ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Role of presepsin in predicting sepsis and mortality in COVID-19 pneumonia

Presepsinin COVID-19 pnömonisinde sepsis ve mortaliteyi öngörmedeki rolü

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SUMMARY

Aim: Aim: We aimed to investigate the prognostic significance of Presepsin (PSP) in patients with Coronavirus Disease 2019 pneumonia who were admitted to the emergency department (ED).

Material and Methods: This study was conducted as a prospective, case-controlled, observational study. 123 patients with a diagnosis of Covid-19 pneumonia were chosen for the case group and 123 volunteers were enrolled as a control group. 62 of the patients were classified into the sepsis group and 61 patients were placed into the non-sepsis group. The follow-up and treatment of the patients were carried out according to the Covid-19 Severe Pneumonia, ARDS, Sepsis, and Septic Shock Management Guideline of the Türkiye Ministry of Health. The PSP level was studied in patients with and without sepsis diagnosed with Covid-19 pneumonia.

Results: There was no statistically significant difference between the control group, the sepsis group, and the non-sepsis group when the PSP values were compared. However, when the ROC curve was studied for the case group, a statistically significant difference between the survivors and non-survivors was discovered ($p<0.05$).

Conclusion: No statistically significant distinction in PSP values between the control group and the septic and non-septic patient groups with Covid-19 pneumonia was found. However, PSP values were shown to be statistically significant in mortality of Covid-19 pneumonia and survival.

Keywords: Covid-19, emergency medicine, Human Presepsin Protein, pneumonia, sepsis

ÖZET

Amaç: Bu çalışmada, acil servise başvuran Coronavirus Disease 2019 pnömonisi olan hastalarda Presepsin (PSP)'in prognostik önemini araştırmayı amaçladık.

Materyal ve Metotlar: Bu çalışma, prospektif, vaka-kontrollü, gözlemsel bir çalışma olarak yapılmıştır. Covid-19 pnömonisi tanısı konulan 123 hasta vaka grubu olarak seçilmiş ve 123 gönüllü de kontrol grubu olarak çalışmaya alınmışlardır. Hastaların 62'si sepsis grubuna, 61'i ise sepsis olmayan grup olarak sınıflandırılmıştır. Hastaların takibi ve tedavisi, Türkiye Sağlık Bakanlığı Covid-19 Ciddi Pnömoni, ARDS, Sepsis ve Septik Şok Yönetim Kılavuzu'na göre yapılmıştır. PSP düzeyi, Covid-19 pnömonisi tanısı konulan hastalarda sepsisli ve sepsisli olmayanlar arasında incelenmiştir.

Bulgular: PSP değerleri karşılaştırıldığında, kontrol grubu, sepsis grubu ve sepsis olmayan grup arasında istatistiksel olarak anlamlı farklılık bulunmamıştır. Ancak vaka grubu için ROC eğrisi incelendiğinde, sağ kalanlar ve sağ kalmayanlar arasında istatistiksel olarak anlamlı fark saptanmıştır ($p<0,05$).

Sonuç: Covid-19 pnömonisi olan hastalarda kontrol grubu ile sepsis ve sepsis olmayan hasta grupları arasında PSP değerleri arasında istatistiksel olarak anlamlı fark bulunmamıştır. Ancak PSP değerleri, Covid-19 pnömonisi mortalitesi ve sağ kalımında istatistiksel olarak anlamlı bulunmuştur.

Anahtar Kelimeler: Acil tıp, covid-19, Human Presepsin Protein, pnömoni, sepsis

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INTRODUCTION

Coronavirus Disease 2019 (Covid-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, is a life-threatening disease that progresses to severe pneumonia and respiratory failure (1). CD14 is a glycoprotein expressed on the surface membranes of monocytes, macrophages, and activated granulocytes (2). There are two forms of CD14, membrane-bound and soluble. The soluble form, which is present in plasma, is degraded by cathepsin D or other proteases to produce a subtype known as presepsin (PSP). PSP is released into the bloodstream through exocytosis and proteolysis (3). The production scheme of PSP is shown in Figure 1.

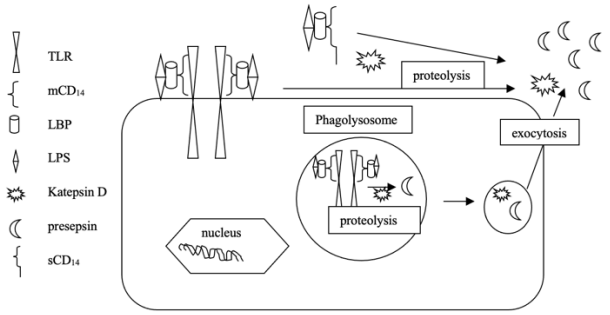

Figure 1. Production mechanism of Presepsin. LBP: Lipoprotein Binding Protein, LPS: lipopolysaccharide, TLR: Toll-like receptor. mCD14: membran CD14. sCD14: soluble CD14.

It has been reported that PSP increases remarkably in sepsis or septic shock (4). Studies have shown that PSP has higher sensitivity and specificity for sepsis diagnosis compared to the commonly used biomarker, procalcitonin (5). In order to manage the high patient volume in emergency department (ED), early triage and appropriate patient guidance are crucial for the effective use of limited resources. In this respect, the use of fast, efficient, and easily accessible biomarkers reduces the emergency room crowd and increases the quality of patient care.
In our study, we aimed to determine the relationship between PSP values and the severity of pneumonia in patients presenting to the ED with Covid-19 pneumonia.

MATERIALS AND METHODS

Ethics–Design

Our study received ethical committee approval from the Clinical Research Ethics Committee of the Ministry of Health Ankara Training and Research Hospital (25.09.2020-E.33228). The study was conducted in accordance with the latest version of the Helsinki Declaration and the "Good Clinical Practice Guidelines".
Our study was a prospective, observational, case-control study conducted in the emergency department of a 3rd level training and research hospital located in the city center between 01.11.2020 and 01.11.2021.

Study design and sampling

The research was planned as a descriptive-relational study between April 2019 and September 2019 and was conducted at Firat University Hospital-General Surgery Clinic. The population of the study consisted of all adult patients who were diagnosed as obese and non-obese and were admitted to the General Surgery Clinic of Firat University Hospital between May and July. The sample of the study was determined as 200 people (100 obese, 100 non-obese-control groups) with 0.3 effect size, 0.05 error level, 0.95 confidence interval, and 0.95 *Patients and setting*

There was a difference between the mean/median of PSP levels between the control group and groups with and without sepsis who had Covid-19 pneumonia in their lung computed tomography. Our hypothesis is two-tailed, with an alpha of 0.05 and a power of 0.80, G power with both group ratios as 1, and the sample size was determined as 40 for a single group, 120 for the case group and 120 for the control group, with a total of 240 patients. For the case group, patients with Covid-19 pneumonia who applied to the clinic and did not have exclusion criteria were selected. For the control group, individuals who did not have exclusion criteria were of the same gender, had a maximum age difference of 10 years, and gave informed consent were included.

The exclusion criteria for the study were: patients under 18 years of age or pregnant, patients who did not agree to participate in the study or did not sign informed consent, and those with comorbidities that could affect PSP levels (Acute coronary syndrome and ischemic heart disease, chronic renal failure, ischemic or hemorrhagic cerebrovascular events, diagnosed oncological patients, other conditions that cause shock (such as anaphylaxis, hemorhagic shock)).

Definitions

Sepsis: The presence of organ failure associated with suspected or proven infection. The Guick Sepsis-related Organ Failure Assessment (qSOFA) criteria including hypotension (systolic blood pressure <100mmHg), altered mental status (Glaskow Coma Scala (GCS) ≤13), and tachypnea (respiratory rate ≥22/min) was used for sepsis diagnosis. If two or more of these criteria are positive, a diagnosis of sepsis is made.

Analysis of PSP

Samples were stored at -80°C in a SANYO MDF U6186S (Serial No. 51013460) device, centrifuged in an Eppendorf 5810 (Serial No. 5810BH062103) device, and vortexed in a NÜVE NM 110 (Serial No. 02-1205) device. ELISA kit

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(Catalog no: E3754Hu) from BT LAB company, which works with a double- antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method, was used for PSP analysis. The measurements were performed using an ELx 800 Microplate Reader (BIO-TEK Instruments, INC/USA) and an ELx 50 washer (BIO-TEK Instruments, INC/USA). The standard curve was plotted from the prepared standards between 40 ng/L - 640 ng/L, and the calculations were made accordingly. The measurement values were between 5-1000 ng/L.

Statistical Analysis

Demographic data were analyzed descriptively and in frequency. Normality distribution was tested using the Kolmogorov-Smirnov test. As two-group comparisons of numerical variables did not follow a normal distribution, the Mann-Whitney U test was used. As three-group comparisons of numerical variables did not follow a normal distribution, the Kruskal-Wallis test was used. Categorical variables were analyzed using the Chi-square test. The ROC curve was plotted for sensitivity against 1-specificity. Cox regression analysis was conducted for mortality in the case group. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 18 version (Chicago, IL, USA)

RESULTS

In our study, a total of 246 participants were included, with half forming the patient group and the other half forming the control group. Among the patients, 62 (50.4%) were in the sepsis group, and 61 (49.6%) were in the non-sepsis group. The study population flowchart is shown in Figure 2.

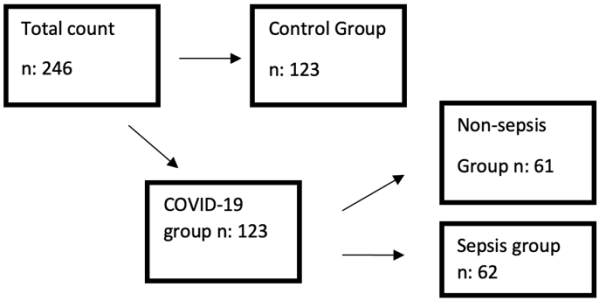

Figure 2. Number and distribution of patients included in the study

Demographic characteristics and comorbidities of the patients were compared based on their diagnostic groups. No statistically significant differences were found between the diagnostic groups in terms of age and gender (p>0.05) (Table 1).

Table 1. Evaluation of sociodemographic and comorbidity characteristics by patient groups

	COVID-19 (Sepsis group) (n=62, %25.2)	COVID-19 (non-sepsis group) (n=61, %24.8)	Control Group (n:123, %50)	*p*
Sex, n (%)*				
Female	29 (46.8)	29 (47.5)	58 (47.2)	
Male	33 (53.2)	32 (52.5)	65 (52.8)	0.996[1]
Age, year				
Age mean ± SD	69.4 ± 13.4	63.7 ±16.6	65.3±15.2	0.095[4]
Median (IQR)	72 (61-79)	68 (54-76)	68 (57-76)	0.142[2]
Hypertension, n (%)	36 (58.1)	22 (36.1)	55 (44.7)	0.046[1]
Diabetes Mellitus, n (%)	19 (30.6)	16 (26.2)	35 (28.5)	0.863[1]
COPD/ Ashtma, n (%)	11 (17.7)	3 (4.9)	10 (8.1)	0.039[1]
Heart Disease, n (%)	12 (19.4)	15 (24.6)	21 (17.1)	0.480[1]
Neurologic Disease, n (%)	6 (9.7)	3 (4.9)	8 (6.5)	0.640[3]

[1] Chi-square Test, [2] Kruskal Wallis Test, [3]Fisher Test, [4]Analysis of Variance, *Column Percentage, IQR: Inter Quantile Range (25% and 75% values are presented.), COVID-19: Coronavirus Disease 2019, COPD: Chronic Obstructive Pulmonary Disease

When serum PSP values were compared among the three groups, no statistically significant differences were found (p=0.766, Kruskal Wallis test) (Table 2).

Table 2. Evaluation of vital findings and PSP level by patient groups

	COVID-19 (Sepsis group) (n=62, %25.2)	COVID-19 (non-sepsis group) (n=61, %24.8)	Control Group (n:123, %50)	*p* value
Systolic BP, mmHg Median (IQR)	125.5 (109-147)	126 (119-142)	135 (120-161)	0.001[1]
Diastolic BP, mmHg Median (IQR)	68.5 (58-83)	73 (65-79)	72 (62-83)	0.344[1]
Pulse Rate, min. Median (IQR)	95 (83-110)	88 (80-96)	91 (80-96)	0.030[1]
Oxygen Saturation, SpO2 Median (IQR)	80 (67-85)	94 (92-95)	97 (96-98)	<0.001[1]
Respiratory Rate, min. Median (IQR)	31 (24-40)	21 (19-24)	20 (19-21)	<0.001[1]
PSP Median (IQR)	147.9 (128.4-179.5)	150.1 (132.1-171.6)	150.3 (135.1-164.6)	0.766[1]

[1] Kruskal Wallis test, BP: Blood Pressure, COVID-19: Coronavirus Disease 2019, IQR: Inter Quantile Range (25% and 75% values are presented.)

Laboratory results of the blood samples taken from the patients upon admission to the emergency department are presented in Table 3.

Table 3. Evaluation of laboratory results by case groups

	COVID-19 (Sepsis group) (n=62, %50.4)	COVID-19 (non-sepsis group) (n=61, %49.6)	*p*-value
WBC Median (IQR)	8.2 (6.8-12.9)	6.4 (4.4-8.2)	<0.001[1]
NLR Median (IQR)	6.6 (4.0-11.5)	3.1 (2.1-5.6)	<0.001[1]
Urea Median (IQR)	48.0 (32.7-84.5)	34.5 (23.0-41.7)	<0.001[1]
Creatinine Median (IQR)	1.0 (0.7-1.7)	0.9 (0.7-1.6)	0.025[1]
CRP Median (IQR)	127.2 (66.5-181.2)	39.2 (12.2-83.0)	<0.001[1]
Sedimantation Median (IQR)	47.5 (15.2-66.7)	36 (13-64)	0.340[1]
Procalcitonin Median (IQR)	0.24 (0.09-0.67)	0.05 (0.03-0.11)	<0.001[1]
D-dimer Median (IQR)	1530 (715-3540)	530 (370-890)	<0.001[1]
Troponine Median (IQR)	25.1 (12.6-52.9)	10.7 (7.2-21.8)	<0.001[1]
CK-MB Median (IQR)	2.5 (1.6-4.7)	1.1 (0.9-1.8)	<0.001[1]
Lactate Median (IQR)	2.3 (1.4-3.2)	1.9 (1.4-2.5)	0.116[1]

[1]Mann Whitney U test, WBC: White Blood Cell, NLR: Neutrophil-Lymphocyte Ratio, CRP: C-reactive protein CK-MB: Creatine Kinase Myocardial Band, COVID-19: Coronavirus Disease 2019 IQR: Inter Quantile Range (25% and 75% values are presented.)

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Among the evaluated parameters, significant differences were found in WBC, NLR, urea, creatinine, CRP, procalcitonin, d-dimer, troponin-t, and CK-MB, except for sedimentation and lactate. These values were statistically significant in the sepsis group (creatinine p=0.025, p<0.001 for other parameters) (Mann Whitney U test).

Mortality Assessment in Patient Groups

Of the 246 patients included in our study, 123 were diagnosed with Covid-19 pneumonia. Among the patients diagnosed with pneumonia, 62 (50.4%) were diagnosed with sepsis and were included in the sepsis group, while the remaining 61 (49.6%) patients with pneumonia but without sepsis were included in the non-sepsis group. In the sepsis group, 5 patients (8%) died within the first 24 hours, and 16 patients (25.8%) died between 24 hours and 14 days. No patient in the non-sepsis group died within the first 24 hours, while 4 patients (6.5%) died between 24 hours and 14 days. The overall survival rate of Covid-19 pneumonia patients during the two-week follow-up was found to be 79.7% (Figure 3).

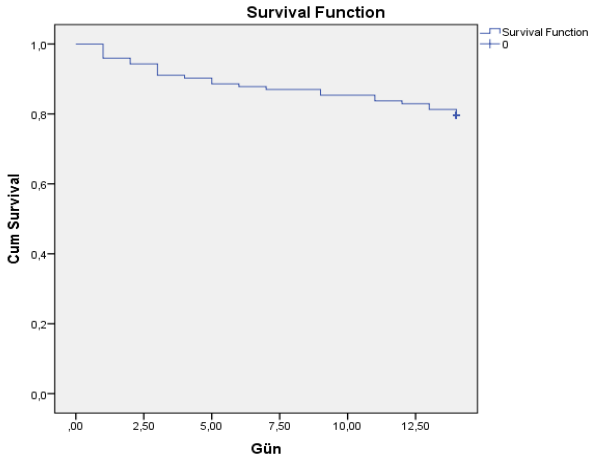

Figure 3. Mortality graph of patients with Covid-19 pneumonia at two-week follow-up

Multivariate analysis showed that the most important factors that increased mortality risk in our patient group were age, with each unit increase in age increasing mortality risk by 7% (p=0.019, OR=1.07, CI=1.01-1.14). Among laboratory values, it was found that CK-MB and especially lactate elevation were associated with mortality. Each unit increase in lactate (mmol/L) was found to increase mortality risk by 23%, while each unit increase in CK-MB (mcg/L) was found to increase mortality risk by 2% (p=0.022 for CK-MB, OR=1.02, CI=1.01-1.03) (p=0.007 for lactate, OR=1.23, CI=1.06-1.44). (Table 4)

Table 4. Assessment of factors affecting mortality using univariate and multivariate Cox regression analysis

	Univariate Analysis*		Multivariate Cox Regression Model	
	OR(95% GA)	*P*	Adjusted OR (95% GA)	*P*
Age, year	1.05 (1.01-1.08)	0.004	1.07 (1.01-1.14)	0.019
Diastolic BP, mmHg	0.95 (0.92-0.97)	0.001	0.98 (0.95-1.02)	0.579
Saturation, %	0.93 (0.91-0.95)	<0.001	0.96 (0.92-1.01)	0.191
WBC	1.06 (1.01-1.12)	0.039	0.87 (0.70-1.07)	0.210
Creatinine	1.28 (1.12-1.47)	<0.001	1.66 (0.92-2.97)	0.089
CRP	1.01 (1.01-1.01)	0,001	1.01 (0.99-1.01)	0.95
Procalcitonin	2.77 (1.81-4.22)	<0.001	1.27 (0.58-2.75)	0.545
CK-MB	1.01 (1.01-1.01)	0.001	1.02 (1.01-1.03)	0.022
Lactate	1.24 (1.13-1.37)	<0.001	1.23 (1.06-1.44)	0.007
PSP	1.01 (0.99-1.01)	0.288	-	-

*Variables with p <0.05 determined by univariate cox regression analysis were included in multivariate cox regression analysis. The most relevant of the related variables was included in the model. WBC: White Blood Cell, CRP: C-reactive protein, CK-MB: Creatine Kinase Myocardial Band, BP: Blood Presure

It was observed that PSP levels were higher in non-survivors. The median value of PSP was 161.3 ng/L (IQR=139.3-190.1) in deceased patients (n=25) while it was 145.6 ng/L (IQR=129.5-169.8) in surviving patients. Therefore, ROC analysis was conducted to test the possible predictive value of PSP levels for mortality, and it was found to be statistically significant (p=0.045-AUC=0.630) (Figure 4, Table 5).

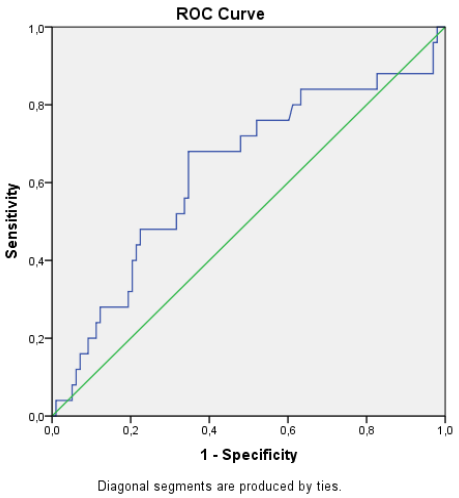

Figure 4. ROC curve of PSP on mortality

Table 5. ROC Analyse of PSP on mortality by sepsis (+) and sepsis (-)

Area	p value	95% Confidence Interval	
0.630	0.045	0.502	0.759

The value of 155.1 for PSP was the point where the sum of sensitivity and specificity percentages was highest in terms of mortality prediction. For this value, sensitivity was 68.0% and specificity was 65.3%.

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DISCUSSION

In a case series conducted by Fukada et al., PSP and CRP levels were found to be higher upon admission in patients with moderate and severe Covid-19 compared to those with mild disease (6). In a study of 143 Covid-19 patients evaluated in the emergency department, PSP was found to be higher in patients who died compared to those who survived. In this study, PSP was a highly specific predictor of 30-day mortality in Covid-19 patients (92%) (7). Zaninotto et al. showed that PSP is a more accurate prognostic index than commonly used parameters such as CRP or procalcitonin in Covid-19 patients (8). A systematic review evaluating a total of 167 Covid-19-positive cases found a statistically significant relationship between PSP and Covid-19 severity based on different PSP threshold values (9). In many studies, PSP has been identified as a sufficiently specific biomarker to identify patients requiring more aggressive treatment from the early stages of the disease. Our study also suggests that PSP is significant in predicting mortality in Covid-19 pneumonia but meaningless for diagnosing sepsis.

The most important factor identified in our study that increases mortality risk is age, with each unit increase in age resulting in a 7% increase in mortality risk. Age has also been found to be associated with mortality in Covid-19 disease in previous studies (10-13). In a study evaluating 344 intensive care patients conducted by Yang Wang et al., gender was found to be unrelated to mortality, while age was found to be associated with mortality (14). Similarly, in our study, age was found to be associated with mortality, while gender was unrelated to mortality.

In our study, statistically significant differences were found in certain blood parameters evaluated, except for sedimentation and lactate, including WBC, NLO, urea, creatinine, CRP, procalcitonin, d-dimer, troponin-t, and CK-MB in the sepsis group. In addition, a significant relationship was found between CK-MB and lactate elevation and mortality. In a meta-analysis of 21 studies including 3377 Covid-19 -positive patients, it was found that severe Covid-19 significantly increased WBC compared to mild Covid-19 and decreased lymphocyte and platelet counts (15). In another study, d-dimer elevation was identified as the strongest independent predictor of mortality (16). In our study, unlike this study result, no statistically significant relationship was found between d-dimer and mortality.

In a systematic review that included 207 studies conducted by Izcovich et al., the same laboratory parameters studied in our work, including sedimentation, lactate, WBC, NLR, urea, creatinine, CRP, procalcitonin, d-dimer, troponin-t, and CK-MB values, were found to be statistically significant in terms of prognosis and mortality (17). In our study, however, only CK-MB and lactate levels were found to be associated with mortality, and no significant relationship was found between sedimentation and lactate values and prognosis. In our study, elevated levels of CK-MB and, especially lactate, were found to be associated with mortality, with each unit (mmol/L) increase in lactate increasing mortality risk by 23% and each unit (mcg/L) increase in CK-MB increasing mortality risk by 2%.

Many studies in the literature have reported a significant statistical relationship between PSP and sepsis or between PSP and Covid-19 (6,9,18). However, in our study, even though we separated Covid-19 pneumonia cases into sepsis and non-sepsis groups, no significant statistical relationship was found. This suggests that PSP values may not be useful for distinguishing sepsis in Covid-19 pneumonia patients, but may be useful for predicting mortality.

LIMITATIONS

Our study was conducted at a single center during the second year of the pandemic when mutations were emerging. The results obtained by our team need to be confirmed with a different population.

CONCLUSION

In our study, no significant relationship was found between groups for PSP. Therefore, we believe that routine PSP testing is not necessary for patients with suspected Covid-19. However, when comparing the PSP values of deceased

Maltepe tıp derg. Cilt: 15 Sayı: 3/2023
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