ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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Beyin Omurilik Sıvısında Prokalsitonin, C-Reaktif Protein ve Laktat Biyobelirteçlerinin Santral Sinir Sistemi Enfeksiyonu Tanısındaki Karşılaştırılmalı Yeri

Comparative Diagnostic Value of Procalcitonin, C-Reactive Protein, and Lactate Measurements in Cerebrospinal Fluid for the Diagnosis of Central Nervous System Infections

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ÖZ

Giriş: Bu çalışmada menenjit tanısında ve bakteriyel/viral menenjit ayırıcı tanısında beyin omurilik sıvısı (BOS) prokalsitonini, C-reaktif proteini (CRP) ve laktat seviyesinin tanısal değerinin araştırılması ve karşılaştırılması amaçlanmıştır.

Yöntem: Sağlık Bilimleri Üniversitesi İzmir Tepecik Eğitim ve Araştırma Hastanesinde 2015 Ocak – 2018 Eylül tarihleri arasında BOS örneği alınan hastalar dahil edilmiştir. Çalışma prospektif planlanmış olup hastalar önce menenjit ve kontrol grubu olarak iki gruba, menenjit hastaları da viral ve bakteriyel olarak iki alt gruba ayrıldı. BOS biyokimya değerleri, hücre sayımı, gram boyaması, viral moleküler panel ve bakteriyel kültürü, BOS CRP ve BOS prokalsitonin bakıldı ve p değeri <0,05 ise istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya 47'si hasta 49'u kontrol grubu olmak üzere toplam 96 kişi dahil edildi. Hasta grubunun 12'si (25.6%) viral menenjit, 35'i (74.4%) bakteriyel menenjitti. BOS prokalsitonin değerinin yüksekliğinin hem kontrol ile menenjit grubu arasında hem de menenjit grubunun alt grup ayırıcı tanısında anlamlı farklılıkta olduğu, yüksek duyarlılık ve özgüllükte eşik değeri saptadık. Ayrıca BOS CRP ve laktat değerleri için menenjit alt grup ayırıcı tanısında kesim değeri oluşturulabileceği fakat prokalsitonin kadar yüksek duyarlılık ve özgüllükte olmadığı sonucuna ulaşıldı.

Sonuç: Beyin omurilik sıvısındaki prokalsitonin ve CRP'nin özellikle bakteriyel menenjit tanısında yararlı bir belirteç olabileceğini saptandı, ancak ayırıcı tanıda biyobelirteçlerin diğer parametrelerle birlikte kullanılması gerekmektedir.

Anahtar Kelimeler: beyin omurilik sıvısı, biyobelirteç, c-reaktif protein, laktat, prokalsitonin, menenjit

ABSTRACT

Objective: To evaluate the diagnostic value of procalcitonin, C-reactive protein (CRP), and lactate measurements in cerebrospinal fluid (CSF) for the identification of meningitis and the differential diagnosis of bacterial and viral meningitis.

Method: Patients who underwent CSF sampling between January 2015 and September 2018 at our hospital in Izmir were included in this study. This prospective study included two patient groups: those with meningitis and controls, and patients with meningitis were further subdivided into viral and bacteriological etiology subgroups. Biochemistry, cell count, Gram staining, molecular viral panel, bacterial cultures, CRP, and procalcitonin were examined in the CSF. P-value of <0.05 was considered statistically significant.

Results: In this study, 96 patients (47 cases and 49 controls) were included. Meningitis of viral and bacterial etiology was diagnosed in 12 (25.6%) and 35 (74.4%) patients, respectively. High CSF procalcitonin levels were highly discriminatory between controls and all meningitis patients, as well as between meningitis subgroups, with high sensitivity and specificity for the cut-off values. CSF CRP and lactate were also able to provide cut-off values for the differential diagnosis of meningitis subgroups. However, their sensitivity and specificity were not as high as those of procalcitonin.

Conclusion: Procalcitonin and CRP measured in CSF may represent valuable biomarkers, particularly for diagnosing bacterial meningitis, although these biomarkers should be used in conjunction with other parameters for differential diagnosis.

Keywords: cerebrospinal fluid, biomarkers, C-reactive protein, lactate, procalcitonin, meningitis

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INTRODUCTION

Infections of the central nervous system (CNS) are a major global health problem. Among these, meningitis is one of the most common diseases with the highest mortality rates. Delays in diagnosis and treatment are associated with increased morbidity and mortality (1).

A recent increase in CNS infections has been noted, most likely due to factors, such as increased life expectancy, organ transplantation, number of immunocompromised patients, surgical procedures, and diagnostic advances. Diagnosis of meningitis is based on examination of the cerebrospinal fluid (CSF). Gram staining and culture of CSF have been shown to have variable specificity and sensitivity in diagnosing meningitis (2). Although measurements of CSF procalcitonin (PCT), C-reactive protein (CRP), and lactate levels have been proposed to aid in the differential diagnosis of bacterial meningitis (BM) and viral meningitis (VM), a consensus has not been reached due to a lack of studies in the literature (3).

This study aims to evaluate and compare the diagnostic value of CSF PCT, CRP and lactate levels in diagnosing meningitis and the differential diagnosis of BM and VM.

MATERIALS AND METHODS

This was a prospective, cross-sectional, controlled, descriptive, single-center study. Patients who underwent CSF sampling under aseptic conditions between January 1, 2015, and September 30, 2018, were identified. Based on the collected patient data (clinical observation results, physical examination, and laboratory values), two patient groups were defined as controls and meningitis. The latter group was further subdivided into viral and bacterial cases of meningitis. Exclusion criteria were age below 18 years, pregnancy, malignancy, immunosuppression, and acute cerebrovascular events. Patients were excluded from this study if there was suspicion of contamination during lumbar puncture, traumatic lumbar puncture, lack of appropriate storage conditions for the specimens, or lack of timely examination of the specimens. Written informed consent was obtained from all patients.

The study protocol was approved by the Ethics Committee of Health Sciences University Tepecik Research and Training Hospital (date: December 11, 2018; meeting number: 14; decision number: 12).

Control group: With patients' consent, they were selected from patients who underwent routine preoperative lumbar puncture under spinal anesthesia with no clinical and laboratory findings of CNS infection.

Patients with bacterial meningitis: These patients had clinical manifestations of meningitis (fever, headache, nuchal rigidity, confusion) with negative viral panel test results and

** Positive CSF bacterial cultures or

** In patients with negative cultures, identification of microorganisms on Gram stain and CSF biochemistry consistent with bacterial meningitis (CSF WBC > 5/mm3 (predominantly neutrophils), or CSF protein level > 45 mg/dl, or CSF/serum glucose ratio < 0.6), or

** In case of culture negativity and absence of microorganisms on Gram stain, CSF biochemistry results highly suggestive of meningitis (CSF WBC > 1000/mm3 (at least 75% neutrophils) or CSF protein > 100 mg/dl or CSF/serum glucose ratio < 0.4 or CSF glucose < 40 mg/dl) and dramatic clinical and laboratory response to antibiotherapy within 24 hours (1-8).

Patients with viral meningitis: In addition to the clinical manifestations of meningitis, negative culture and Gram stain along with the following:

** Positive CSF viral DNA/RNA, PCR, or antigen/antibody positivity (2, 8-10).

Routine biochemical parameters (lactate, protein, glucose), cell counts and percentages (leukocytes, neutrophils, lymphocytes), Gram staining results, viral panel (HSV type I-I, enterovirus, adenovirus, HHV 6-7, parechovirus, CMV, VZV), and bacterial cultures were performed at the time of puncture. CRP and PCT in CSF were assayed within three hours or stored at -80°C if this was not possible. Samples were thawed at 37°C before procedures.

C-reactive protein was measured by nephelometric quantitative ELISA (Vitros CRP® Slides) with a detection threshold of 0.1 mg/dl, whereas PCT was measured by quantitative electrochemical luminescence immunoassay (Elecys Brahms procalcitonin®) with a detection threshold of 0.01 ng/ml.

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C-reactive protein was measured nephelometrically using quantitative ELISA (Vitros CRP® Slides) with a detection threshold of 0.1 mg/dl, whereas PCT was measured using quantitative electrochemical luminescence immunoassay (Elecys Brahms procalcitonin®) with a detection threshold of 0.01 ng/ml.

Statistical analysis: Data were entered and analyzed into the database created using SPSS® 18.0 statistical software pack (IBM Corporation, Armonk, New York, United States) and MedCalc.® v. 12.5 (MedCalc Software, Ostend, Belgium) software. Categorical variables were presented as frequency and percentage. The mean, standard deviation, median, minimum, and maximum values were presented for continuous variables. The normal distribution of the variables was also tested using the Kolmogorov–Smirnov method.Graphic exploration, normality tests, and sample sizes showed that not all variables met the conditions for normal distributions. Thus, for these variables, non-parametric methods were preferred for comparison.

For pairwise comparisons between independent groups, the Mann–Whitney test was used, whereas the Kruskal–Wallis test was used for multiple comparisons. The association between variables was tested using correlation methods. Cross-tables were created for categorical variables, and comparisons were performed using the chi-square test. Biomarkers with significant differences between meningitis cases and controls were explored using the receiver operating curves (ROC) method, and cut-off values were calculated using the Youden Index. The test statistics (specificity and sensitivity) were estimated using these cut-off values. For all statistical comparisons, the type I error margin was set at a level of 0.05, and a two-way test was used. A p-value of 0.05 was considered to signify the significance of the difference between the groups.

RESULTS

In this study, 96 subjects were included, of whom 49 (%51) were controls, and 47 (49%) were patients. Males comprised 61% and 51% of the control subjects and patients, respectively. A diagnosis of viral meningitis was reached in 12 and bacterial meningitis in 35 patients. The median age was 44.9 years (21-67) in controls, 40 years (19-73) in bacterial meningitis patients, and 37 (25-65) in viral meningitis patients. Age did not significantly differ between meningitis patients and controls or between subgroups of meningitis (BM vs. VM) patients. Pairwise and triple subgroup comparisons also showed no significant difference in gender distribution between the groups. Table 1 shows the comorbid conditions, clinical findings, complete blood count, and CSF biomarkers in the controls, BM, and VM groups.

Because statistically significant differences between controls and meningitis patients were found regarding blood leukocyte count, neutrophil count/percentage, CRP and PCT (p<0,001), subgroup comparisons were performed. A comparison between patients with VM and controls regarding blood leukocyte CRP and PCT showed only significant elevation of CRP in patients with VM (pp<0,027). Comparison of BM and patients with VM in terms of these parameters showed significantly higher CRP and PCT in patients with BM (p<0,001).

It was possible to identify an organism with Gram staining in 20 of the 35 patients in the BM group, of whom 12 (60%) had Gram-positive diplococci, six (30%) had Gram-negative bacilli, and two (10%) had Gram-negative diplococci. In 12 (60%) of the patients with bacteria identified by Gram staining, microorganisms grew in the culture, including S. pneumoniae in eight (66.6%), H. influenzae in two (16.6%), E. coli in one (8.3%), and N. meningitidis in one (8.3%). In the VM group, herpes simplex type I virus was found in 11 of the 12 patients (91.6%), whereas one (8.4%) had enterovirus.

There were significant differences between all study groups regarding PCT, protein, lactate, and glucose ratio (CSF/serum) in CSF ($p < 0.001$). In addition, the BM and VM groups showed significant differences in CSF leukocyte, lymphocyte percentage, neutrophil number/percentage, and CRP levels ($p < 0.001$).

In the ROC analysis of CSF lactate levels, the area under the curve (AUC) was 0.93 (95% CI: 0.87-1.0; $p < 0.0001$), with the best cut-off value of > 1.1 mmol/L (95% CI: 0.89-1.1) (Sensitivity: 91.4%; Specificity: 97.9%) (Figure 1).

For discriminating meningitis patients from controls, a cut-off value of > 0.07 ng/ml was determined for CSF procalcitonin levels, which was one of the important target biomarkers in our study (AUC: 0.95; 95% CI: 0.9-1.0; $p < 0.0001$).

For this CSF PCT cut-off value, irrespective of bacterial or viral etiology, the sensitivity was 89.3%, and the specificity was 93.8% (Figure 1).

The cut-off value for CSF lactate levels in patients with BM was 1.1 mmol/L, similar to the case for differentiating controls and meningitis patients. However, while the sensitivity of this value for differentiating BM was higher, the specificity was lower (sensitivity 100%, specificity 97.6%). For CSF PCT in patients with bacterial meningitis, the cut-off value increased from 0.07 ng/ml to 0.1 ng/ml. Therefore, if this value is used for diagnostic purposes, specificity and sensitivity increase (Figure 1).

Similarly, a cut-off value of > 1.1 mmol/L was found for CSF lactate, with similar specificity to other comparisons for specificity (97.6%). However, the confidence interval and the area under the curve decreased, reducing the sensitivity up to 66.6% for this figure (Table 2).

A cut-off value of > 0.05 ng/ml was found in the ROC analysis of CSF PCT for differentiation between patients with VM and controls. However, sensitivity (83.3%) and specificity (83.6%) were significant (p=0.0004) (Figure 1).

The AUC for CSF CRP was 0.91, with a cut-off value of > 0.87 mg/L for discriminating patients with BM from patients with VM. The sensitivity of this value was 82.8%. On the other hand, for lactate levels, a higher value was required in the differentiation within meningitis patients (> 1.77 mmol/L) (Figure 2).

The cut-off value of CSF PCT to differentiate between bacterial and viral meningitis was > 0.18 ng/ml (Figure 3).

With regard to CSF PCT, the highest correlation coefficient was observed with serum PCT (r:0,816, $p < 0.001$). In addition, among other CSF parameters, lactate showed a strong and significant correlation with PCT. Although it was not as significant as that of CSF lactate, the CSF neutrophil percentage also had a moderate and positive correlation, as expected. The parameters were significantly correlated with CSF PCT levels (Table 3).

Similar to PCT, the highest correlation coefficient with CSF CRP was found with serum CRP levels. Furthermore, in contrast with CSF PCT, changes in CSF CRP levels were moderately correlated with changes in CSF protein levels (Table 3).

The CSF glucose ratio was moderately and negatively correlated with each biomarker. Similarly, CSF CRP and PCT levels showed significant correlations within the meningitis group. No significant correlations were identified for other biomarkers examined in this study.

Table 1. Patients' Demographic, Clinical Characteristics and Biomarker Levels				
Parameters	**Control group (49)**	**Bacterial meningitis (35)**	**Viral meningitis (12)**	**P value**
Demographic data				
Male n (%)	30 (61.2)	16 (45.7)	8 (66.7)	0.272
Age[1]	45 (21-67)	40 (19-73)	37 (25-65)	0.163
DM n (%)	8 (16.3)	6 (17.1)	3 (25)	0.775
HT n (%)	9 (18.4)	6 (17.1)	3 (25)	0.83
Clinic				
Body temperature[2] (°C)	36.87 (±0.53)	38.6 (±0.73)	37.9 (±0.56)	<0.001[3]
Headache, n (%)	0 (0)	24 (68.6)	9 (75)	<0.001[3]
Confusion, n (%)	0 (0)	18 (51.4)	5 (41.7)	<0.001[3]
Neck stiffness, n (%)	0 (0)	25 (71.4)	7 (58.3)	<0.001[3]
Blood counts				
Leukocyte count[1] (/mm^3)	7600 (4400-14500)	11924 (1834-20833)	10734 (4141-21024)	<0.001[3]
Neutrophil count[1] (/mm^3)	4200 (2100-7100)	11000 (1700-19100)	7050 (2800-15600)	<0.001[3]
Neutrophil %[1]	54.62 (33.8-84)	88.9 (75.5-96.7)	68.1 (50-82.1)	<0.001[3]
Platelets[1] (*10^3/mm^3)	268 (155-492)	230 (97-248)	242 (168-327)	0.193
CRP[1] (mg/L)	0.8 (0.01-4.1)	9.59 (0.19-24.68)	2.02 (0.23-4.61)	<0.001[3]
Procalcitonin[1] (ng/ml)	0.04 (0.01-0.47)	11.13 (1.54-34.65)	0.07 (0.02-0.31)	<0.001[3]
CSF counts				
Leukocyte count[1] (/mm3)	0	3354 (358-6057)	253 (27-479)	<0.001[3]
Neutrophil count[1] (/mm3)	0	2775 (332-5356)	72 (4-195)	<0.001[3]
Neutrophil %[1]	0	82 (±7.85)	22.2 (±9.96)	<0.001[3]
Lymphocyte count[1] (/mm3)	0	418 (16-1933)	157 (21-366)	<0.001[3]
Lymphocyte %[1]	0	14.1 (1.9-34.1)	72.7 (53.9-89)	<0.001[3]
Lactate[1] (mmol/L)	0.75 (0.07-1.35)	3.73 (1.12-6.97)	1.5 (0.07-2.67)	<0.001[3]
CRP[1] (mg/L)	0	4.32 (0-10.88)	0.07 (0-0.87)	<0.001[3]
Procalcitonin[1] (ng/ml)	0.02 (0.01-0.1)	0.74 (0.08-1.72)	0.08 (0.01-0.18)	<0.001[3]
Protein[1] (mg/dl)	31 (20-43)	261.1 (60.8-380.6)	69.2 (20.1-115.3)	<0.001[3]
CSF/Serum Glucose[2]	0.99 (±0.35)	0.3 (±0.12)	0.77 (±0.1)	<0.001[3]

DM: Diabetes Mellitus. HT: Hypertension. CRP: C-reactive protein. CSF: Cerebrospinal Fluid

[1] Median value. It is given with the lowest and highest value.

[2] Mean values are given with standard deviation value.

[3] p <0.05 value was considered significant and this suggests that there was a significant difference in at least two of the 3 groups. The significant values were clarified by performing a paired group comparison.

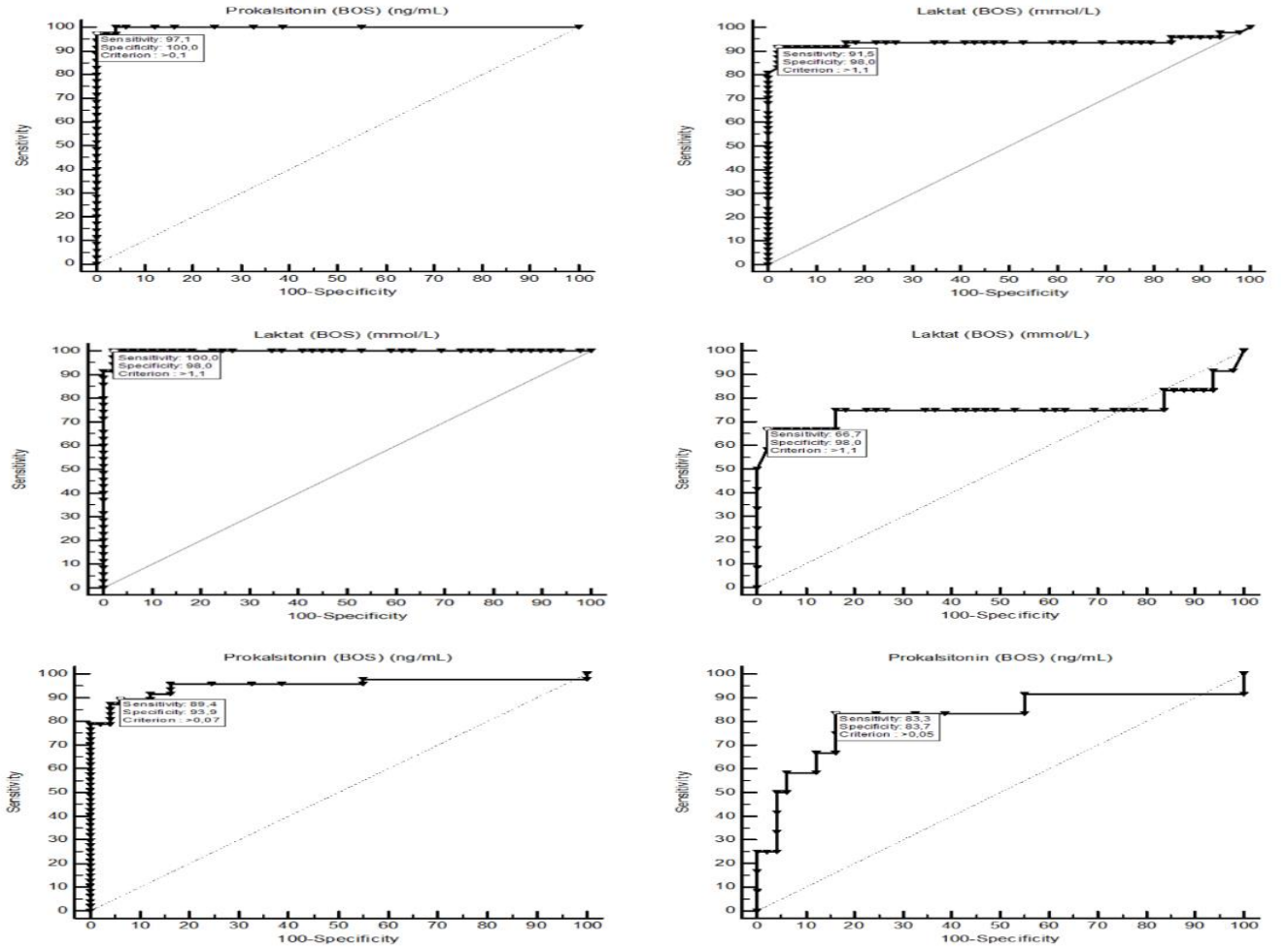

Figure 1. Evaluation of cut-off values of lactate and procalcitonin in cerebrospinal fluid with Youden index (A: Control vs Meningitis B: Control vs Bacterial Meningitis C: Control vs Viral Meningitis).

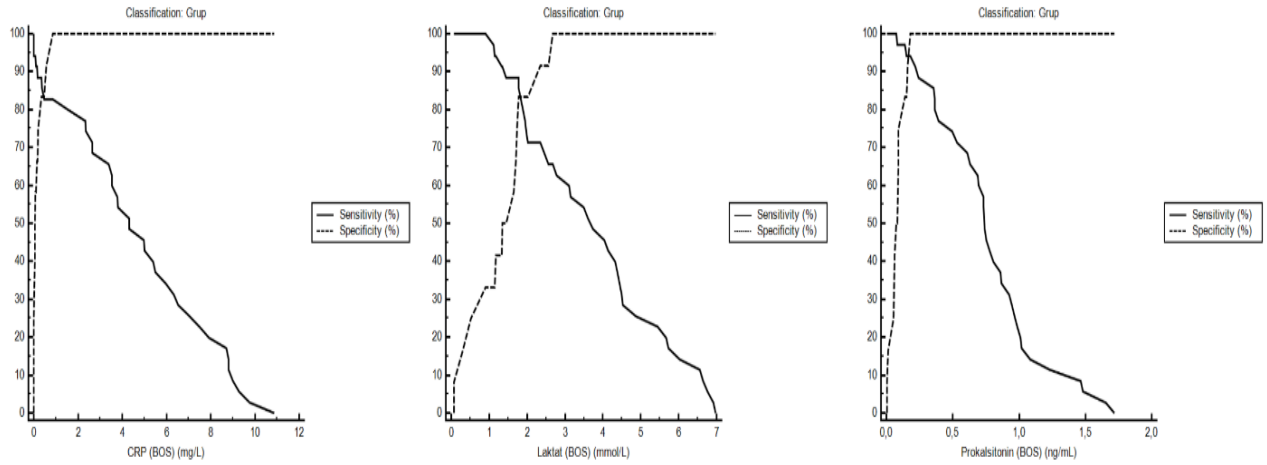

Figure 2. Evaluation of biomarkers in cerebrospinal fluid by ROC analysis (Bacterial / Viral Meningitis comparison).

Table 2. Cut-Off Values of CSF Biomarkers in Diagnosis (Bacterial Meningitis, Viral Meningitis and Control Group Comparisons)

CONTROL/BM CSF Biomarkers	ROC analysis data					
	AUC	%95 CI	**Cutoff value**	Sensitivity (%)	Specificity (%)	P value
Lactate (mmol/L)	0.99	0.99-1	**>1.1**	100	97.6	<0.0001
Procalcitonin (ng/ml)	0.99	0.99-1	**>0.1**	97	100	<0.0001
CONTROL/VM CSF Biomarkers						
Lactate (mmol/L)	**0.75**	**0.52-0.98**	**>1.1**	**66.6**	97.9	0.0333
Procalcitonin (ng/ml)	0.81	0.64-0.99	**>0.05**	83.3	83.6	0.0004
BM/VM CSF Biomarkers						
Lactate (mmol/L)	0.89	0.80-0.98	**>1.77**	**88.5**	**83.3**	<0.0001
Procalcitonin (ng/ml)	0.98	0.94-1	**>0.18**	**94.2**	**100**	<0.0001
CRP (mg/L)	0.91	0.84-0.99	**>0.87**	**82.8**	**100**	<0.0001

CRP: C-Reactive Protein. BM: Bacterial Meningitis, VM: Viral Meningitis ,CSF: Cerebrospinal Fluid, AUC: Area Under the ROC Curve (Area Under the ROC Curve), CI: Confidence Interval, p <0.05 is significant.

Table 3. Correlations Value of CSF Procalcitonin and CSF CRP

Correlations		**Total**	
		r	**p**
CSF CRP	CSF lactate	.288	0.05
CSF CRP	**Serum CRP**	.754	0.000
CSF CRP	CSF procalcitonin	.566	.566
CSF Procalcitonin	Serum neutrophil	.499	0.001
CSF Procalcitonin	**Ser. Procalcitonin**	.816	0.000
CSF Procalcitonin	CSF lactate	.580	0.000

Spearman's rho Test r: Correlation Coefficient , CRP: c-reactive protein, *CSF:* Cerebrospinal fluid
***p<0.01 *p<0.05*

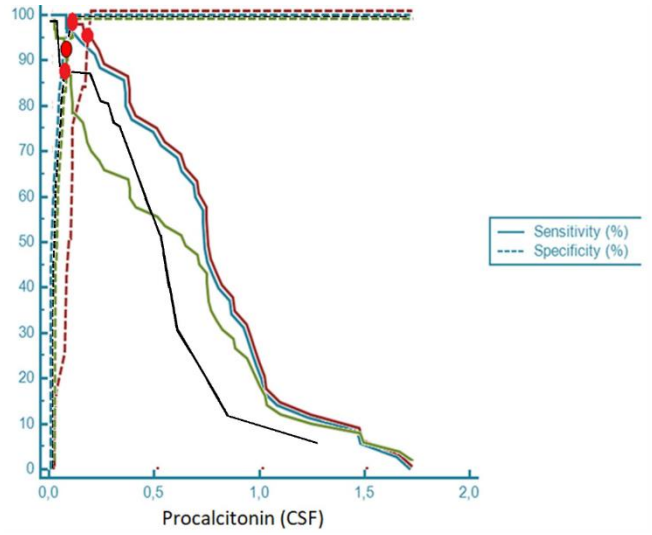

Figure 3. Cut-off values by Youden index for procalcitonin in cerebrospinal fluid in Viral meningitis / Control, Meningitis / Control, Bacterial meningitis / Control, Bacterial meningitis / Viral meningitis comparisons.

DISCUSSION

As was reported in many previous studies in the literature, demographic characteristics, such as age, gender, or comorbid conditions, did not appear to have a significant predictive role in the occurrence of meningitis (10-12).

Although the BM and VM subgroups did not differ in age or comorbid conditions, an increased risk of bacterial meningitis in association with increased age and diabetes was previously described (13-15). The divergence in our results may be because the number of patients with comorbid conditions in our study was low, limiting the statistical power.

In a study by Morales-Casado et al. involving 154 patients, comparisons between patients with bacterial and viral meningitis showed significant differences in serum leukocyte count, CRP, and PCT (13). In our study, although CRP and PCT levels were elevated in the overall group of meningitis patients, leukocyte counts were comparable across the BM and VM groups. This finding is consistent with a few previous studies (15, 16). Although we failed to detect a significant difference between patients with BM and VM regarding leukocyte count in this study, Morales-Cascado et al. observed contrasting findings, probably because most VM cases were due to Enteroviruses in that study, in contrast with herpes viruses in our study.

Elevated CSF lactate concentrations may assist in the differential diagnosis of bacterial meningitis in patients previously untreated with antimicrobial agents. For example, in Li et al.'s study comparing 178 patients with or without bacterial meningitis following cranial neurosurgery (PNBM), the median (min, max) CSF lactate levels in those with PNBM were 5.3 mmol/L (2.2-10.6) vs. 2.3 mmol/L (1.2-4.4) in those without PNBM ($p < 0.001$), with a cut-off of 3.45 mmol/L for CSF lactate levels in the ROC analysis (AUC=0.943, sensitivity 90.0%, and specificity 84.4%; $p < 0.001$).

This study found significantly higher CSF lactate levels in PNBM than in patients with non-PNBM, and the authors concluded that CSF lactate levels have a significant diagnostic value for PNBM (10). On the other hand, despite its high sensitivity in diagnosing bacterial meningitis and the positive predictive value of CSF lactate levels, this parameter is generally non-specific and provides little additional diagnostic information. Furthermore, CSF lactate levels may be elevated in association with other conditions, such as cerebral hypoxia/ischemia, anaerobic glycolysis, vascular pathologies, and metabolism of CSF leukocytes. In a prospective 2016 study by Morales-Casado et al., the role of specific clinical and epidemiologic variables as determinants of bacterial meningitis was explored in 154 patients presenting to the emergency unit with signs and symptoms of acute meningitis. A CSF lactate level of > 1.8 mmol/L had 99% sensitivity and 98% specificity for the differential diagnosis of bacterial meningitis (AUC: 0.992; 0.979-1; $p < 0.001$) (13). In line with other studies, our patients with meningitis had significantly higher lactate levels than the controls. Furthermore, patients with BM had a significant elevation in their lactate level compared with patients with VM. Thus, these findings suggest that measurement of CSF lactate levels in patients with confusion may be useful in establishing a more rapid diagnosis of BM and in the differential diagnosis of VM and BM in subclinical cases.

The original study examining CRP levels in CSF was conducted by Shimetani, who reported considerably higher levels of CSF CRP in bacterial meningitis compared with only 10% of those with viral meningitis, although no quantitative data were presented. Subsequent studies have provided more details on this issue (17). In a meta-analysis, serum and CSF CRP concentrations were assessed in terms of their utility in discriminating bacterial meningitis from viral meningitis, with a sensitivity of 69%–99% and a specificity of 28%–99%.

In a previous meta-analysis, the value of serum and CSF concentrations of CRP in discriminating between bacterial and viral meningitis was investigated. Accordingly, CRP serum concentrations had a sensitivity of 69%–99% and a specificity of 28%–99%. The corresponding figures for CRP CSF concentrations were 18%–100% and 75%–100%, respectively. In contrast with our findings, others found no significant differences in CSF CRP levels between patients with bacterial or viral meningitis (13). Furthermore, elevated CSF CRP levels have been reported in neurodegenerative, inflammatory, or malignant conditions of the central nervous system (18, 19). We believe that excluding patients with malignancy or neurodegenerative conditions may represent the superiority of our study about assessments of the role of CRP in differential diagnosis.

Although serum PCT measurements are routinely performed, the role of CSF PCT in central nervous system infections remains unclear. Several studies on CSF PCT levels have provided controversial results. Many studies have proposed that quantitative PCT measurements may represent a diagnostic marker for BM (21, 24, 25). Bacterial endotoxins have been a significant inducer of PCT. Because viruses do not produce endotoxins, the elevation in PCT in association with viral infections is modest or absent. In our study, serum and CSF PCT concentrations were quite concordant. Patients with bacterial meningitis had significantly higher CSF PCT than those with viral meningitis or controls, suggesting that the source of PCT

in the CSF may be related to the injury in the blood– brain barrier. In addition, the linear relationship between CSF PCT and protein content and leukocytes in CSF supports this notion (26-28).

Shimetani et al. found no difference between patients with meningitis and those with non-inflammatory central nervous system disorders in terms of CSF PCT levels (17), whereas Gendrel et al. reported that CSF PCT levels were undetectable in children with BM or VM (26).

In Konstantinidis et al.'s study, CSF PCT levels were significantly higher in patients with BM than in patients with VM or controls. In addition, according to their results, CSF PCT may be useful in differentiating infections of different origins, i.e., bacterial or viral (29). Jereb et al. provided confirmatory findings for the association between CSF PCT and bacterial infections. In contrast, in patients with Hantavirus infections, elevated serum PCT levels were similar to those in patients with severe bacterial infections (24). Again, Kepa et al. measured CSF PCT in patients with intracranial infections and concluded that CSF PCT had lower sensitivity than serum PCT in the differential diagnosis of meningitis (30).

Our study had certain limitations. First, its sample size was relatively small, limiting its statistical power; however, it could provide meaningful results. Second, the presence of meningitis could not be confirmed in all patients with positive CSF cultures, which represents the gold standard diagnostic method. This may have caused a bias. To reduce the effect of this potential methodological drawback, we used the international CSF diagnostic criteria as individual positive markers. In choosing these parameters, we hoped to eliminate the inclusion of patients with aseptic meningitis to avoid diagnostic confusion, although it should be noted that a slight possibility remains.

In bacterial meningitis patients with positive or negative bacterial CSF cultures, we found no significant differences in CSF PCT levels. This is in support of our selection criteria based on CSF chemistry in the bacterial meningitis group.

These results suggest that PCT and CRP may be useful markers in diagnosing meningitis in general and bacterial meningitis in particular. Currently, no reference values exist for CSF CRP and PCT levels. Although our results indicate a good level of sensitivity and negative predictive value, the combined use of these parameters is required for better interpretation.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Health Sciences University Tepecik Research and Training Hospital (date: December 11, 2018; meeting number: 14; decision number: 12).

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