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A new adjunct in the differentiation of encephalitis and meningitis after negative cerebrospinal fluid culture: systemic inflammatory immune index

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ABSTRACT

Objectives: Encephalitis and meningitis can have serious and potentially life-threatening consequences. This study aims to investigate whether the effects of systemic immune inflammation index (SII) and neutrophil/lymphocyte (N/L) ratio on differential diagnosis, severity, and clinical outcomes are superior to each other in patients diagnosed with encephalitis and meningitis in the emergency department.

Methods: Patients aged 18 years and older who presented to the adult emergency department of the hospital and were diagnosed with meningitis or encephalitis between January and December 2022 were included in the study. Patients under 18 and those with missing data in their files were excluded from the study. N/L ratio, SII values, and other associated parameters were compared between the group with mortality and the group who survived both diseases.

Results: There were significant differences in neutrophil, lymphocyte, N/L ratio, SII, and C-reactive protein (CRP) values between meningitis and encephalitis patients. N/L ratio and SII values were significantly lower in encephalitis patients than in meningitis patients. There was no significant difference in any of the parameters between surviving and deceased patients.

Conclusions: Simple calculable ratios such as SII and N/L ratio can be a supportive parameter in the differential diagnosis of the disease. However, it has been observed that using these indices is not a useful tool in determining the severity and prognosis of patients with encephalitis and meningitis.

Keywords: Systemic inflammatory immune index, neutrophil-lymphocyte ratio, encephalitis, meningitis

Encephalitis and meningitis are infectious diseases that can cause severe and potentially life-threatening outcomes for the central nervous system [1, 2]. Early diagnosis and treatment can reduce the risk of death and the likelihood of long-term neurological complications [2, 3]. Recognition of symptoms, physical examination, and relevant laboratory tests are important for rapid diagnosis. Cerebrospinal fluid (CSF) analysis, CSF culture, polymerase chain reaction (PCR) tests, and other imaging techniques can also be

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used to confirm the diagnosis [2, 4].

The neutrophil/lymphocyte (N/L) ratio indicates the inflammatory response [5]. In central nervous system infections such as meningitis and encephalitis, the N/L ratio can provide valuable information about the severity and prognosis of the disease. Studies have shown that the N/L ratio is effective in diagnosing and determining the prognosis of infectious diseases such as meningitis and encephalitis [6, 7]. A high N/L ratio indicates an increase in the severity of infection and a worsening prognosis [5].

The systemic immune-inflammation index (SII) is commonly used in many infectious and non-infectious diseases, such as cancer [8, 9]. It is calculated using the formula 'SII = P × N/L' based on the complete blood count N, L, and platelet (P) counts [9]. SII has been reported to play an important role in the early diagnosis of diseases and in providing valuable information about the severity and prognosis of infections [9-11]. In cases where the lumbar puncture is contraindicated or unsuccessful, decision-making for patient management can be difficult for clinicians.

This study investigates the impact of the SII and N/L ratio on early differential diagnosis and prognosis in patients diagnosed with encephalitis and meningitis in the emergency department. This study aims to determine whether SII and N/L ratios are superior to each other in the differential diagnosis, severity, and clinical outcomes of meningitis and encephalitis cases.

METHODS

Study Design and Setting

This study was a single-center retrospective cross-sectional study conducted in the emergency medicine clinic of a tertiary care hospital located in a metropolitan area with an approximate population of 4.5 million. The study received approval from the Izmir Katip Celebi University Non-Interventional Clinical Research Ethics Committee (Decision No: 0012, Date: 26.01.2023).

Study Population

Patients aged 18 years and older who presented to the adult emergency department of the hospital and were diagnosed with meningitis or encephalitis between 01 January 2022 and 31 December 2022 were included in the study. Patients under 18 and those with missing data in their files were excluded from the study.

Data Collection and Processing

The participants were divided into two groups according to their diagnoses of meningitis and encephalitis. Demographic characteristics (age and gender), initial laboratory test results including neutrophil, lymphocyte, and platelet counts, as well as the calculated N/L ratio and SII, C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, sodium, potassium, pH, lactate, bicarbonate values from arterial blood gas analysis, bacterial growth in CSF culture, patients' level of consciousness at the initial examination (alert, confused, comatose), clinical diagnosis (meningitis, encephalitis), hospital admission or intensive care unit (ICU) admission status, and patient outcomes were recorded from the medical records.

Outcome Measures

To determine the superiority of the N/L ratio and SII values in differential diagnosing meningitis and encephalitis. On the other hand, to predict the severity and clinical outcomes of the disease, these parameters were compared with other variables that could be associated with disease severity and clinical outcomes. Additionally, the N/L ratio, SII values, and other as-

Table 1. Demographic distribution of the cases included in the study

	Meningitis	Encephalitis	*p* value
Age (years)	62 ± 18	58 ± 19	0.283
Gender, n (%)			0.069
Female	11 (30.6)	32 (49.2)	
Male	25 (69.4)	33 (50.8)	

Data are shown as mean ± standard deviation or n (%)

sociated parameters were compared between the group with mortality and the group who survived both diseases.

Statistical Analysis

Data obtained in the study were analyzed using IBM SPSS Statistics for Macos, Version 26.0. Armonk, NY: IBM Corp. Categorical variables were expressed as numbers and percentages, while numerical variables were expressed as mean and standard deviation when presenting the descriptive statistics. Shapiro-Wilk test was used as the normality test. Since the data did not follow a normal distribution, the Mann-Whitney U test was used to compare two group means. The chi-square test was used for comparisons of categorical variables. A p - value of < 0.05 was considered statistically significant. Results were presented with a 95% confidence interval.

RESULTS

Of the 101 included cases, 65.4% were diagnosed with encephalitis. When examining the gender distribution, 69.4% of meningitis patients were male, and 30.6% were female. In contrast, 50.8% of encephalitis patients were male, and 49.2% were female. There was no significant difference in gender distribution (p = 0.069) (Table 1).

The laboratory values and SII, N/L ratio of the cases included in the study are presented in Table 2. There were significant differences in neutrophil, lymphocyte, N/L ratio, SII, and CRP values between the meningitis and encephalitis groups. Neutrophil and CRP levels were significantly higher in the meningitis group compared to the encephalitis group (respectively 14.4 ± 9.1 vs. 9.9 ± 5.3, p = 0.012, 81 ± 92 vs. 45 ± 69, p = 0.008). Lymphocyte levels were significantly higher in the encephalitis group compared to the meningitis group (1 ± 0.6 vs. 1.6 ± 2.1, p = 0.014). N/L ratio and SII values were also significantly lower in the encephalitis group compared to the meningitis group (N/L ratio: 10.6 ± 12.1 vs. 20.4 ± 21.7, p = 0.002; SII: 2749 ± 4101 vs. 5557 ± 7712, p = 0.015). Other laboratory values (platelet, BUN, creatinine, sodium, potassium, pH, lactate, bicarbonate) did not show significant differences between meningitis and encephalitis groups.

Table 3 compares clinical characteristics such as level of consciousness, CSF culture results, and outcomes of the cases included in the study. There was no significant difference in the level of consciousness

Table 2. Laboratory values and SII, N/L ratio of the cases included in the study

	Meningitis	Encephalitis	*p* value
Neutrophil (×10³/µL)	14.4 ± 9.1	9.9 ± 5.3	**0.012**
Lymphocyte (×10³/µL)	1 ± 0.6	1.6 ± 2.1	**0.014**
Platelet (×10³/µL)	242 ± 95	247 ± 82	0.645
N/L Ratio	20.4 ± 21.7	10.6 ± 12.1	**0.002**
SII	5557 ± 7712	2749 ± 4101	**0.015**
CRP (mg/dL)	81 ± 92	45 ± 69	**0.008**
BUN (mg/dL)	23 ± 19	22 ± 12	0.480
Creatinine (mg/dL)	1.43 ± 1.64	1.22 ± 0.7	0.826
Sodium (mEq/L)	136 ± 7	136 ± 8	0.997
Potassium (Eq/L)	4 ± 0.8	4.1 ± 0.6	0.801
pH	7.39 ± 0.09	7.40 ± 0.09	0.790
Lactate (mmol/L)	2.5 ± 2.9	2.2 ± 2.5	0.812
Bicarbonate (mEq/L)	24.1 ± 4.6	24.9 ± 4.4	0.554

Data are shown as mean±standard deviation. SII = Systemic immune-inflammation index, N/L = neutrophil/lymphocyte, CRP = C-reactive protein, BUN = Blood urea nitrogen

Table 3. Consciousness, CSF culture results, and outcome patterns of the cases included in the study

	Meningitis	Encephalitis	*p* value
State of consciousness, n (%)			0.699
Alert	17 (47.2)	24 (36.9)	
Confused	15 (41.7)	32 (49.2)	
Closed	4 (11.1)	9 (13.8)	
Bacterial CSF culture, n (%)			**< 0.001**
Positive	24 (66.7)	8 (12.3)	
Negative	12 (33.3)	57 (87.7)	
Hospital admission, n (%)			0.220
Service	25 (69.4)	34 (52.3)	
ICU	11 (30.6)	31 (47.7)	
Outcome, n (%)			0.947
Survive	29 (80.6)	52 (80)	
Exitus	7 (19.4)	13 (20)	

CSF = Cerebrospinal fluid, ICU = Intensive Care Unit

between meningitis and encephalitis cases ($p = 0.699$). However, there was a significant difference in bacterial CSF culture results ($p < 0.001$), with higher positive results in meningitis cases. There was no significant difference between hospital admission service and intensive care unit (ICU) admission ($p = 0.220$). Lastly, the survival rates were similarly high in meningitis and encephalitis cases (80.6% and 80%,

Table 4. Comparison of surviving and exitus cases included in the study

	Survive	Exitus	*p* value
Age (years)	61 ± 18	60 ± 19	0.919
Neutrophil (×10^3/µL)	11.2 ± 6.2	12.7 ± 10.3	0.905
Lymphocyte (×10^3/µL)	1.2 ± 0.7	2.1 ± 3.8	0.743
Platelet (×10^3/µL)	242 ± 81	256 ± 107	0.695
N/L Ratio	13.5 ± 13.6	16.1 ± 26.2	0.461
SII	3465 ± 4538	4907 ± 9348	0.633
CRP (mg/dL)	52 ± 72	79 ± 101	0.305
BUN (mg/dL)	21 ± 14	25 ± 17	0.461
Creatinine (mg/dL)	1.34 ± 1.21	1.13 ± 0.6	0.264
Sodium (mEq/L)	136 ± 8	135 ± 7	0.313
Potassium (mEq/L)	4.1 ± 0.7	3.8 ± 0.8	0.086
pH	7.40 ± 0.07	7.37 ± 0.151	0.453
Lactate (mmol/L)	2 ± 1.9	3.5 ± 4.4	0.403
Bicarbonate (mEq/L)	25.3 ± 3.7	22 ± 6.3	0.076

Data are shown as mean ± standard deviation. N/L = neutrophil/lymphocyte, SII = Systemic immune-inflammation index, CRP = C-reactive protein, BUN = Blood urea nitrogen

respectively, $p = 0.947$).

Table 4 compares the demographic and laboratory values of the survived cases and those with an exit. There were no statistically significant differences between the two groups regarding age, neutrophil, lymphocyte, platelet, N/L ratio, SII, CRP, BUN, creatinine, sodium, pH, and lactate values ($p > 0.05$). However, the two groups had no significant difference regarding potassium and bicarbonate values ($p = 0.086$ and $p = 0.076$, respectively).

DISCUSSION

Encephalitis and meningitis are serious infectious diseases of the central nervous system that require early diagnosis and treatment. Meningitis is caused by inflammation of the meninges (the brain membranes), while encephalitis is caused by direct inflammation of the brain tissue. Therefore, meningitis patients tend to have a higher level of inflammation [4].

In this study, the N/L ratio and SII values were higher in meningitis patients than in encephalitis patients. Similarly, although the N/L ratio and SII values of patients with an exit were higher than survivors, they did not reach statistical significance. When we look at the reasons for the high values in meningitis, it is associated with the higher inflammation seen in meningitis, inflammation of the brain membranes, and increased inflammatory cells in the affected area [1, 3]. The brain membranes act as a protective barrier, preventing inflammatory cells in the blood and other immune cells fighting the infection from entering the brain tissue. Therefore, it is more difficult for the bacteria or virus to penetrate the brain tissue, and if the blood-brain barrier falls, the inflammatory response is more severe.

In this study, it was observed that the rate of negative CSF culture was higher in encephalitis patients, with 87.7% of the patients having negative CSF cultures. In contrast, the positive CSF culture rate was higher in meningitis patients. These results indicate differences in CSF culture results between encephalitis and meningitis. In encephalitis, inflammation is generally limited to the brain tissue, and unlike meningitis, there is no infection in the cerebrospinal fluid (CSF) [2, 12]. Therefore, encephalitis is often associated with negative CSF culture.

On the other hand, in meningitis, the infection spreads directly to the CSF, and cultures are used to detect bacteria or viruses in the CSF. The positivity of CSF cultures is an important factor in diagnosing meningitis. However, there are also meningitis cases with negative CSF cultures associated with pathogens that cannot be detected by CSF cultures or incorrect culture collection or processing techniques [3, 4]. The difference in CSF culture results between encephalitis and meningitis and the possibility of negative CSF culture in meningitis infections directs the clinician to other supportive parameters in the differential diagnosis. Using SII and N/L ratios is a cost-effective and rapid parameter in this context. SII and N/L ratios may serve as supportive parameters in the differential diagnosis to validate false-positive or false-negative results in CSF examination. Additionally, they can be a valuable aid in diagnosing the disease in cases where the lumbar puncture is contraindicated or unsuccessful.

The inflammation caused by meningitis can lead to higher CRP levels due to increased bacterial load in the CSF [3, 4]. On the other hand, in encephalitis cases, as the main cause of inflammation is a viral infection, CRP levels are usually lower or within the normal range [2, 11]. In this study, CRP levels were significantly higher in meningitis than in encephalitis cases.

The demographic results indicate no significant difference in age and gender distribution between meningitis and encephalitis patients. This result is an expected finding and suggests that age and gender are evenly distributed for conditions where the blood-brain barrier is compromised [12]. Finding results compatible with the literature ensures the reliability of our study.

Limitations

Our study's retrospective and single-center nature is a major limitation, and therefore, the results cannot be generalized to the entire population. Another limitation of the study is the need for more consideration of the presence of neurological sequelae when evaluating disease severity and clinical outcomes.

CONCLUSION

Simple calculable ratios such as SII and N/L ratio can

be a supportive parameters in the differential diagnosis of the disease. Knowing SII and N/L ratios can help to start treatment early. However, using these indices is not useful in determining the severity and prognosis of patients with encephalitis and meningitis. However, these results need to be confirmed by further research.

Authors' Contribution

Study Conception: CA, ESB; Study Design: EK; Supervision: ESB, EK; Funding: N/A; Materials: OSÇ, CA; Data Collection and/or Processing: OSÇ, EK; Statistical Analysis and/or Data Interpretation: ESB; Literature Review: CA, EK; Manuscript Preparation: MGE, ESB and Critical Review: ESB.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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