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Diagnostic effectiveness of blood and cerebrospinal fluid (CSF) parameters in patients diagnosed with meningitis in the emergency department

Mustafa Uğuz[1], Nur Zafer Kirdağ[2], Berfin Çirkin Doruk[1]

[1]Department of Infectious Disease, Mersin City Hospital, Mersin, Turkey

[2]Emergency Department, Mersin City Hospital, Mersin, Turkey

ABSTRACT

Objective: To evaluate laboratory findings that predict bacterial meningitis in emergency service and their diagnostic effectiveness.

Methods: This retrospective cohort study analyzed data from patients presenting with meningitis symptoms at a referral hospital in Mersin, Turkey, between January 2019 and January 2022. Clinical findings and laboratory results, including leukocyte count, C-reactive protein (CRP), and procalcitonin levels in blood, were examined. Logistic regression, *Chi* square test, and receiver operating characteristics (ROC) curve analyses assessed the predictive value of these parameters.

Results: A total of 199 participants were included in the study; 99 patients were diagnosed with meningitis after lumbar puncture and 100 served as controls. Patients with meningitis exhibited significantly higher leukocyte counts (median: 11 890×10^3/μL *vs.* 7 905×10^3/μL, $P<0.001$) and CRP levels (median: 6.00 mg/dL *vs.* 0.95 mg/dL, $P<0.001$) compared to controls. Procalcitonin levels were significantly elevated in meningitis patients (median: 0.21 ng/mL *vs.* 0.10 ng/mL, $P<0.001$). Logistic regression identified albumin (*OR*=0.16, 95% *CI*=0.06-0.40), and CRP (*OR*=1.18, 95% *CI*=1.08-1.28) as independent predictors of meningitis. ROC analysis for CRP demonstrated a sensitivity of 80.6% and specificity of 70.0% at a cut-off value of 2.23 mg/dL (AUC=0.792).

Conclusions: Elevated albumin levels and CRP contents in the blood were significant predictors of meningitis in emergency service. Early identification of predictive markers may aid in timely lumbar puncture and management of atypical cases.

KEYWORDS: Meningitis; Lumber puncture; Albumin; C-reactive protein; Predictive markers; Emergency department

Summary

Question: What laboratory findings can predict bacterial meningitis in emergency department patients?

Findings: This study identified albumin and C-reactive protein-levels as significant predictors meningitis. CRP demonstrated a sensitivity of 80.6% and specificity of 70.0% at a cut-off value of 2.23 mg/dL.

Meaning: These findings emphasize the utility of specific blood markers in aiding the early diagnosis of bacterial meningitis in emergency settings. Although no single marker is definitive, these results can guide clinicians in performing timely lumbar punctures, especially in atypical cases.

To whom correspondence may be addressed. E-mail: drmustafauguz@gmail.com

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1. Introduction

Acute bacterial meningitis is still a significant health problem in all groups despite the vaccination programs, prophylaxis practices and developing health policies implemented worldwide[1]. It still results in mortality rates ranging from 2% to 30% and morbidity rates of up to 20%[2]. In addition, most patients with meningitis have a history of recent antibiotic treatment for any reason, and the diagnosis of bacterial meningitis can be confirmed in a small number of these patients[3]. This situation leads to prolonged hospitalization, the need to use combination therapies, possible drug side effects, and prolonged or unnecessary intensive care unit stays. Therefore, it is vital to distinguish bacterial meningitis in emergency services and to initiate early treatment after confirming the diagnosis[3]. In the diagnostic phase, clinical findings do not have high sensitivity in distinguishing bacterial meningitis, especially in patient groups such as older age and immunosuppressed patients, and laboratory markers are used to support the diagnosis[4]. Although the culture method applied from the sample taken from the cerebrospinal fluid (CSF) is accepted as the gold standard in diagnosis, the time it takes to complete and the low culture positivity rates are handicaps for diagnosis[5]. CSF culture is considered the gold standard to the diagnosis of bacterial meningitis, yet is only positive in 70%-85% of persons with bacterial meningitis who have not received antimicrobial therapy prior to lumbar puncture[6].

Lumbar puncture is the most effective diagnostic method in the diagnosis of meningitis. However, there are also limitations to the application of the method. Lumbar puncture is contraindicated in cases such as increased intracranial pressure, the presence of brain abscess, intracranial mass and bleeding diathesis[7]. Therefore, new methods are needed that will support the data obtained as a result of the examination of the CSF sample at the time of admission to the emergency department or that can be used in diagnosis and follow-up in cases where lumbar puncture is not possible.

This study aimed to evaluate the laboratory data and lumbar puncture findings obtained during admission in cases with meningitis clinic who applied to the emergency department and examined the early predictive laboratory findings that can be used for the diagnosis of meningitis.

2. Patients and methods

2.1. Study setting

Our study is a retrospective-cross-sectional study. Patients who applied to the tertiary emergency department between January 2019 and January 2022 and were diagnosed with meningitis, and patients who applied to the tertiary emergency department on the same dates with complaints of high fever and who were not diagnosed with meningitis during follow-up and who did not require hospitalization (as the control group) were included in our study. The study population consists of 99 patients and 100 controls.

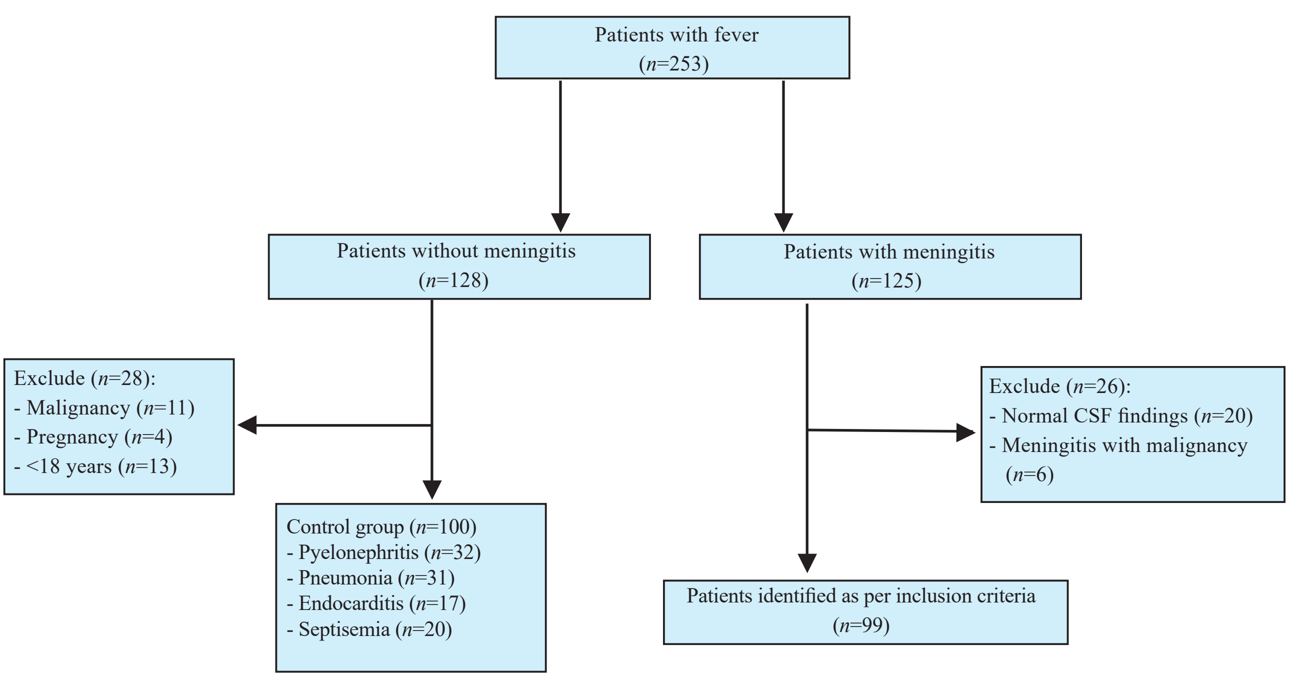

Figure 1. The study flowchart. CSF: Cerebrospinal fluid.

2.2. Ethical statement

For this study, ethics committee approval was obtained from Karabük University Ethics Committee with the decision dated 16.05.2023 (No.1389).

2.3. Inclusion and exclusion criteria

Patients who applied to the hospital with a meningitis clinic and were diagnosed with meningitis with CSF findings were included in the study. As the control group, patients who applied to the emergency department with complaints of high fever during the same date, who were not diagnosed with meningitis as a result of examination and tests and who did not require hospitalization were included. Patients to be included in the meningitis and control groups were formed from patients over the age of 18, not pregnant, not diagnosed with any malignancy and whose information could be fully accessed from the database. Patients whose records could not be fully accessed, those under the age of 18, those who were pregnant, those diagnosed with malignancy or those being followed up with a diagnosis of malignancy were excluded from the study. The study flowchart is shown in Figure 1.

2.4. Data Collection

The data of the patients included in the study were examined retrospectively. Demographic data and medical history were recorded. The values of blood lactate, sedimentation rate, procalcitonin, *D*-dimer, C-reactive protein (CRP), albumin, leukocytes, lymphocytes, and platelets were recorded.

2.5. Statistical analysis

While evaluating the findings obtained in the study, SPSS 22.0 software (IBM SPSS, Chicago, IL, USA) was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, median, standard deviation, interquartile range 25-75, frequency) were used to calculate the conformity of the parameters to the normal distribution, as well as Student's *t* test was used to compare the quantitative data in cases where it conformed to the normal distribution, and Mann Whitney *U* test was used in cases where it did not conform to the normal distribution. Correlation analyses were used to investigate the relationships of continuous data. *Chi* square test was used to compare qualitative data and significance was determined at $P<0.05$ during the tests.

3. Results

Of the patients included in the study, 97 (48.0%) were female. The median age of the patients was 45 (33-59). The most common complaint was fever, reported by 64 (64.7%) patients in the meningitis group and 68 (68.0%) in the control group. The diagnoses of the patients in the control group were as follows: pyelonephritis (n=32), pneumonia (n=31), endocarditis (n=17), and septicemia (n=20). The demographic data of the patients are summarized in Table 1. When the meningitis group and the control group were compared; no difference was found between the median ages of both groups (P=0.778). When the gender data were evaluated, the number of male patients in the meningitis group was found to be significantly higher (P<0.001). The median leukocyte

Table 1. Comparison of laboratory and demographic values of meningitis and control groups.

Variables	Meningitis group (n=99)	Control group (n=100)	χ^2/U	P
Age, years, median, Q1, Q3	48 (27, 64)	45 (33, 59)	3 263.5	0.778
Sex, n, %				
Male	66 (66.7%)	36 (36.0%)	15.60	<0.001
Female	33 (33.3%)	64 (64%)		
Fever	64 (64.7%)	68 (68.0%)	1.00	0.068
Loss of consciousness	17 (17.4%)	6 (6.0%)	5.03	0.025
Headache	45 (45.5%)	20 (20.0%)	10.60	0.001
Vomiting	38 (38.4%)	12 (12.0%)	15.20	<0.001
ALT, μ/L, median, Q1, Q3	30 (17, 46)	22 (16, 32)	2 410	0.002
Albumin, g/dL, median, Q1, Q3	3.80 (3.40, 4.00)	4.10 (3.89, 4.40)	1 681.5	<0.001
WBC, $\times10^3/\mu$L, median, Q1, Q3	11 890 (8 080, 19 800)	7 905 (6 090, 9 583)	1 669	<0.001
Neutrophils, $\times10^3/\mu$L, median, Q1, Q3	10 100 (5 650, 17 210)	5 065 (3 955, 6 322)	1 492.5	<0.001
Platelet, $\times10^3/\mu$L, median, Q1, Q3	222 (163, 296)	256 (200, 324)	2 565	<0.001
Lymphocyte, $\times10^3/\mu$L, median, Q1, Q3	1 070 (760, 1770)	1 840 (1 335, 2 475)	1 829	<0.001
Procalcitonin, ng/mL, median, Q1, Q3	0.21 (0.10, 1.20)	0.10 (0.02, 0.20)	2 107.5	<0.001
CRP, mg/dL, median, Q1, Q3	6.00 (2.80, 18.90)	0.95 (0.33, 2.80)	1 391.5	<0.001

ALT: Alanine amino transferase, WBC: White blood cell, CRP: C-reactive protein.

Table 2. Logistic regression analysis of meningitis diagnosis.

Variables	Wald	*OR*	95% *CI*	*P*
Albumin (g/dL) (per 1 g/dL ↑, normal: 3.5-5.0)	14.21	0.16	0.06-0.40	<0.001
Platelet ($\times10^3/\mu$L) (per 10^3 ↑, normal: 150-400)	0.69	0.99	0.99-1.00	0.439
Lymphocyte ($\times10^3/\mu$L) (per 10^3 ↑, normal: 1.0-3.0)	5.59	0.99	0.99-1.00	0.008
Procalcitonin (ng/mL) (per 1 ↑, normal: <0.1)	3.38	0.92	0.84-1.00	0.066
C-reactive protein (mg/dL) (per 1 ↑, normal: <0.5)	14.69	1.18	1.08-1.28	<0.001

Omnibus χ^2 (5) = 74.60, P<0.001, R^2=0.495 (Negelkerke).

count of the patients in the meningitis group was determined as 11 890 $\times10^3/\mu$L (8 080 $\times10^3/\mu$L -19 800 $\times10^3/\mu$L), while the median in the control group was determined as 7 905 $\times10^3/\mu$L (6 090 $\times10^3/\mu$L -9 583 $\times10^3/\mu$L), and the leukocyte count was found to be statistically significantly higher in the meningitis group (P<0.001). Similarly, the median procalcitonin value was 0.21 (0.10-1.20) in the meningitis group, which was higher than the control group (P<0.001). Lymphocyte and platelet counts were lower in the meningitis group than the control group (P<0.001 for both) (Table 1).

In the logistic regression analysis performed for meningitis diagnosis, lymphocyte count, albumin and CRP values were determined as independent parameters for diagnosis. However, although procalcitonin and platelet values were significantly different between the two groups, they were not determined as independent parameters for meningitis diagnosis (Table 2).

In the ROC analysis performed for the CRP value for meningitis diagnosis, the sensitivity was determined as 80.6% and the specificity as 70.0% for a cut-off value of 2.23 (AUC: 0.792, CI=0.720-0.865, P<0.001).

When 99 meningitis patients included in our study were evaluated with CSF findings, the median leukocyte count in CSF fluid was 326/mm^3 (20/mm^3-4 800/mm^3). The median CSF protein was 132 mg/dL (10 mg/dL-730 mg/dL). Microorganisms were detected in 12 (12.1%) cases in CSF gram staining examination and the agent was isolated in CSF culture in all 12 cases.

A total of 16 cases with CSF culture growth were detected. When we look at the agent basis, *Streptococcus pneumoniae* growth was found in 13 patients, *Stapylococcus aureus* growth was found in two cases and *Brucella* spp. was found in one patient. One patient in whom *Staphylococcus aureus* was detected had a ventriculoperitoneal shunt and the other had a history of previous brain surgery. No history of surgery or trauma was detected in the other patients.

In culture positive cases, the mean leukocyte ratio in CSF fluid was determined as 903 per mm^3 (90 per mm^3-4 800 per mm^3). In the group with no growth in CSF culture, the leukocyte ratio in CSF fluid was determined as 214 per mm^3 (20 per mm^3-2 100 per mm^3) and the difference was found to be statistically significant (P<0.001). When the CSF biochemical parameters were evaluated; in meningitis cases; CSF protein median was 132 mg/dL (20 mg/dL-730 mg/dL) and CSF glucose median was 44 mg/dL (4 mg/dL-125 mg/dL). In the culture-negative group, CSF protein median was 67 mg/dL (12 mg/dL-110 mg/dL) and CSF glucose median was 46 mg/dL (10 mg/dL-63 mg/dL). In culture-positive cases, the CSF protein ratio was found to be significantly higher than in the culture-negative group (P<0.005). No significant difference was found between CSF glucose rates (P>0.05).

Of the patients diagnosed with meningitis, 12 (12.1%) were using oral penicillin group, 9 (9.1%) were using oral levofloxacin. No growth was detected in CSF culture of 21 (21.2%) patients with a history of antibiotic use.

4. Discussion

Meningitis may have an atypical course due to antibiotic use, immunosuppression and vaccination studies in the early stages of the disease. This often causes diagnostic difficulties and loss of time for treatment during emergency room visits[8]. It has been reported that mortality per hour increases significantly due to treatment delays[9]. Evaluation of blood tests together with CSF examination is important for confirming the laboratory diagnosis and planning the appropriate treatment. Although growth in CSF culture is the gold standard for meningitis diagnosis, the long turnaround time and the fact that it is affected by various reasons such as previous antibiotic use are handicaps. Therefore, although there are rapid and highly specific diagnostic methods such as the polymerase chain reaction method to isolate the agent in CSF, there is a need for early predictive markers that can be detected in the blood along with the patient's current clinical findings due to disadvantages such as not being available in every center and high cost[9]. In our study, the most common complaint in patients diagnosed with meningitis was fever, similar to the literature[10]. The proportion of male patients in the meningitis group was found to be significantly higher (P<0.001). No significant difference was found between the groups in terms of age.

Although there are publications indicating that white blood cell count does not play a predictive role in the diagnosis of meningitis, in our study white blood cell was found to be statistically significantly higher in the meningitis group compared to the control group (P<0.001)[11,12]. This finding can be explained by the fact that the control group consisted of cases with milder clinical presentations that would not require hospitalization.

Khalili *et al.* suggested that procalcitonin levels could be used to diagnose bacterial meningitis at the time of presentation, to determine prognosis, and to evaluate treatment response, supporting our findings[12]. Simon *et al*. demonstrated that procalcitonin is a more specific and sensitive method than CRP value in the diagnosis of bacterial meningitis. The same study also stated that procalcitonin has high specificity and sensitivity in the distinction between bacterial/viral meningitis[14]. Since viral agents could not be revealed in our study, no comments could be made on the use of procalcitonin in the distinction between bacterial and viral meningitis.

In our study, the sensitivity and specificity of CRP were determined as 80.6% and 70.0% for the diagnosis of bacterial meningitis with a cut-off value of 2.23 mg/dL, respectively. Lee *et al*. stated that lumbar puncture should be performed with a preliminary diagnosis of meningitis when CRP values were determined to be >10 mg/L in febrile infant[14] while Simon *et al*. stated that procalcitonin values were more reliable in the detection of bacterial infection than CRP[11]. Jakar *et al*. suggested that viral meningitis could be considered in cases with a meningitis clinic and a serum CRP level lower than 6 mg/dL, and that CRP was a strong marker for pyogenic meningitis in the group with a serum CRP level higher than 48 mg/dL[15]. Only 9.1% of the patients included in our study with a diagnosis of meningitis could be identified with gram staining in CSF microscopy. The detection rate of microorganisms with Gram staining as 92%[5]. It has been reported that the sensitivity of CSF Gram staining is 60%-98% and the specificity is approximately 100% depending on the patient population, bacterial type, and previous antibiotic use[6,16]. When the reason for the low microorganism rate in Gram staining in our study was examined, it was thought that the cytocentrifugation method was not used for Gram staining, some patients had previously used antibiotics, and those with viral meningitis could not be detected. In our study, the median leukocyte value in CSF microscopy of patients diagnosed with meningitis was 326/mm^3 (20/mm^3-4 800/mm^3), and the median leukocyte value in CSF samples of those with only culture positive was 903/mm^3 (90/mm^3-4 800/mm^3). Monem *et al.* reported that CSF leukocyte count was above 1 000/mm^3 in 20.9% of 110 meningitis patients and 100/mm^3-1 000/mm^3 in 70.1%[10]. Freedman *et al*. stated that meningitis diagnosis should be avoided if CSF leukocyte count is below 30/mm^3[17]. In our study, the median CSF protein value was determined as 132 mg/dL (20 mg/dL-730 mg/dL) and the median CSF glucose was determined as 44 mg/dL (4 mg/dL-125 mg/dL). Jimenez *et al*. also determined CSF glucose values are as an average of 40 mg/dL in bacterial meningitis cases, but they reported that it was frequently below 25 mg/dL, and these rates are consistent with the rates reported in our study[18].

The findings obtained in our study showed that the elevation of leukocyte count, CRP and procalcitonin are predictive laboratory findings supporting the meningitis clinic in cases presenting to emergency services with meningitis clinic, but these values do not have a sufficient role on their own in making the diagnosis of meningitis. The predictive values obtained in the study may help clinicians in the decision to perform lumbar puncture in cases presenting with atypical clinic. However, this is a narrow-scope study in which a relatively low number of cases were included in order to show the general population. Although leukocyte, CRP and procalcitonin values were found to be predictive values in the diagnosis of meningitis, the issue needs to be supported by studies with a larger number of cases.

Conflict of interest statement

The authors report no conflict of interest.

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There was no extramural funding received for conducting this study.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Study concept and design: MU; Analysis and interpretation of data: BCD, MU, and NZK; Drafting of the manuscript: BCD, MU; Critical revision of the manuscript for important intellectual content: BCD, MU, and NZK; Statistical analysis: MU.

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