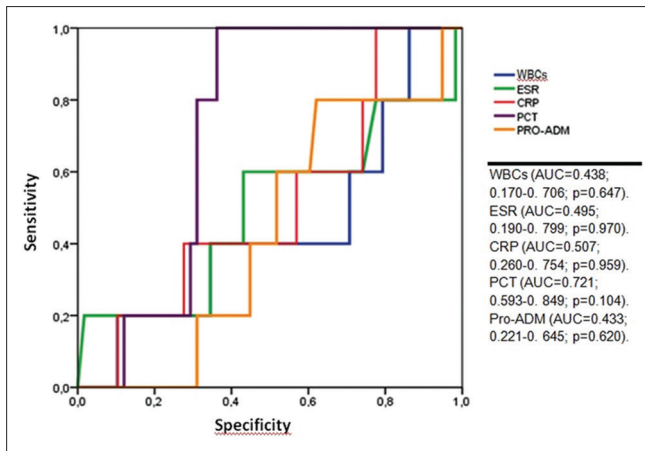


Figure 6: Comparison of biomarkers with receiver operating characteristic analysis regarding mortality prediction

Table 6: Comparison of pretreatment values of patients with exitus and those who recovered

	Mortality, mean±SD		Test, P
	Recovered	Exitus	
WBCs	13.15±6.98	11.95±5.78	0.647
ESR	58.19±32.32	59.80±40.33	0.970
CRP	151.94±115.12	147.42±105.60	0.959
PCT	0.70±1.05	0.80±0.91	0.104
ProADM	0.90±0.52	0.74±0.38	0.620
CURB-65	1.16±1.37	2.80±0.84	0.012
PSI Score	74.40±58.40	161.60±33.05	0.004
	n (%)	n (%)	P
PSI stage			
1	27 (46.6)	0.0	0.03
2	2 (3.4)	0.0	
3	9 (15.5)	0.0	
4	9 (15.5)	1 (20.0)	
5	11 (19.0)	4 (80.0)	
Culture			
No	52 (89.7)	2 (40.0)	0.018
Yes	6 (10.3)	3 (60.0)	
Complication			
No	49 (84.5)	0.0	0.0001
Yes	9 (15.5)	5 (100.0)	

PSI: Pneumonia severity index, SD: Standard deviation, WBCs: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive protein, PCT: Procalcitonin, ProADM: Proadrenomedullin, CURB-65: Confusion, blood urea nitrogen, respiratory rate, blood tension and age (65 and above)

observed in 87% of the patients, and 61% of them had a history of antibiotic use.^[3] In studies by Kutz *et al.*^[20] and Mirjam Christ-Crain, in which the preanalytical factors that affect the biomarker levels in CAP were researched, antibiotic use history and the male gender were found to be related with low-ProADM levels. Increased age, chronic liver disease, and chronic renal failure were found to be related to the high ProADM levels. However, it was suggested that preanalytical factors would not be important regarding treatment if a biomarker algorithm was carried out with the clinical

scores and an extended cutoff value was used. Patients with a history of antibiotic therapy were excluded from our study. In a multicenter study by Huang *et al.*^[8] carried out in the United States that included 1653 patients with CAP, the length of hospitalization, intensive care unit admission rates, vasopressor receiving, and culture positivity, which had a clinical importance, were observed to increase when the plasma ProADM levels increased. In our study, culture positivity was present in the patients who were at high-risk and who developed complications. However, no positive correlation was found regarding plasma ProADM levels. Our study does not support previous studies in terms of culture positivity.^[3,8,20]

When the relationship between ProADM levels and the clinical severity scores of other biomarkers were analyzed in our study, a positive correlation was observed between ProADM and severity scores. However, this correlation was not stronger than other biomarkers. In a study evaluating cardiovascular (ProADM, pro-atrial natriuretic peptide, copeptin, and proendothelin-1) and inflammatory (WBC count, CRP, and PCT) biomarkers for short- and long-term mortality in CAP, cardiovascular markers were found to be superior, particularly regarding mortality. This was thought to be due to underlying cardiovascular disease and septic cardiomyopathy.^[7] Although not predicted in advance, cardiac complications are seen at a higher rate in those with underlying diseases, particularly in patients with pneumonia. In the same study, ProADM levels increased with pneumonia severity and that these were the best predictor of mortality. In a multicenter study by Schuetz *et al.*^[21] that included 925 patients, the values of the biomarkers were analyzed in the prediction of undesired clinical results for pneumonia and lower respiratory tract infections, and cardiovascular markers, particularly ProADM, were reported to be superior to the inflammatory markers. This present study does not support Schuetz *et al.*'s results.

In our study, a significant relationship was found between ProADM values and the clinical scoring systems. In a prospective study of 491 patients with CAP who referred to the emergency services, the severity scores and biomarkers were evaluated against poor clinical outcomes. ProADM levels were found to be correlated with clinical severity scores and were even seen to improve the scores. Regarding poor clinical outcomes, the highest predictive value was reported to be provided by the combination of Severe CAP score and ProADM.^[22] In a mono-center research by Courtais *et al.*,^[23] carried out in France, the prognostic values of the ProADM levels of 109 CAP cases admitted to the emergency service were analyzed, and ProADM levels were found to be low in patients with low PSI stage, and

PSI was found to be correlated with ProADM levels. In our study, the distribution of the ProADM levels was statistically significant according to the PSI stages. However, the distribution of the clinical severity scores was not statistically significant according to the risk groups. Although our findings are in line with Courtais *et al.*'s research the clinical severity scores of the patients who received inpatient or outpatient treatment were incompatible with the majority of other studies regarding risk groups.

The patients were followed up for newly developing complications, and complications were found to develop in 14 of the total. Of these, two patients were in the CURB-65 low-risk group (Score 1), three were in the medium-risk group (Score 2), and nine were in the high-risk group. According to the PSI scores, three patients were at Stage III, and others were in the high-risk group (three patients were Stage IV and eight patients were Stage V). When the clinical severity scores and biomarkers were evaluated regarding complication development, PSI ($P < 0.001$), CURB-65 ($P < 0.001$), and PCT level ($P = 0.048$) were found to be statistically significant. Culture positivity was also observed to be related to complication development ($P = 0.0001$). In the ROC analysis, in which the ProADM was compared with other markers regarding the prediction of complication development, ProADM levels were not observed to be superior. In our study, no statistically significant relationship was observed between ProADM levels and the prediction of complication development.

In a mono-center prospective study that involved 228 patients with CAP in Spain, ProADM provided a high predictive value for 30-day complication development, and this value was reported to be unaffected by different etiologies. In a multivariate analysis, only the CURB-65 score and ProADM were determined as predictive of complications, and the ProADM ROC analysis for mortality was found to be similar to the clinical scores and superior to other biomarkers.^[9]

In a multicenter study by Schuetz *et al.*^[21] in which cardiovascular markers were found to be superior, they also found out that ProADM alone was more accurate than PSI and CURB-65 in predicting complications. It was also emphasized that adding ProADM levels to clinical scores also improved the risk assessment. In a multicenter study with 1359 cases, ProADM was found to significantly improve CURB-65 regarding mortality and complications and increased ProADM levels were reported to be related to complications even in the low-risk CURB-65 groups.^[24]

In another prospective observational multicenter study with 226 cohorts, Gordo-Remartínez *et al.*^[25] reported

that a combination of PSI and ProADM did not improve prognostic strength, but revealed ProADM to be a good predictor of poor clinical outcomes.

In a leading study including 1653 cohorts, Huang *et al.*^[8] reported that the length of hospitalization, intensive care unit admission rates and vasopressor receiving were observed to increase when ProADM levels increased and that a significant relationship exists between ProADM and mortality. ProADM was emphasized to be limited to only high-risk cases regarding complication and prognosis in this study, which reported that the combination of PSI and ProADM did not affect the risk analysis, unlike other studies. In a review of 14 articles, in which 182 articles were analyzed, the increase in ProADM, mortality, and complication were considered to be correlated. However, sensitivity was reported to be low in studies with only a small number of cases in particular.^[26] Unlike the widely accepted situation and previous studies, no statistically significant relationship was observed between ProADM and complication in our study. However, in a study by Akpınar *et al.*^[27] which was correlated with our study and included patients with severe pneumonia in the intensive care unit, ProADM was found to be high in all patients, and no relationship was identified between mortality and the development of complications.

In our study, mortality was observed in five patients (7.9%) and no additional mortality occurred during the 1-month follow-up period. All of the patients in which mortality was observed had comorbid conditions. According to the PSI, all of these patients were in the high-risk group, whereas three were in the high-risk group and two were at the medium-risk group according to CURB-65. The mean ProADM level of the patients with mortality was 0.74 nmol/L, and 0.90 nmol/L in the recovered patients. In our study, none of the biomarkers was associated with mortality ($P > 0.05$), and ProADM was not superior to other markers in terms of mortality.

Mortality and ProADM levels were found to be correlated in many of the studies reported above, but with little differences.^[3,7-10,21,22,24,28-32] These studies associate ProADM with mortality in general. However, it is notable that there is a lack of consensus as to whether or not adding ProADM values to the clinical severity scores increases the prognostic value. For instance, Huang *et al.*,^[8] Suberviola *et al.*^[33] and Gordo-Remartínez *et al.*^[25] have all reported that a combination of ProADM with clinical scores provides no additional benefit to the prediction of mortality and risk classification, whereas Christ-Crain *et al.*^[3] believe that adding ProADM values to the PSI scores improves prognostic predictions slightly. Since we conclude that ProADM levels are not associated with mortality, no additional statistical

analysis was required for the predicted value of its combination with clinical severity scores.

There are some limitations in this study. First, it is a mono-center study with a small cohort of 63 patients. The second limitation is statistically significant difference in sex and age between pneumonia patients and control group. Third, the majority of patients included in the cohort were in the low-risk population groups. Patients not only who were diagnosed with pneumonia but also who developed pneumonia during the hospitalization were included. Our study, in which patients were admitted consecutively, and which had extended inclusion criteria, is a study that imitated real life and aimed to evaluate the prediction potential of ProADM for the prognosis and mortality of pneumonia in our country.

Despite all of the above limitations, even though ProADM is significantly associated with mortality, it is considered inadequate to decide on treatment alone when all positive or negative studies are evaluated together. The practicality of its combination with clinical severity scores is another matter in question. In this regard, an interpretation made by Christ-Crain *et al.*^[3] seems to get the point across: A single biomarker has considerably promoted the important variables. Thus, ProADM is only a descriptive marker for clinical opinion and/or validated scores. However, we should highlight that ProADM is not superior.

Conclusion

ProADM alone may be useful in the evaluation of pneumonia severity but is certainly not sufficient, according to our study. As suggested in many previous studies, ProADM may be descriptive of known severity scores, and indeed, its benefits cannot be denied.

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Conflicts of interest

There are no conflicts of interest.

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