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Clinical Characteristics and the Role of Biomarkers in the Differential Diagnosis of Community-Acquired Central Nervous System Infections: A Five-Year Retrospective Study

Toplum Kökenli Santral Sinir Sistemi Enfeksiyonlarının Ayırıcı Tanısında Klinik Özellikler ve Biyobelirteçlerin Rolü: Beş Yıllık Retrospektif Çalışma

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Abstract

Introduction: Community-acquired central nervous system infections (CA-CNSIs) are associated with substantial morbidity and mortality, and early differentiation between purulent and aseptic meningitis remains a major clinical challenge. Readily available admission biomarkers may facilitate timely clinical differentiation.

Materials and Methods: We conducted a retrospective cohort study including adult patients (≥18 years) hospitalized with CA-CNSIs at Şişli Hamidiye Etfal Training and Research Hospital over a 5-year period. Epidemiological, clinical, and laboratory characteristics were evaluated. The diagnostic performance of routinely available biomarkers was assessed using receiver operating characteristic analysis. Multivariable Firth penalized logistic regression was applied, with internal validation performed using bootstrap resampling.

Results: Seventy patients were included (median age, 45 years; 63% male). Purulent meningitis accounted for 46% of cases, whereas aseptic meningoencephalitis comprised 24%. Patients with purulent meningitis had significantly higher leukocyte counts and C-reactive protein (CRP) and procalcitonin levels, as well as a lower cerebrospinal fluid (CSF)-to-serum glucose ratio. The CSF-to-serum glucose ratio demonstrated the highest discriminative ability for differentiating purulent from aseptic meningitis [area under the curve (AUC), 0.97], followed by CRP (AUC, 0.89). In the multivariable analysis, the CSF-to-serum glucose ratio remained independently associated with purulent meningitis, with CRP providing additional discriminatory value.

Conclusion: In this real-world cohort, the CSF-to-serum glucose ratio was the most robust admission biomarker for differentiating purulent from aseptic meningitis. CRP provided additional discriminatory value, supporting the combined use of routinely available biomarkers to improve early clinical decision-making in patients with suspected CA-CNSIs.

Keywords: Central nervous system infections, meningitis, bacterial, cerebrospinal fluid, biomarkers, C-reactive protein

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Öz

Giriş: Toplum kökenli santral sinir sistemi enfeksiyonları (TK-SSSE), belirgin morbidite ve mortalite ile ilişkilidir. Pürülan menenjit ile aseptik menenjitin erken dönemde ayırt edilmesi klinikte önemli bir sorun olmaya devam etmektedir. Başvuru sırasında rutin olarak elde edilebilen biyobelirteçler, bu ayrımı zamanında yapmaya yardımcı olabilir.

Gereç ve Yöntem: Üçüncü basamak bir eğitim ve araştırma hastanesinde, beş yıllık dönemde TK-SSSE nedeniyle yatırılarak izlenen ≥18 yaş erişkin hastalar retrospektif kohort tasarımında değerlendirildi. Epidemiyolojik, klinik ve laboratuvar veriler incelendi. Rutin biyobelirteçlerin tanısal performansı alıcı işletim karakteristiği eğrisi analizi ile değerlendirildi. Çok değişkenli analizde Firth penalizasyonlu lojistik regresyon kullanıldı; iç doğrulama bootstrap yeniden örnekleme ile yapıldı.

Bulgular: Çalışmaya 70 hasta dahil edildi (medyan yaş 45 yıl; %63 erkek). Olguların %46'sı pürülan menenjit, %24'ü aseptik meningoensefalit idi. Pürülan menenjitli hastalarda lökosit sayısı, C-reaktif protein (CRP) ve prokalsitonin düzeyleri anlamlı olarak daha yüksek; beyin omurilik sıvısı (BOS)/serum glukoz oranı ise daha düşüktü. Pürülan ve aseptik menenjitin ayrımında en yüksek ayırt edici gücü BOS/serum glukoz oranı gösterdi [eğri altındaki alan (AUC) 0,97]; bunu CRP izledi (AUC: 0,89). Çok değişkenli analizde BOS/serum glukoz oranı pürülan menenjit ile bağımsız olarak ilişkili bulunurken, CRP ek ayırt edicilik sağladı.

Sonuç: Bu kohortta pürülan ve aseptik menenjitin ayırıcı tanısında en güçlü başvuru biyobelirteci BOS/serum glukoz oranı olarak saptandı. CRP'nin ek katkısı, TK-SSSE şüphesi olan hastalarda erken klinik karar vermeyi desteklemek amacıyla rutin biyobelirteçlerin birlikte değerlendirilmesini desteklemektedir.

Anahtar Kelimeler: Santral Sinir sistemi enfeksiyonları, bakteriyel menenjit, aseptik menenjit, serebrospinal sıvı, biyobelirteçler, C-reaktif protein

Introduction

Central nervous system infections (CNSIs) are among the most severe infectious diseases, characterized by rapid clinical progression and associated with high morbidity and mortality[1]. The most common clinical presentations include meningitis, encephalitis, meningoencephalitis, and brain abscess. Early diagnosis and timely initiation of appropriate therapy are critical for improving prognosis. However, the initial manifestations are often non-specific and typically include fever, headache, neck stiffness, altered consciousness, and focal neurological deficits. Consequently, the diagnosis of CNSIs requires a comprehensive clinical and laboratory evaluation[2].

Timely recognition of factors that may influence disease course is also crucial for effective patient management[3]. Previous studies have demonstrated that admission variables, such as the level of consciousness, cerebrospinal fluid (CSF) cell count, and protein concentration, are associated with unfavorable outcomes[3-5].

The limited sensitivity of microbiological diagnostic methods frequently results in unidentified pathogens, necessitating empirical therapy[6]. Although studies focusing on specific clinical subgroups are available, there remains a need for comprehensive investigations addressing community-acquired (CA) CNSIs from epidemiological, clinical, microbiological, and therapeutic perspectives[7].

This study aimed to comprehensively evaluate the epidemiological characteristics and the clinical and laboratory findings at presentation in patients with CA-CNSIs. The primary objective was to identify clinical and laboratory parameters that could aid in differentiating purulent from aseptic meningitis. In addition, the study sought to identify risk factors associated with adverse clinical outcomes, thereby contributing to the diagnostic and prognostic process.

Materials and Methods

Study Design and Patient Selection

This retrospective cohort study reviewed the medical records of adult patients hospitalized with a diagnosis of CA CNSI at Şişli Hamidiye Etfal Training and Research Hospital in İstanbul, Türkiye, between January 1, 2020, and December 31, 2024. Due to the retrospective design of the study, informed consent was not required.

Inclusion and Exclusion Criteria

Patients aged ≥18 years who were hospitalized in the Department of Infectious Diseases during the study period with a preliminary diagnosis of CA-CNSI based on clinical and laboratory findings were included. Patients younger than 18 years, those with hospital-acquired CNSI, and those with secondary CNSI resulting from non-primary causes of meningitis (e.g., post-traumatic meningitis) were excluded.

All consecutive patients who met the predefined inclusion criteria during the 5-year study period were included. No sampling was performed.

Clinical Classification

Patients were classified according to predefined clinical and CSF findings. Accordingly, cases were categorized as aseptic meningoencephalitis, purulent meningitis, tuberculous

meningitis (TBM), cryptococcal meningitis (CM), brain abscess, or neurosyphilis.

Purulent meningitis was generally characterized by neutrophil-predominant CSF pleocytosis, biochemical findings suggestive of bacterial infection, and a compatible clinical presentation. Aseptic meningoencephalitis was characterized by lymphocyte-predominant CSF pleocytosis, relatively preserved CSF glucose levels, and the absence of microbiological evidence of bacterial infection.

Cases of purulent meningitis were further classified as laboratory-confirmed or non–laboratory-confirmed based on microbiological evidence [CSF culture, multiplex polymerase chain reaction (PCR) panel, or microscopic examination]. Final diagnoses were established by integrating objective laboratory findings, microbiological results, when available, and clinical assessment.

Data Collection

Epidemiological characteristics, clinical symptoms, laboratory findings, microbiological diagnostic methods, empirical and targeted treatment strategies, and clinical outcomes (recovery, sequelae, and mortality) were assessed. Laboratory data were retrieved from existing records maintained by the hospital's microbiology and biochemistry laboratories, including CSF analysis, cultures, commercial multiplex PCR meningitis/encephalitis panels, and antibiograms. Procalcitonin was generally measured at admission as part of the initial infectious disease workup in patients presenting with suspected CNS infection. All data were recorded using a standardized data collection form designed by the investigator, de-identified before analysis, and anonymized. The dataset was securely stored in a digital format and was accessible only to the investigator.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval date: 22.04.2025; approval number: 2980). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation or median (first–third quartile) for continuous variables, depending on the data distribution, and as counts and percentages for categorical variables. Group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate, and the Mann–Whitney U test for non-parametric data.

All analyses were performed using R software (R Foundation for Statistical Computing)[8]. Multivariable logistic regression analysis was initially performed to identify candidate predictors for differentiating purulent from aseptic meningitis. Model simplification was conducted using stepwise selection based on the Akaike Information Criterion to obtain the most parsimonious model. The final model was then re-estimated using Firth penalized logistic regression method to mitigate potential separation issues related to the limited sample size and low event frequency[9].

Receiver operating characteristic (ROC) curve analyses were performed to evaluate the discriminative ability of individual laboratory parameters to differentiate purulent from aseptic meningitis. Each biomarker was analyzed separately. Optimal cut-off values were determined using the Youden index (maximum sensitivity + specificity – 1). ROC analysis was also performed for the final penalized logistic regression model using model-predicted probabilities. The area under the curve (AUC) and corresponding 95% confidence intervals (CIs) were calculated using DeLong's method, and AUC values were compared when appropriate[10].

Model validation was performed using bootstrap resampling (case resampling, B = 1000), with the model reconstructed and performance metrics recalculated during each iteration[11]. Data cleaning and preprocessing were conducted using the tidyverse package. To ensure reproducibility, a fixed random seed was applied (set.seed = 123). Missing data were handled using complete-case analysis. Among the variables included in the final multivariable model, missing data were observed for the CSF/serum glucose ratio in seven patients and for procalcitonin in three patients, whereas no missing data were observed for C-reactive protein (CRP). Bootstrap samples without representation from both outcome classes were excluded from ROC/AUC calculations and bootstrap iterations. For multiple comparisons, the Benjamini–Hochberg correction was applied.

Results

A total of 70 patients were included in the study. The median age was 45 years (first–third quartile, 35–62; range, 18–92 years), and 63% were male. At least one comorbidity was present in 54% of the patients, with hypertension (23%) and diabetes mellitus (16%) being the most common. The rate of immunosuppression was 23%, and predisposing factors were identified in 40% of the cases. More than half of the patients (56%) had sought medical care before admission, and 33% had received antibiotics. None of the patients had a documented history of pneumococcal vaccination. The median time from symptom onset to hospitalization was 3 days. The most

common presenting symptoms were headache (77%), altered consciousness (57%), and fever (56%). The demographic and clinical characteristics of the patients are summarized in Table 1.

Laboratory investigations revealed a median leukocyte count of 11,260/µL, a CRP level of 24 mg/L, a CSF cell count of 330/mm^3, and a CSF/serum glucose ratio of 0.37. Gram staining was positive in 18% of the cases. The most frequently isolated pathogen was *Streptococcus pneumoniae*, followed by *Listeria monocytogenes*. Multiplex PCR identified causative pathogens more frequently than culture. Tuberculosis (TB) PCR was performed in 55 patients, of whom four (7.3%) tested positive. TB culture was performed in 57 patients, yielding four (7.0%) positive results. In addition, acid-resistant bacilli testing was performed in 57 patients, with five (8.8%) positive results. Detailed laboratory findings are presented in Table 2.

Table 1. Demographic and clinical characteristics of the patients.

Characteristic	n = (%) or Median [IQR]; [min–max]
Age (years)	45 [35–62]; [18–92]
Sex	
Female	26 (37)
Male	44 (63)
Comorbidity	38 (54)
Hypertension	16 (23)
Diabetes mellitus	11 (16)
Other (cardiac, renal, and hepatic diseases)	11 (16)
Immunosuppression	16 (23)
Predisposing factor	28 (40)
History of head trauma or surgery	2 (3)
Splenectomy	1 (1)
Chronic ENT infection	2 (3)
Chronic alcohol use	3 (4)
Smoking	12 (17)
Prior healthcare visit	39 (56)
Prior antibiotic use	23 (33)
History of vaccination	0 (0)
Symptom-to-admission interval (days)	3 [1–7]; [1–365]
Presenting symptoms	
Fever	39 (56)
Headache	54 (77)
Nausea/vomiting	26 (37)
Altered consciousness	40 (57)
Seizure	9 (13)
Personality change	13 (19)
Neck stiffness	28 (40)
Kernig and/or Brudzinski sign	9 (13)
Focal neurological deficit	8 (11)
Cranial nerve involvement	12 (17)

Data are presented as n (%) or median [1st–3rd quartile]; [min–max]. IQR, interquartile range; ENT, ear, nose, and throat; min, minimum; max, maximum.

The most common clinical diagnoses were purulent meningitis (46%) and aseptic meningoencephalitis (24%). In addition, 12 patients (17%) were diagnosed with TBM, and three patients (4%) were diagnosed with CM. Among patients with purulent meningitis, 53% (n = 21) had microbiologically confirmed disease. Compared with clinically diagnosed cases, confirmed purulent meningitis cases had significantly lower CSF/serum glucose ratios (p = 0.007) and were more likely to present with focal neurological deficits (p = 0.033). During follow-up, neurological sequelae developed in 12 patients (18%), and the overall mortality rate was 13%.

To explore prognostic factors, patients who died were compared with survivors. Mortality was associated with a higher frequency of renal or hepatic disease (p = 0.006) and lower lymphocyte counts (p = 0.007). Older age, altered consciousness, focal neurological deficits, and lower CSF/serum glucose ratios were also more common among non-survivors, although these findings reached only borderline significance. No other significant demographic, clinical, or microbiological differences were observed. Key comparisons are presented in Table 3. Given the limited number of deaths, multivariable regression analysis for mortality prediction was not performed to avoid overfitting.

Patients were classified into three groups: purulent meningitis, aseptic meningoencephalitis, and TBM. Cases of CM (n = 3)

Table 2. Laboratory findings.

Parameter	Median [IQR]; [min–max]
Blood parameters	
Leukocyte (cells/µL)	11,260 [7,570–15,600]; [1,610–37,840]
Neutrophil (cells/µL)	8,235 [5,220–13,180]; [1,160–34,570]
Lymphocyte (cells/µL)	1,155 [700–1,920]; [180–7,730]
Hemoglobin (g/dL)	13.0 [11.6–14.0]; [7.7–18.4]
Platelet (×10^3/µL)	224 [163–289]; [95–615]
CRP, mg/L	24 [4–156]; [0–528]
Procalcitonin (ng/mL)	0 [0–2]; [0–100]
CSF parameters	
Cell count (cells/mm^3)	330 [130–873]; [0–9,800]
Protein (mg/dL)	291 [95–890]; [14–10,084]
CSF/serum glucose ratio	0.37 [0.13–0.50]; [0.00–0.83]
Gram stain positivity	11 (18%)

Data are presented as n (%) or median [1st–3rd quartile]; [minimum–maximum], as appropriate. CSF, cerebrospinal fluid; CRP, C-reactive protein; IQR, interquartile range; min, minimum; max, maximum.

were excluded from the comparative subgroup analyses because the small sample size precluded meaningful statistical comparisons. The median age was significantly higher in the purulent meningitis group than in the TBM group ($p = 0.003$). Leukocyte, neutrophil, CRP, and procalcitonin levels were markedly higher in patients with purulent meningitis than in those with aseptic meningoencephalitis or TBM (all $p \leq 0.003$). Conversely, lymphocyte counts were higher in the aseptic meningoencephalitis group ($p = 0.007$), and the CSF/serum glucose ratio was significantly higher in the aseptic meningoencephalitis group than in both of the other groups ($p < 0.001$). CSF cell counts were also higher in the purulent meningitis group than in the other groups ($p \leq 0.008$), whereas CSF protein levels were higher only in comparison with the aseptic meningoencephalitis group ($p = 0.004$). Clinically, neck stiffness was more common in patients with purulent meningitis than in those with aseptic meningoencephalitis ($p < 0.001$). Human immunodeficiency virus (HIV) positivity

Table 3. Comparison of clinical and laboratory characteristics between survivors and non-survivors.

Variable	Survivors (n = 61[1])	Non-survivors (n = 9[1])	p-value[2]
Age, years	44 [30–58]	49 [42–63]	0.065
Male sex, n (%)	34 (55.7)	5 (55.6)	0.99
Renal/hepatic disease, n (%)	1 (1.6)	3 (33.3)	**0.006**
Altered consciousness, n (%)	32 (52.5)	8 (88.9)	0.068
Focal neurological deficit, n (%)	5 (8.2)	3 (33.3)	0.060
Lymphocyte count (/μL)	1,280 [730–2,030]	800 [480–950]	**0.007**
WBC (/μL)	10,200 [7,900–12,800]	11,300 [8,400–13,500]	0.41
CRP (mg/L)	38 [15–92]	45 [21–110]	0.57
CSF cell count (/mm^3)	210 [90–540]	280 [100–640]	0.49
CSF protein (mg/dL)	135 [90–220]	150 [95–230]	0.62
CSF/serum glucose ratio	0.38 [0.24–0.50]	0.07 [0.02–0.25]	0.068

[1]Data are presented as median [IQR] or n (%), as appropriate.

[2]Wilcoxon rank-sum test was used for continuous variables and Fisher's exact test for categorical variables.

CSF, cerebrospinal fluid; CRP, C-reactive protein; WBC, white blood cell; IQR, interquartile range.

Table 4. Variables showing statistically significant differences in pairwise comparisons according to clinical diagnosis.

Variable	Comparison	Higher in	Adjusted p-value
Age	Purulent vs. TBM	Purulent	**0.003**
WBC	Aseptic vs. purulent	Purulent	**0.013**
WBC	Purulent vs. TBM	Purulent	**0.001**
Neutrophil count	Aseptic vs. purulent	Purulent	**0.012**
Neutrophil count	Purulent vs. TBM	Purulent	**0.002**
Lymphocyte count	Aseptic vs. purulent	Aseptic	**0.007**
CRP	Aseptic vs. purulent	Purulent	**<0.001**
CRP	Purulent vs. TBM	Purulent	**0.002**
Procalcitonin	Aseptic vs. purulent	Purulent	**0.001**
Procalcitonin	Purulent vs. TBM	Purulent	**0.003**
CSF cell count	Aseptic vs. purulent	Purulent	**0.008**
CSF cell count	Purulent vs. TBM	Purulent	**0.001**
CSF protein	Aseptic vs. purulent	Purulent	**0.004**
CSF/serum glucose ratio	Aseptic vs. purulent	Aseptic	**<0.001**
CSF/serum glucose ratio	Aseptic vs. TBM	Aseptic	**<0.001**
Neck stiffness	Aseptic vs. purulent	Purulent	**<0.001**
HIV positivity	TBM vs. purulent	TBM	**0.011**

[1]Post-hoc Dunn and Fisher's exact tests; p-values adjusted for multiple comparisons. Aseptic meningoencephalitis (n = 17), purulent meningitis (n = 32), and TBM (n = 12). CSF, cerebrospinal fluid; CRP, C-reactive protein; WBC, white blood cell; TBM, tuberculous meningitis; HIV, human immunodeficiency virus.

was significantly more frequent in the TBM group than in the purulent meningitis group ($p = 0.011$). These comparisons are summarized in Table 4.

In the differential diagnosis of aseptic and purulent meningitis, ROC curve analysis showed that the CSF/serum glucose ratio had the highest discriminative ability (AUC = 0.971), followed by CRP (AUC = 0.885) and procalcitonin (AUC = 0.838). According to the DeLong test, the CSF/serum glucose ratio demonstrated significantly greater discriminative performance than all other parameters (all $p < 0.001$). Detailed diagnostic performance metrics are presented in Table 5.

The multivariable analysis was restricted to patients with purulent and aseptic meningitis. After excluding other diagnostic categories and applying complete-case analysis, 43 patients were included in the final model. Multivariable Firth penalized logistic regression analysis was performed to differentiate purulent from aseptic meningitis because this approach reduces small-sample bias and mitigates potential separation in limited datasets. The model included the CSF/serum glucose ratio, CRP, and procalcitonin. The model was statistically significant [likelihood ratio test: $\chi^2(3) = 36.42$, $p < 0.001$] and demonstrated excellent discriminative ability (AUC = 0.990, 95% CI: 0.972–1.000). The CSF/serum glucose ratio showed a strong and significant negative association, whereas CRP showed a significant positive association. Procalcitonin was not statistically significant. Detailed results are presented in Table 6.

The reported odds ratio for the CSF/serum glucose ratio reflects the effect of a one-unit increase. Because the physiological range of this variable is between 0 and 1, a one-unit increase represents a theoretical extreme rather than a clinically typical change. Therefore, smaller incremental differences (e.g., 0.1-unit increases) are more clinically meaningful when interpreting the effect size.

Internal validation using bootstrap resampling confirmed the stability of the model. The 95% CI for the AUC was 0.969–1.000. The mean optimism was 0.055, yielding an optimism-corrected AUC of 0.936, suggesting that the high apparent AUC was not solely attributable to overfitting. Bootstrap CIs for the odds ratios were consistent with the primary estimates. Calibration analysis further supported the predictive performance of the model, with a Brier score of 0.039, an apparent Emax of 0.100, and a bias-corrected Emax of 0.148. These findings indicate that the model demonstrated high discriminative ability and good calibration.

Discussion

In this study, CA-CNSIs were evaluated from both epidemiological and clinical perspectives. The high prevalence of comorbidities and an overall mortality rate of 13% highlight the substantial clinical burden associated with this patient population. Among the clinical presentations, purulent meningitis was the most common, and the CSF/serum glucose ratio emerged as the most effective biomarker for differential diagnosis. These findings

Table 5. ROC curve analysis for the determination of optimal cut-off values in differentiating purulent and aseptic meningitis.

Variable	AUC	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	0.885	16.75	0.84	0.82	0.90	0.74	0.84
Procalcitonin	0.838	0.39	0.78	0.94	0.96	0.68	0.83
CSF cell count	0.785	578.00	0.57	0.94	0.94	0.56	0.70
CSF/serum glucose ratio	0.971	0.49	1.00	0.88	0.93	1.00	0.95
CSF protein	0.792	195.00	0.79	0.81	0.88	0.68	0.80
Neutrophil count	0.761	11,115.00	0.59	0.88	0.90	0.54	0.69
Symptom-to-admission interval (days)	0.572	4.50	0.74	0.47	0.72	0.50	0.65
Lymphocyte count	0.781	1,745.00	0.84	0.65	0.82	0.69	0.78
ALT (U/L)	0.537	27.50	0.34	0.82	0.79	0.40	0.51

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CSF, cerebrospinal fluid; ROC, receiver operating characteristic; ALT, alanine aminotransferase.

Table 6. Multivariable Firth penalized logistic regression analysis for the differential diagnosis between purulent and aseptic meningitis.

Variable	OR [exp(β)]	95% CI	p-value
CSF/serum glucose ratio	0.000002	0.000000–0.002619	<0.001
CRP	1.021	1.003–1.053	0.013
Procalcitonin	0.962	0.896–1.031	0.200

OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid; CRP, C-reactive protein.

underscore the importance of integrating epidemiological insights with biomarker-based approaches for the diagnosis and prognostic assessment of CNSIs.

In our cohort, nearly half of the patients had at least one comorbidity, and 23% were immunosuppressed. Compared with a large prospective European cohort, our study showed a similar prevalence of comorbidities (48%), whereas the rate of immunosuppression was notably higher (23% vs. 16%)[4]. The most common comorbidities were hypertension and diabetes mellitus. Notably, immunosuppression was not significantly associated with mortality, suggesting that it may not directly influence the clinical course. Nevertheless, several multicenter studies have reported that immunosuppression adversely affects prognosis[12]; this discrepancy may be attributable to differences in patient populations and pathogen distribution. The relatively small sample size of our study may also have contributed to this finding. Furthermore, the rate of prior antibiotic use was 33%, substantially higher than the 9% reported in the European cohort[4]. This difference may reflect community-level antibiotic use as well as structural characteristics of healthcare access in Türkiye. Collectively, these findings underscore the regional epidemiological burden of CA-CNSIs.

In our study, the most common clinical presentation was purulent meningitis (46%), followed by aseptic meningoencephalitis (24%) and TBM (17%). This distribution is largely consistent with that reported in a large multicenter study involving 37 centers across 20 countries, in which 50% of cases were classified as meningitis and 34% as meningoencephalitis[13]. Similarly, a retrospective study from Türkiye reported purulent meningitis (44%) and aseptic meningoencephalitis (39%) as the predominant clinical presentations[14]. In our cohort, patients with microbiologically confirmed purulent meningitis had lower CSF/serum glucose ratios and were more likely to present with focal neurological deficits. Consistent with these findings, previous studies have demonstrated significantly lower CSF/serum glucose levels in patients with confirmed bacterial meningitis[15]. Although some reports suggest that culture-positive cases are associated with more severe disease and poorer prognosis[16], this association was not observed in our cohort. This discrepancy may be explained by the limited sample size or differences in pathogen distribution.

In our cohort, the median time from symptom onset to hospital admission was 3 days, which was longer than the median of 1 day reported in a nationwide Danish cohort[17]. Delayed presentation has been associated with increased mortality and the development of neurological sequelae[18], and the 13% mortality rate observed in our study is consistent with these findings. The delay in presentation may reflect patterns of healthcare access in our country as well as the widespread use of antibiotics in the community.

The most common presenting symptoms were headache (77%), altered consciousness (57%), and fever (56%). Neck stiffness (40%) and other meningeal signs, such as Kernig and Brudzinski signs, were observed less frequently. Although this proportion may appear relatively low compared with that reported in studies focusing exclusively on bacterial meningitis, our cohort included a heterogeneous spectrum of CNS infections. Therefore, the frequency of meningeal signs may vary depending on the underlying etiology, disease stage, and clinical context at presentation. Consequently, the absence of neck stiffness does not exclude the diagnosis of CNS infection and likely reflects the overall clinical heterogeneity of this population[4,19]. Furthermore, the frequencies of seizures (13%) and focal neurological deficits (11%) in our cohort were comparable to those reported in large international studies[17], highlighting the consistency of clinical manifestations across different populations.

In our study, the causative pathogen could not be identified in approximately half of the cases, a proportion consistent with that reported in international cohorts[13,14]. In addition, 33% of the patients had received antibiotics before specimen collection, which may have reduced culture positivity, contributed to the high proportion of microbiologically unconfirmed cases, and potentially influenced the interpretation of biomarker findings. Among the culture-positive specimens, *Streptococcus pneumoniae* was the most frequently isolated pathogen, followed by *Listeria monocytogenes*. Multiplex PCR detected pathogens more frequently than conventional culture, highlighting the limited sensitivity of culture, as reported previously[16]. Notably, PCR has been shown to provide substantial diagnostic value, particularly in culture-negative cases following prior antibiotic use[20]. More recently, studies have suggested that metagenomic next-generation sequencing may further improve pathogen detection by identifying organisms that remain undetected using conventional methods[21]. Therefore, our findings support the expanding role of molecular diagnostic techniques in the evaluation of CA-CNSIs.

Our findings indicate that renal or hepatic disease and low lymphocyte counts were significant risk factors for mortality. Similar findings have been reported in large cohorts of CA bacterial meningitis, in which comorbidities were associated with an increased risk of mortality[4,22]. Previous studies have also reported associations between inflammatory markers, such as the neutrophil-to-lymphocyte ratio, and mortality in adults with bacterial meningitis[23]. However, this parameter was not evaluated directly in our study. In addition, low CSF glucose levels have been identified as an independent

predictor of poor prognosis[24]. Altered consciousness and focal neurological deficits have also been strongly associated with mortality in previous studies[4,17]. Although these factors were more common among patients who died in our study, they reached only borderline statistical significance, likely owing to the limited sample size and heterogeneity of the causative pathogens. Overall, these findings reinforce that mortality prediction in CNSIs cannot rely on a single parameter but requires the integrated assessment of multiple clinical and laboratory indicators. However, because of the limited number of deaths (n = 9), these findings should be interpreted with caution, as the small number of events limits the robustness of the mortality analysis.

Patients with purulent meningitis exhibited significantly higher leukocyte, neutrophil, CRP, and procalcitonin levels than those with aseptic meningoencephalitis or TBM. These findings are consistent with the literature, which demonstrates the more pronounced inflammatory response associated with bacterial infections[16]. In contrast, the higher CSF/serum glucose ratios and lymphocyte counts observed in patients with aseptic meningoencephalitis support the utility of these parameters in the differential diagnosis of viral infections[25]. The greater frequency of neck stiffness in patients with purulent meningitis and the higher prevalence of HIV positivity in those with TBM suggest that clinical features may aid the diagnostic process. However, as emphasized in previous studies, these findings alone do not provide reliable discriminatory criteria[17,26].

ROC analysis identified the CSF/serum glucose ratio as the parameter with the highest discriminative ability (AUC = 0.971). This finding is consistent with recent clinical studies identifying CSF glucose as an important diagnostic parameter in the evaluation of CNSIs[24]. Although CRP and procalcitonin contributed to diagnostic performance, their discriminative ability was inferior to that of the CSF/serum glucose ratio. In the Firth penalized logistic regression model, the CSF/serum glucose ratio remained an independent and robust predictor, whereas CRP provided significant incremental value and procalcitonin was no longer statistically significant. Although previous studies have emphasized the diagnostic utility of serum CRP and procalcitonin for distinguishing purulent meningitis[28,29], their contribution in our cohort was more limited. Notably, the inclusion of CRP improved the overall diagnostic performance, supporting evidence that the combined assessment of multiple biomarkers provides more reliable diagnostic information than reliance on a single parameter[29]. The optimal cut-off values were determined using the Youden index to maximize combined sensitivity and specificity. Notably, the identified cut-off value for the CSF/serum glucose ratio (0.49) is consistent with values reported in previous studies of bacterial meningitis[25]. This agreement supports the potential clinical applicability of the cut-off identified in our cohort, although external validation in larger populations remains necessary.

Bootstrap analysis and calibration assessment supported the methodological robustness of the model, with a low Brier score indicating good predictive accuracy. These findings are consistent with the recommended methodological standards for the development and validation of clinical prediction models[30]. Our results highlight the importance of integrating multiple biomarkers, particularly the CSF/serum glucose ratio, in the differential diagnosis of CNS infections. Furthermore, the validated model demonstrated strong methodological performance, suggesting that it may provide a valuable foundation for the development of more reliable diagnostic tools. Although external validation in larger cohorts remains essential, the internal validation procedures applied in this study increase confidence in the model's performance.

From a clinical perspective, the proposed multivariable model may support clinical decision-making by providing an integrated probability estimate rather than relying on individual biomarkers alone. Although the CSF/serum glucose ratio demonstrated excellent standalone performance, the combined assessment of multiple biomarkers improved overall discrimination and may increase diagnostic confidence, particularly in borderline cases. These findings are consistent with current international guidelines for CNS infections, which emphasize the role of CSF biochemical parameters in early differential diagnosis[6,26]. Our results primarily reinforce current clinical practice while suggesting that the combination of biomarkers may provide additional support for diagnostic decision-making. However, prospective multicenter studies and external validation in diverse populations are required before routine clinical implementation. Further comparisons with emerging molecular diagnostic approaches may also help define the incremental value of predictive modeling in clinical practice.

Study Limitations

This study has several limitations. It was conducted at Şişli Hamidiye Etfal Training and Research Hospital using a retrospective design, which may have introduced selection bias related to referral patterns and limited the generalizability of the findings to other clinical settings. The relatively small sample size may also have reduced statistical precision. In addition, complete-case analysis was applied in the multivariable model, which may have reduced statistical power and introduced bias if the missing data were not completely at random. As an observational study, the possibility of unmeasured confounding cannot be excluded. Furthermore, the absence of long-term follow-up limited the assessment

of late neurological sequelae. The study population consisted exclusively of adult patients; therefore, the findings may not be directly applicable to pediatric populations, in whom CNSIs differ in epidemiology and clinical presentation. Future prospective multicenter studies are warranted to validate these findings.

Conclusion

This study highlights the epidemiological and clinical characteristics of CA-CNSIs and demonstrates that the CSF/serum glucose ratio is a particularly strong diagnostic biomarker. Although CRP provided additional diagnostic value and procalcitonin showed limited utility, the findings suggest that the combined assessment of multiple biomarkers offers greater diagnostic reliability than reliance on individual markers alone. The proposed model, supported by bootstrap and calibration analyses, demonstrated methodological robustness, suggesting that it may provide a valuable foundation for the development of diagnostic approaches for clinical practice. Future studies involving larger cohorts are warranted to validate these findings and facilitate the development of more robust prediction models that may improve the early diagnosis of CNSIs.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval date: 22.04.2025; approval number: 2980). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Due to the retrospective design of the study, informed consent was not required.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: H.M.T., O.D., C.A.T., N.D.D., D.Y.S., İ.D., Concept: H.M.T., O.D., C.A.T., D.Y.S., Design: H.M.T., O.D., C.A.T., D.Y.S., İ.D., Data Collection or Processing: H.M.T., S.A., Analysis or Interpretation: O.D., Literature Search: H.M.T., N.D.D., D.Y.S., İ.D., Writing: H.M.T.

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References

1. Sheybani F, Haddad M, Shirazinia M. Epidemiology and etiology of community-acquired CNS infections in Iran: a narrative review. Future Neurol. 2023;18(4).
2. Hasbun R. Approach to the patient with central nervous system infection. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 10th ed. Philadelphia: Elsevier; 2025. p.1109–1114.e1.
3. Ter Horst L, van Zeggeren IE, Olie SE; I-PACE Study Group; van de Beek D, Brouwer MC. Predictors of unfavourable outcome in adults with suspected central nervous system infections: a prospective cohort study. Sci Rep. 2023;13(1):21250.
4. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849-59.
5. Matsuki Y, Oda T, Fukao E, Sugiura A, Yokozawa T, Honma Y. Prognostic Factors for Japanese Adults With Acute Community-Acquired Bacterial Meningitis: A Retrospective Study. Cureus. 2024;16(4):e57642.
6. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC; ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22 Suppl 3:S37-62.
7. Sigfrid L, Perfect C, Rojek A, Longuere KS, Lipworth S, Harriss E, Lee J, Salam A, Carson G, Goossens H, Horby P. A systematic review of clinical guidelines on the management of acute, community-acquired CNS infections. BMC Med. 2019;17(1):170.
8. R Core Team. R: A language and environment for statistical computing. Version 4.3 [software]. Vienna: R Foundation for Statistical Computing; 2025. Available from: https://www.r-project.org/ [accessed 4 Mar 2025].
9. Suhas S, Manjunatha N, Kumar CN, Benegal V, Rao GN, Varghese M, Gururaj G. Firth's penalized logistic regression: A superior approach for analysis of data from India's National Mental Health Survey, 2016. Indian J Psychiatry. 2023;65(12):1208-13.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.
11. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman & Hall; 1994. doi:10.1201/9780429246593.
12. Glimåker M, Naucler P, Sjölin J. Etiology, clinical presentation, outcome and the effect of initial management in immunocompromised patients with community acquired bacterial meningitis. J Infect. 2020;80(3):291-7.
13. Erdem H, Inan A, Guven E, Hargreaves S, Larsen L, Shehata G, Pernicova E, Khan E, Bastakova L, Namani S, Harxhi A, Roganovic T, Lakatos B, Uysal S, Sipahi OR, Crisan A, Miftode E, Stebel R, Jegorovic B, Fehér Z, Jekkel C, Pandak N, Moravveji A, Yilmaz H, Khalifa A, Musabak U, Yilmaz S, Jouhar A, Oztoprak N, Argemi X, Baldeyrou M, Bellaud G, Moroti RV, Hasbun R, Salazar L, Tekin R, Canestri A, Čalkić L, Praticò L, Yilmaz-Karadag F, Santos L, Pinto A, Kaptan F, Bossi P, Aron J, Duissenova A, Shopayeva G, Utaganov B, Grgic S, Ersoz G, Wu AKL, Lung KC, Bruzsa A, Radic LB, Kahraman H, Momen-Heravi M, Kulzhanova S, Rigo F, Konkayeva M, Smagulova Z, Tang T, Chan P, Ahmetagic S, Porobic-Jahic H, Moradi F, Kaya S, Cag Y, Bohr A, Artuk C, Celik I, Amsilli M, Gul HC, Cascio A, Lanzafame M, Nassar M. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis. 2017;36(9):1595-611.

14. Altunal LN, Öztürk S, Aydın M, Özel AS, Kadanalı A. Clinical characteristics of 98 patients diagnosed with central nervous system infection. ANKEM Derg. 2021;35(3):77-84.
15. Patel S, Jhala P, Sharma H. A study of the etiology, clinical profile, and diagnosis of various types of central nervous system infections in a tertiary care center. Cureus. 2024;16(2):e54250.
16. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010;23(3):467-92.
17. Bodilsen J, Storgaard M, Larsen L, Wiese L, Helweg-Larsen J, Lebech AM, Brandt C, Østergaard C, Nielsen H; DASGIB study group. Infectious meningitis and encephalitis in adults in Denmark: a prospective nationwide observational cohort study (DASGIB). Clin Microbiol Infect. 2018;24(10):1102.e1-5.
18. Hovmand N, Christensen HC, Lundbo LF, Kronborg G, Darsø P, Blomberg SNF, Benfield T. Pre-hospital symptoms associated with acute bacterial meningitis differs between children and adults. Sci Rep. 2023;13(1):21479.
19. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, van der Ende A, van de Beek D. Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. Lancet Infect Dis. 2016;16(3):339-47.
20. Leber AL, Everhart K, Balada-Llasat JM, Cullison J, Daly J, Holt S, Lephart P, Salimnia H, Schreckenberger PC, DesJarlais S, Reed SL, Chapin KC, LeBlanc L, Johnson JK, Soliven NL, Carroll KC, Miller JA, Dien Bard J, Mestas J, Bankowski M, Enomoto T, Hemmert AC, Bourzac KM. Multicenter evaluation of biofire filmarray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol. 2016;54(9):2251-61.
21. Zhang S, Wu G, Shi Y, Liu T, Xu L, Dai Y, Chang W, Ma X. Understanding etiology of community-acquired central nervous system infections using metagenomic next-generation sequencing. Front Cell Infect Microbiol. 2022;12:979086.
22. Parente Filho SLA, Lima LMB, Dantas GLA, Silva DA, Rolim VM, Oliveira Filho AMP, Melo ITVE, Silva Junior GBD, Daher EF. Prognostic factors among critically ill patients with community-acquired acute bacterial meningitis and acute kidney injury. Rev Bras Ter Intensiva. 2018;30(2):153-9.
23. Giede-Jeppe A, Atay S, Koehn J, Mrochen A, Luecking H, Hoelter P, Volbers B, Huttner HB, Hueske L, Bobinger T. Neutrophil-to-lymphocyte ratio is associated with increased cerebral blood flow velocity in acute bacterial meningitis. Sci Rep. 2021;11(1):11383.
24. Khodashenas N, Rajaei Ghafouri R, Jafari Rouhi A, Balafar M. Early detection of cerebrospinal fluid/serum glucose ratio: A promising value for mortality prognosis in patients with acute bacterial meningitis. J Gen Fam Med. 2025;26(4):305-11.
25. Kazancioglu S, Bastug A, Ozbay BO, Tezcan H, Buyuktarakci C, Akbay A, Bodur H. The usefulness of hematological parameters and cerebrospinal fluid indexes in the differential diagnosis of acute bacterial from viral meningitis. Diagn Microbiol Infect Dis. 2023;107(1):116005.
26. van de Beek D, Brouwer MC, Koedel U, Wall EC. Community-acquired bacterial meningitis. Lancet. 2021;398(10306):1171-83.
27. Singh S, Mahto K, Kumar A, Kumar P, Kumar S, Prasad MK. Diagnostic Test Accuracy of Serum and Cerebrospinal Fluid C-Reactive Protein in Bacterial Meningitis: A Systematic Review and Meta-Analysis. Infect Chemother. 2025;57(2):248-60.
28. Sanaei Dashti A, Alizadeh S, Karimi A, Khalifeh M, Shoja SA. Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: A cross-sectional study. Medicine (Baltimore). 2017;96(35):e7637.
29. Efthimiou O, Seo M, Chalkou K, Debray T, Egger M, Salanti G. Developing clinical prediction models: a step-by-step guide. BMJ. 2024;386:e078276.