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Diagnostic and Prognostic Values of Serum C-reactive Protein, Procalcitonin, Soluble Urokinase Plasminogen Activator Receptor, and Neopterin Levels in Hospitalized Patients in the Intensive Care Unit with Ventilator-associated Pneumonia

Yoğun Bakım Ünitesinde Yatan Ventilatör İlişkili Pnömonili Hastalarda Serum C-reaktif Protein, Prokalsitonin, Solubl Ürokinaz Plazminojen Aktivatör Reseptörü ve Neopterin Düzeylerinin Tanısal ve Prognostik Değeri

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Abstract

Introduction: This study investigated the association and prognostic values of serum C-reactive protein (CRP), procalcitonin (PCT), soluble urokinase plasminogen activator receptor (suPAR), and neopterin levels in patients with ventilator-associated pneumonia (VAP).
Materials and Methods: This prospective observational age-and gender-matched study included 38 adult patients who were diagnosed with VAP and 40 adult patients without VAP. The Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Clinical Pulmonary Infection Scores were calculated, and the daily positive end-expiratory pressure values of the patients were recorded. The serum levels of CRP, PCT, suPAR, and neopterin were measured once in controls (control group) and on days 0, 3, and 5 and at the end of treatment in the VAP group.
Results: The CRP, PCT, neopterin, and suPAR levels were significantly higher in the VAP group than in the control group. APACHE II and SOFA values were higher in the VAP group than in the control group. C-reactive protein value on day 0 of >14.5 ng/ml and PCT level on day five of >1.23 ng/ml were 100% specific for the prediction of mortality in the VAP group.
Conclusion: Measuring CRP, PCT, neopterin, and suPAR levels may aid in the early diagnosis of VAP in patients hospitalized in the ICU. High CRP and PCT levels, as well as high APACHE II and SOFA scores, may have prognostic value in the follow-up of patients with VAP.
Keywords: APACHE, prognosis, SOFA, ventilator-associated pneumonia, soluble urokinase plasminogen activator receptor (suPAR)

Öz

Giriş: Bu çalışmada C-reaktif protein (CRP), prokalsitonin (PKT), solubl ürokinaz plazminojen aktivatör reseptörü (SuPAR) ve neopterin düzeylerinin yoğun bakımda yatan hastalarda ventilatör ilişkili pnömoni (VİP) ile ilişkisi ve mortalite ile ilişkili prognostik değerinin belirlenmesi amaçlanmıştır.
Gereç ve Yöntem: Bu prospektif gözlemsel yaş ve cinsiyet eşlenmiş çalışmaya, yoğun bakımda VİP tanısıyla yatan 38 erişkin hasta ile yoğun bakımda yatan ancak VİP olmayan 40 erişkin kontrol grubu olarak dahil edildi. Hastaların Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II (APACHE II),

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Öz

Ardışık Organ Yetmezliği Değerlendirme Skoru (SOFA) ve Klinik Pulmoner Enfeksiyon Skorları belirlendi, günlük ekspirasyon sonu pozitif basınç değerleri ölçüldü. Serum CRP, PKT, suPAR ve neopterin düzeyleri hasta grubunda 0. gün, 3. gün, 5. gün ve tedavi bitiminde, kontrol grubunda ise bir kez ölçüldü.

Bulgular: Ventilatör ilişkili pnömoni tanısı alan hastalarda CRP, PKT, suPAR ve neopterin kontrol grubundan anlamlı olarak yüksek bulundu. APACHE II ve SOFA skorları da VİP grubunda daha yüksekti. Sıfırıncı günde CRP değerinin >14,5 ng/ml olması ve beşinci günde PKT seviyesinin >1,23 ng/ml olması VİP mortalitesi için %100 spesifik saptandı.

Sonuç: C-reaktif protein, PKT, suPAR ve neopterin gibi belirteçler, yoğun bakımda yatan VİP hastalarında erken tanıda yardımcı olabilir. Yüksek CRP ve PKT seviyeleri ile birlikte yüksek APACHE II ve SOFA skorlarının VİP'te prognostik değeri olabilir.

Anahtar Kelimeler: APACHE, prognoz, SOFA, ventilatör ilişkili pnömoni, solubl ürokinaz plazminojen reseptörü (suPAR)

Introduction

Ventilator-associated pneumonia (VAP) is one of the most common causes of mortality and morbidity in patients hospitalized in intensive care units (ICU). In addition to the current diagnostic methods, new and more reliable diagnostic tests are required, as diagnosis can be difficult. The soluble urokinase plasminogen activator receptor (suPAR) reflects immune activation, which includes the plasminogen activating pathway and the regulation of the immune system such as the modulation of cell adhesion, migration, and proliferation. The plasma level of suPAR indicates immune activation and is increased in several infectious diseases, such as human immunodeficiency virus infection, tuberculosis, sepsis, and other conditions. High suPAR levels have been associated with increased inflammation, disease progression, and fatal outcomes, which means that suPAR levels may be used as a marker in the monitoring of certain infectious diseases and sepsis and in the determination of prognosis[1].

Several other biomarkers can be used to monitor disease activity and estimate prognosis in infectious diseases. In addition to the widely known and used example, C-reactive protein (CRP), neopterin, which is produced by activated monocytes, macrophages, and dendritic cells upon stimulation by interferon gamma, can also be used as a useful marker[2]. Additionally, procalcitonin (PCT), which is a member of the calcitonin superfamily, may be a critical marker in the diagnoses of sepsis. Procalcitonin levels can be used in monitoring the response to antimicrobial therapy and in the estimation of prognosis in sepsis, community-acquired pneumonia, and VAP[3,4].

In this study, we investigated the association and prognostic values of serum CRP, PCT, suPAR, and neopterin levels in patients with VAP. With these tests, we followed up patients in an attempt to reduce mortality and morbidity rates in these patients by suggesting or adapting appropriate therapies.

Materials and Methods

This prospective observational study was conducted following the Declaration of Helsinki. Ethical approval of this study was obtained from the Local Ankara Training and Research Hospital Non-Interventional Ethical Committee (approval date: 11.06.2015, approval no.: E-15-526). Informed consent was obtained from each participant or their next of kin.

Study Design and Patient Population

This prospective observational age- and gender-matched study included 38 adult patients who were diagnosed with VAP and 40 adult patients without VAP. The control group included patients who were hospitalized in the ICU, did not have nosocomial infection, and did not have any underlying diseases such as chronic kidney failure, rheumatoid arthritis, and malignancy. Furthermore, the control group consisted of patients who did not have the above-mentioned diseases but were followed up in the ICU for various reasons.

The diagnosis was VAP if new or progressive infiltration was identified on a chest X-ray image 48 h after intubation and at least two of the following findings: hyperthermia (>38 °C) or hypothermia (<36 °C), leukocytosis (white blood cells ≥12,000/mm^3) or leukopenia (white blood cells <4,000/mm^3), purulent tracheobronchial secretion or an increase in secretion, and a decrease in oxygenation or an increase in respiratory rate findings. All patients received the standard treatment for VAP, as recommended by national and international guidelines (Turkish Thoracic Society Consensus Report on the Diagnosis and Treatment of Hospital-Developing Pneumonia in Adults, American Thoracic Society guidelines for the managements of adults with hospital acquired, ventilator associated and healthcare associated pneumonia).

During ICU care, the severity of patients' condition was graded using Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment Score (SOFA), and Clinical Pulmonary Infection Scores (CPIS); scores were

calculated on admission. Daily positive end-expiratory pressure levels were also recorded in the VAP group.

Blood samples use for the measurement of CRP, PCT, suPAR, and neopterin serum levels were drawn once initially before antimicrobial treatment for both groups and on days three and five and at the end of treatment in the VAP group. All serum and plasma samples were kept at -80 °C until the time of study. The enzyme-linked immunosorbent assay (ELISA) was used for the determination of suPAR levels (Lot no. 191NJ2-1, Ref. A001; ViroGates A/S, Birkerød, Denmark), following the manufacturer's protocol. Neopterin levels were also determined using a commercial ELISA kit (Lot no. mnpk 1603, Ref. EIA-1476; DRG, Springfield, IL, USA), according to the manufacturer's instructions. The absorbance of the samples was measured at 450 nm using a VERSAmax Tunable Microplate Reader (Molecular Devices, LLC, CA, USA). C-reactive protein levels (Ref. 447280; Beckman Coulter, CA, USA) were determined using the nephelometric method, and PCT levels (Lot no. 121800, Ref. 05056888 200; Roche, CA, USA) were determined using electrochemiluminescence immunoassay in accordance with the manufacturer's instructions.

The results of the VAP and control groups were compared. A subgroup analysis was made for the VAP group, and the scores and levels of the biomarkers of the survivor and nonsurvivor groups were compared statistically. The reproducing microorganisms of the deep tracheal aspirate culture in patients with VAP were also reported.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software package for Windows 11.5 (Chicago, USA, SPSS inc.). The distribution of descriptive statistics was expressed as mean±standard deviation for variables with normal distribution and as median (minimum-maximum) for variables without normal distribution, while nominal variables were presented as case numbers (n) and percentages (%). The mean values of two groups were compared with Student's t-test, and median values of two groups were compared with the Mann-Whitney U test. Nominal variables were evaluated with Pearson's chi-square tests or Fisher's exact tests in 2×2 tables. It was ascertained from a receiver operating characteristic (ROC) curve analysis whether the PCT, neopterin, CRP, and suPAR had distinctive properties for the results. A cut-off point was calculated from Youden's index for each parameter, which has a distinctive property. Sensitivity and specificity were calculated for each cut-off value, and the value at the highest point of specificity was designated as the cut-off. A p value of <0.05 was considered significant.

Results

This study included 38 patients with VAP and 40 controls (i.e., patients who were hospitalized in the ICU, did not have nosocomial infection, and did not have any underlying disease). The demographic and clinical data of the study population are presented in Table 1. The VAP and control groups had comparable age and gender distribution. In the low tracheal aspirate culture, only one kind of microorganism was detected in 35 (92.2%) patients, and two kinds of microorganisms were detected in three (7.9%) patients. The most frequently detected microorganisms in the cultures were *Acinetobacter* spp. and *Pseudomonas aeruginosa*, followed by *Klebsiella pneumoniae* and others. Only one-third of the VAP group recovered from the infection. The APACHE II and SOFA scores were higher in the nonsurvivor group than in the survivor group (Table 2).

Table 1. Demographic and clinical data of study population

		VAP group (n=38)	Control group (n=40)
Gender	Male	18 (47.4%)	21 (52.5%)
	Female	20 (52.6%)	19 (47.5%)
Age	Mean±SD	70.30±14.69 (22-89)	71±23.40 (25-76)
Tracheal aspirate culture production (n=41)	*Acinetobacter spp.*	27 (65.8%)	-
	Pseudomonas aeruginosa	7 (17%)	-
	Klebsiella pneumoniae	2 (4.8%)	-
	Morganella morganii	1 (2.48%)	-
	Burkholderia cepacia	1 (2.48%)	-
	Staphylococcus aureus	1 (2.48%)	-
	Stenotrophomonas maltophilia	1 (2.48%)	-
	Enterococcus faecalis	1 (2.48%)	-
Outcome	Survivor	13 (34.2%)	-
	Nonsurvivor	25 (65.8%)	-

SD: Standard deviation, VAP: Ventilator-associated pneumonia

Table 2. Comparison of intensive care unit severity scores in nonsurvivor and survivor ventilator-associated pneumonia groups

	Survivor group (n=13)	Nonsurvivor group (n=25)	p value
APACHE	12 (8-29)	17 (10-30)	**0.030**
SOFA	5 (2-9)	7 (3-14)	**0.036**
CPIS	5 (1-8)	4.5 (3-8)	0.937
PEEP	8 (6-8)	8 (6-10)	0.387

Data are presented as median (range) and were compared using Mann-Whitney U tests.
APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score, CPIS: Clinical Pulmonary Infection Score, PEEP: Positive end-expiratory pressure

Table 3. Serum C-reactive protein, procalcitonin, soluble urokinase plasminogen activator receptor, and neopterin levels in ventilator-associated pneumonia and control groups on day 0

	VAP group (n=38)	Control group (n=40)	p value
CRP (ng/ml)	10.90 (2.50-28.90)	0.62 (0.16-16.60)	**0.0001**
PCT (ng/ml)	0.61 (0.04-56.14)	0.34 (0.10-0.249)	**0.0001**
SuPAR (ng/ml)	12.55 (1.15-52.32)	5.12 (1.08-15.11)	**0.0001**
Neopterin (ng/ml)	10.41 (2.85-130.66)	3.75 (0.95-11.47)	**0.0001**

Data are presented as median (range). Intergroup comparisons were assessed by Mann-Whitney U tests.
CRP: C-reactive protein, PCT: Procalcitonin, suPAR: Soluble urokinase plasminogen activator receptor, VAP: Ventilator-associated pneumonia

The serum levels of CRP, PCT, suPAR, and neopterin in the VAP and control groups on day 0 are shown in Table 3. C-reactive protein, PCT, neopterin, and suPAR levels were significantly higher in the VAP group than in the control group. The serum levels of CRP, PCT, suPAR, and neopterin were higher in the nonsurvivor VAP group than in the survivor VAP group, in addition to the values at the end of treatment (Table 4). The highest differences were observed on day 0 for CRP, day three for SuPAR, and day five for PCT and neopterin.

When the CRP measurements were evaluated, the area under the ROC curve of the CRP values at day 0 was 0.886 (p=0.008), and higher CRP values were found to predict a poor prognosis (Figure 1). C-reactive protein level of 14.50 ng/ml value on day 0 was 50% sensitive and 100% specific for prediction of mortality. Procalcitonin levels of >1.23 ng/ml on day five were 60% sensitive and 100% specific for the prediction of mortality in patients with VAP (R=0.856, p=0.0001) (Figure 2). No significant property was identified from the ROC curves of the suPAR and neopterin measurements.

Table 4. Serum C-reactive protein, procalcitonin, soluble urokinase plasminogen activator receptor, and neopterin levels in survivor and nonsurvivor ventilator-associated pneumonia groups

		Survivor group (n=13)	Nonsurvivor group (n=25)	p value
CRP (ng/ml)	Day 0	8.27±3.23	14.64±7.53	**0.001**
	Day 3	7.17±3.15	12.37±6.49	**0.01**
	Day 5	7.95±3.31	14.05±8.47	**0.004**
	End of treatment	8.53±4.09	10.60±7.30	0.466
PCT (ng/ml)	Day 0	0.28 (0.07-6.80)	1.17 (0.04-56.14)	**0.0042**
	Day 3	0.19 (0.03-3.11)	0.83 (0.14-21.57)	**0.009**
	Day 5	0.15 (0.06-1.19)	1.76 (0.04-22.11)	**0.0001**
	End of treatment	0.125 (0.06-31.53)	0.29 (0.11-0.84)	0.274
SuPAR (ng/ml)	Day 0	11.19±8.34	17.44±14.02	0.151
	Day 3	7.50±6.20	19.09±14.31	**0.002**
	Day 5	10.46±8.05	18.39±12.86	**0.05**
	End of treatment	7.68±5.35	9.25±5.71	0.570
Neopterin (ng/ml)	Day 0	6.65 (2.85-47.81)	18.17 (3.89-130.66)	**0.007**
	Day 3	5.62 (2.62-50.22)	18.09 (5.05-123.11)	**0.001**
	Day 5	4.35 (2.18-24.88)	17.24 (4.49-154.22)	**0.0001**
	End of treatment	4.55 (2.63-51.11)	6.00 (1.58-30.15)	0.740

Data are presented as median (range). Intergroup comparisons were assessed by Mann-Whitney U tests.
CRP: C-reactive protein, PCT: Procalcitonin, suPAR: Soluble urokinase plasminogen activator receptor

Discussion

In this study, we investigated the association of serum CRP, PCT, suPAR, and neopterin levels in patients with VAP and compared the levels of these biomarkers with controls who were hospitalized in the ICU, did not have nosocomial infection, and did not have any underlying disease. We found that CRP, PCT, neopterin, and suPAR levels were significantly higher in the VAP group than in the control group. We also demonstrated the prognostic values of serum CRP, PCT, suPAR, and neopterin levels to predict mortality in patients with VAP. C-reactive protein level of 14.50 ng/ml on day 0 and PCT level of >1.23 ng/ml on day five were 100% specific for the prediction of VAP mortality. We failed to demonstrate a cut-off for suPAR and neopterin for the prediction of mortality, although these biomarkers were also elevated in the nonsurvivor VAP group.

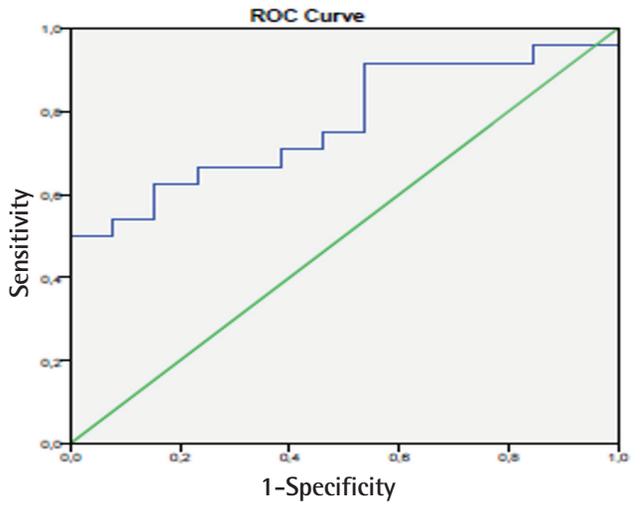

Figure 1. Mortality-related receiver operating characteristic curve of C-reactive protein levels in patients with ventilator-associated pneumonia on day 0

ROC: Receiver operating characteristic

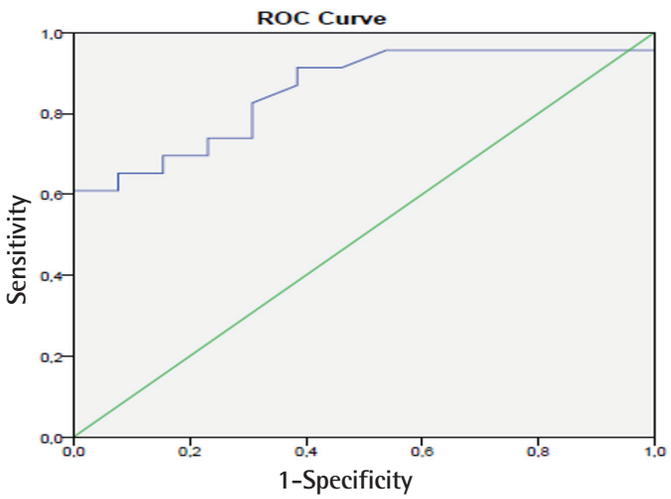

Figure 2. Mortality-related receiver operating characteristic curve of procalcitonin levels in patients with ventilator-associated pneumonia on day five

ROC: Receiver operating characteristic

suPAR is recognized as a biomarker in the assessment of systemic inflammation. Similar to the findings of the present study, Sunnetcioglu et al.[5] found that suPAR levels were substantially higher in patients with VAP than in those without VAP[5]. Several other studies have revealed that serum suPAR levels in patients with VAP were correlated with the disease severity and that sepsis and high serum levels can, in particular, be predictors of mortality[6,7]. In the present study, no prognostic value was identified when the ROC curve was drawn, although the serum suPAR levels of patients with VAP were higher than those of the controls, and suPAR levels were higher in the nonsurvivor VAP group. Similar to our results, Siahanidou et al.[8] found a correlation between suPAR levels and CRP in patients with sepsis.

In the present study, an examination of the ROC curve revealed that neopterin levels were not prognostic, although they were high, similar to suPAR, in the VAP group compared with the control group and the nonsurvivor VAP group. Similar to our results, Prat et al.[9] reported that serum neopterin and PCT levels were correlated with the severity of pneumonia.

Many studies have demonstrated a correlation between serum, CRP, and PCT levels and severity of infection[5,10,11]. Póvoa et al.[12] concluded that daily CRP measurements may be useful in monitoring the progress of VAP. By contrast, Tanrıverdi et al.[13] claimed that serum PCT level is superior to CRP as a prognostic indicator in patients with VAP admitted in the ICU and that PCT levels >1 ng/ml on day three of the disease may be a strong indicator of a poor prognosis. The present study found that CRP levels at the beginning of the treatment and PCT levels on day five have prognostic significance. Moreover, when the risk scoring values were compared, APACHE II and SOFA scores were significantly high among patients with VAP compared with controls, but not for CPIS score. Larsson et al.[14] also found that CPIS scores are less sensitive in the prediction of prognosis. After analyzing the differences in studies, Minne et al.[15] recommended the use of risk evaluation scores in combination to provide greater prognostic value.

The present study differs from previous studies in its analysis of two new biomarkers, i.e., neopterin and suPAR, together as a marker for the prediction of prognosis in patients with VAP. However, this study has several limitations. The main limitations are the low number of patients with VAP and their subgroups and the inability to measure biomarkers (CRP, PCT, neopterin, and suPAR) on days three and five in the control group because of cost limitations. However, the comparison of the relationship between biomarkers and mortality on days three and five and at the end of treatment in the survivor and nonsurvivor VAP groups is the distinctive feature of our study.

Conclusion

C-reactive protein, PCT, neopterin, and suPAR levels may aid in the early diagnosis of VAP in patients admitted in the ICU. High CRP levels on day 0 and PCT levels on day five, as well as high APACHE II and SOFA scores, may be associated with the presence of VAP and may have prognostic value for the follow-up of patients with VAP; however, no prognostic value was observed for suPAR or neopterin. During the follow-up, treatment plans may be arranged to use these biomarkers in risk evaluation scores.

Ethics

Ethics Committee Approval: Ethical approval of this study was obtained from the Local Ankara Training and Research Hospital Non-Interventional Ethical Committee (approval date: 11.06.2015, approval no.: E-15-526).

Informed Consent: Informed consent was obtained from each participant or their next of kin.

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Authorship Contributions

Surgical and Medical Practices: R.Ö., H.B., V.F., S.C., A.Ö., N.T., Ç.K., L.Ş., E.A., A.P.D., Concept: R.Ö., A.Ö., N.T., L.Ş., E.A., Design: R.Ö., A.Ö., N.T., L.Ş., E.A., Data Collection or Processing: R.Ö., H.B., V.F., S.C., N.T., Ç.K., Analysis or Interpretation: R.Ö., H.B., V.F., S.C., L.Ş., E.A., Literature Search: R.Ö., A.Ö., Ç.K., E.A., A.P.D., Writing: R.Ö., H.B., V.F., S.C., A.Ö., N.T., Ç.K., L.Ş., E.A., A.P.D.

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