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Hematologic parameters to predict negative cerebrospinal fluid examination results among neurologically intact patients who underwent lumbar puncture on suspicion of central nervous system infection

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Objective Cerebrospinal fluid (CSF) examination is mandatory whenever central nervous system (CNS) infection is suspected. However, pleocytosis is not detected in a substantial number of suspected patients who undergo CSF examination. This study aimed to identify parameters that can aid in predicting negative CSF examination results (defined as a white blood cell count of <5 cells/high-power field).

Methods The study included 101 neurologically intact patients who underwent lumbar puncture because of suspicion of CNS infection. Patients were divided into negative and positive CSF examination groups, and their initial blood tests were comparatively analyzed.

Results The negative group had a significantly higher proportion of neutrophils in white blood cells (81.5% vs. 75.8%, P=0.012), lower proportion of lymphocytes in white blood cells (9.3% vs. 16.7%, P=0.001), a higher neutrophil-to-lymphocyte ratio (9.1 vs. 4.4, P=0.001), a lower lymphocyte-to-monocyte ratio (1.6 vs. 2.4, P=0.008), and a higher C-reactive protein level (21.0 vs. 5.0 mg/L, P<0.001) than the positive group. In the receiver-operating characteristic analysis, neutrophil-to-lymphocyte ratio and C-reactive protein had an area under the curve of >0.7, and the best cutoff values were 6.0 (accuracy 70.3%) and 12.7 mg/L (accuracy 76.2%), respectively.

Conclusion The neutrophil-to-lymphocyte ratio ≥6 and C-reactive protein level ≥12.7 mg/L was significantly associated with negative CSF examination result.

Keywords Neutrophils; Neutrophil-to-lymphocyte ratio; C-reactive protein; Central nervous system infection

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Capsule Summary

What is already known

Blood tests have not been studied for their role in the prediction of cerebrospinal fluid examination results.

What is new in the current study

Neutrophil-to-lymphocyte ratios of ≥6 and C-reactive protein levels of ≥12.7 mg/L can reliably predict negative cerebrospinal fluid examination results.

INTRODUCTION

No single clinical feature or physical examination can reliably discriminate central nervous system (CNS) infections from other infectious diseases. Even among patients with bacterial meningitis, only about 44% of patients have all triad clinical features, namely fever, nuchal rigidity, and change in mental status.[1] In cases of aseptic meningitis, the clinical features are more indistinct than those in cases of bacterial meningitis, thus making aseptic meningitis much harder to differentially diagnose from other infectious diseases. Presently, cerebrospinal fluid (CSF) examination via lumbar puncture is the only diagnostic method available for diagnosing CNS infections.

Even though lumbar puncture is the standard procedure for diagnosing CNS infections, it is potentially an invasive procedure that may cause complications such as intramedullary hematoma, CSF leakage, headache exacerbation, and infections through the puncture site.[2] Not only can lumbar puncture result in complications but also may require procedural sedation if the patient is uncooperative. In addition, a lumbar puncture can be difficult or almost impossible if the patient has a narrow interspinal space. Moreover, a long postprocedural bed rest time means that the procedure should be performed only after careful consideration.

If a patient in the emergency department (ED) shows classical signs of CNS infection, such as nuchal rigidity or change in mental status, no room should be left for dissent in performing a prompt lumbar puncture. However, in mentally alert patients with complaints of acute-onset headache and fever without focal neurological deficits, physicians find it difficult to decide whether or not to perform a lumbar puncture.

When a neurologically intact patient complains of fever and headache, physicians usually carry out a thorough history taking and physical examination to infer the cause of the fever. If the cause of the fever (e.g., acute rhinitis, sinusitis, pharyngitis, laryngitis, pneumonia, cholecystitis or cholangitis, gastroenteritis, pyelonephritis, cellulitis, or tsutsugamushi) remains indeterminate after an initial history taking and physical examination, a lumbar puncture is usually considered to rule out the possibility of CNS infection. However, a considerable proportion of patients with fever and headache have negative results on CSF examination via lumbar puncture. This study aimed to identify blood test-related parameters that can aid in predicting CSF examination results among neurologically intact ED patients with complaints of acute-onset headache and fever.

METHODS

Study design

A retrospective, cross-sectional study was conducted after receiving approval from the institutional review board of Kangbuk Samsung Hospital. Hematologic and biochemical parameters were comparatively analyzed between the patients with positive and those with negative CSF examination results. Written informed consents were exempted by the institutional review board. To maintain anonymity, the patient's name, hospital number, date of birth, and social security number were deleted after assigning a serial number to each patient.

Selection of the patients

We first selected all subjects aged >19 years who received a lumbar puncture during study period (1 year, from October 2014 to September 2015) and excluded anyone who met the following exclusion criteria: (1) patients without evidence of fever (defined as a subjective febrile sensation, an ear temperature of >37.5°C, or fever within the last week); (2) patients with headache and fever who raised no objection about the necessity of a prompt lumbar puncture (seizure, decreased mental status, or altered mentation); (3) patients who underwent a CSF examination for purposes other than diagnosing an acute CNS infection (e.g., acute demyelinating disease, myelitis, neuritis, hydrocephalus, CNS syphilis, or metastases of malignant tumors); (4) patients with a known immunological deficiency state or hematologic disease; and (5) patients who had been transferred from another hospital. We then divided the remaining subjects into negative and posi-

tive CSF examination groups according to the results of their CSF examination via lumbar puncture.

Data collection and processing

The positive lumbar puncture group was defined as those with ≥5 white blood cells (WBCs)/high-power field in the last collected CSF sample. Cases where red blood cells (RBCs) were detected were corrected through the formula, "CSF WBC count–(CSF RBC count× blood leukocyte/blood RBC× 10^6)".[3]

A tympanic thermometer (Infrared Thermometer IRT 4520; Braun, Kaz Europe SA, Germany) was used to measure body temperature. Fever was defined in this study as a body temperature of ≥37.5℃.[4] The blood test results used in this study were the first blood tests obtained at the ED. The Unicel DxH 800 Cellular Analysis System (Beckman Coulter, Miami, FL, USA) was used for the complete blood cell count. Leukocytosis and leucopenia were defined as a WBC count of ≥9.8 (× 10^9)/L and a WBC count of <4.3 (× 10^9)/L, respectively, according to the reference values used in the laboratory medicine department of our hospital. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio were calculated by using the ratios of neutrophil count to lymphocyte count and platelet count to lymphocyte count, respectively. C-reactive protein (CRP) level was measured by using the cobas 8000 modular analyzer (Roche Diagnostics, Indianapolis, IN, USA), and the minimum reported value was 0.05 mg/dL. Procalcitonin level was measured by using a cobas e411 analyzer (Roche Diagnostics), and the minimum reported value was 0.05 mg/L. We conducted the study in accordance with the Declaration of Helsinki. In order to protect the privacy of the patients, we deleted their names and hospital numbers, and gave them separate serial numbers.[5,6]

Statistical analyses

The continuous variables did not have a normal distribution; thus, they were presented as medians and interquartile ranges, and the categorical variables were described as frequencies (%). We compared the continuous variables by using the Mann-Whitney test and the categorical variables by using the chi-square or Fisher exact test, according to the expected frequency. The blood test parameters that showed significant statistical differences between the two groups were analyzed by using the receiver-operating characteristic (ROC) analysis to verify their usefulness as predictors. After finding the best cutoff value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the cutoff value were calculated. We used the STATA ver. 13.0 (StataCorp., College Station, TX, USA) for our statistical analysis and based the statistical significance on a P-value of <0.05.

RESULTS

A lumbar puncture was performed in 212 patients from October 2014 to September 2015 in our ED. Of these patients, 111 were excluded. Among the excluded patients, 16 had no evidence of fever, 44 had decreased or altered mental status (seizure 3, sedative drug overdose 3, metabolic encephalopathy 10, encephalitis 15, cerebral infarction 8, brain abscess 2, and unknown cause 3), 37 underwent CSF examination for purposes other than diagnosis of an acute CNS infection (demyelinating disease 17, myelitis 7, neuritis 4, hydrocephalus 3, brain syphilis 1, and metastatic malignant tumor 5), 5 had a hematologic disease, 1 had acquired immunodeficiency syndrome, and 8 had been transferred from another hospital to our hospital. Finally, 101 alert and oriented patients with fever and acute headache were included in this study. All the subjects underwent a lumbar puncture in the ED, of whom 45 had positive CSF test results (CSF pleocytosis) and 56 had negative results (no CSF pleocytosis) (Fig. 1).

Comparison of blood test results between the negative and positive CSF examination groups

The blood test parameters that showed significant statistical differences between the two groups were the proportion of neutrophils in WBCs (%), the proportion of lymphocytes in WBCs (%), NLR, lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio, and CRP level. Compared with the positive CSF test group, the negative group had a significantly higher proportion of neutrophils in WBCs (81.5% vs. 75.8%, P=0.012), lower proportion of lymphocytes in WBCs (9.3% vs. 16.7%, P=0.001), higher

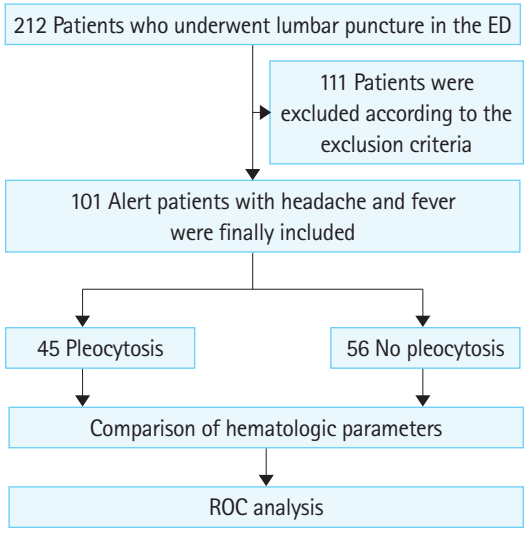

Fig. 1. Schematic diagram of the flow of the investigation and analysis. ED, emergency depertment; ROC, receiver operating characteristic.

NLR (9.1 vs. 4.4, P = 0.001), lower LMR (1.6 vs. 2.4, P = 0.008), and higher CRP level (21.0 vs. 5.0 mg/L, P < 0.001) (Table 1).

Usefulness of hematologic parameters in predicting negative CSF examination results

The area under the ROC curve was calculated for the blood test parameters that showed statistically significant differences between the two groups, in order to determine the predictability of CSF examination results. CRP level had the largest area under the curve (AUC, 0.77; 95% confidence interval [CI], 0.68 to 0.86), followed by the NLR (AUC, 0.70; 95% CI, 0.59 to 0.80). Other parameters had AUC of < 0.7, which indicate that they are less useful as predictors of CSF examination results.

The best cutoff NLR was 6.0 (Table 2). When we used 6.0 as a cutoff value, NLR had a sensitivity of 69.4%, a specificity of 71.1%, a PPV of 75.0%, and a NPV of 65.3% in predicting negative CSF examination results (Table 3).

The best cutoff CRP level was 12.7 mg/L (Table 2). A CRP level of ≥ 12.7 mg/L showed a sensitivity of 71.4%, a specificity of 82.2%, a PPV of 83.3%, and a NPV of 69.8% in predicting negative CSF examination results (Table 3).

Table 1. Comparison of hematologic parameters between the negative and positive CSF examination result groups

Parameters	Negative CSF (n = 56)	Positive CSF (n = 45)	P-value
Leukocyte count (× 10^9/L)			
Median (IQR)	9.6 (6.1–12.8)	8.8 (6.3–10.6)	0.483
≥ 9.8 (no. [%])	26 (46.4)	16 (35.6)	0.270
Neutrophil (%)	81.5 (74.1–87.6)	75.8 (66.2–81.9)	0.012*
Lymphocyte (%)	9.3 (7.2–15.7)	16.7 (11.2–21.8)	0.001*
Monocyte (%)	6.8 (4.7–9.7)	6.4 (4.6–9.0)	0.772
NLR	9.1 (5.1–13.3)	4.4 (3.0–7.3)	0.001*
LMR	1.6 (1.0–3.1)	2.4 (1.9–3.1)	0.008*
RDW (%)	13.2 (12.6–14.0)	12.9 (12.5–13.4)	0.205
Platelet count (× 10^9/L)	200 (156–253)	226 (193–262)	0.079
PLR	222 (161–341)	168 (132–227)	0.017*
Glucose (mmol/L)	1.1 (1.0–1.2)	1.2 (1.1–1.4)	0.287
C-reactive protein (mg/L)	21.0 (9.0–61.0)	5.0 (5.0–9.0)	< 0.001*
Procalcitonin[a] (mg/L)	0.69 (0.05–7.22)	0.07 (0.05–0.43)	0.177
No./total (no. [%])	18/56 (32)	10/45 (22)	

CSF, cerebrospinal fluid; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; RDW, red cell distribution width; PLR, platelet-to-lymphocyte ratio. *P < 0.05.
[a]Not available in all patients.

Table 2. ROC analysis of hematologic parameters associated with negative CSF examination result

Parameters	ROC area (95% CI)	Best cut off value	Sensitivity (%)	Specificity (%)	LR+	LR-
Neutrophil (%)	0.65 (0.54–0.76)	79.4	62.5	68.9	2.01	0.54
Lymphocyte (%)	0.32 (0.21–0.42)	18.1	25.0	60.0	0.63	1.25
NLR	0.70 (0.59–0.80)	6.0	69.4	71.1	2.41	0.43
LMR	0.35 (0.24–0.45)	3.0	26.8	73.3	1.01	1.00
PLR	0.64 (0.53–0.75)	207	57.1	68.9	1.84	0.62
CRP (mg/L)	0.77 (0.68–0.86)	12.7	71.4	82.2	4.02	0.35

ROC, receiver operating characteristic curve; CSF, cerebrospinal fluid; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein.

Table 3. Predictive value of hematologic parameters for negative cerebrospinal fluid examination result

Cut-off value	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	Odds ratio	P-value[a]
NLR ≥ 6	69.4	71.1	70.3	75.0	65.3	5.7	< 0.001
CRP ≥ 12.7 mg/L	71.4	82.2	76.2	83.3	69.8	11.6	< 0.001
Neutrophil[b] ≥ 79.4%	62.5	68.9	65.4	71.4	59.6	3.7	0.002
PLR ≥ 207	57.1	68.9	62.4	69.6	56.4	3.0	0.009

PPV, positive predictive value; NPV, negative predictive value; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio.
[a]P-value of chi-square. [b]Proportion (%) of neutrophils in white blood cells.

Analysis of patients with negative CSF examination results

In this study, 56 patients had negative CSF test results in spite of having both fever and acute headache. Of these patients, 20 had a fever of unknown origin and 36 had a presumptive diagnosis on discharge from the ED or hospitalization. The most common probable diagnosis was gastrointestinal infection in 15 patients (gastroenteritis 9, cholecystitis 3, cholangitis 2, and liver abscess 1), followed by respiratory infection in 13 patients (influenza 2, naso-pharyngitis 3, pneumonia 6, bronchitis 1, and sinusitis 1), suspected urogenital infection in 6 patients (prostatitis 1 and pyelonephritis 5), and soft tissue infection in 2 patients.

Analysis of patients with positive CSF examination results

In this study, 45 patients (44.6%) had positive CSF examination results (CSF pleocytosis) among the 101 patients with acute-onset headache and fever who underwent CSF examination via lumbar puncture. Thirty eight patients (38/45, 84.4%) had the typical CSF profile compatible with viral meningitis (lymphocyte dominant and CSF glucose level of ≥ 50 mg/dL). Three patients (3/45, 6.7%) had a CSF profile compatible with bacterial meningitis (polymorphonuclear dominant and CSF glucose level of < 50 mg/dL). Four patients (4/45, 8.9%) had polymorphonuclear dominance but a CSF glucose level of ≥ 50 mg/dL. All 45 patients with CSF pleocytosis were hospitalized. Aseptic meningitis was later diagnosed in 39 patients (presumed viral 34, zoster meningitis 3, and mumps meningitis 2); tuberculous meningitis in 1; intracranial abscess in 1; and presumed bacterial meningitis in 4.

DISCUSSION

In this study, we found that some of the initial ED blood tests among neurologically intact patients with fever and headache were significantly different between the negative and positive CSF examination result groups. Among the several hematologic parameters studied, only NLR and CRP level had an AUC of > 0.7 in the ROC analysis. Although not sufficient as predictors, a NLR of ≥ 6 showed a diagnostic accuracy of 70.3% and a CRP level of ≥ 12.7 mg/L showed a diagnostic accuracy of 76.2% in predicting negative CSF examination results. These results suggest that some blood test parameters (NLR in WBCs and CRP level) might be able to help clinicians in their collaborative effort in pursuing the focus of fever. If blood test results show a NLR of ≥ 6 or a CRP level of ≥ 12.7 mg/L, clinicians may anticipate a negative CSF examination result and consider not only CNS infection but also other sources of fever.

Thirty-six (64%) of the 56 patients who had a negative CSF examination result after a lumbar puncture had a presumptive diagnosis on discharge from the ED or hospitalization. The most frequent presumptive diagnosis was gastrointestinal infection, followed by respiratory and urogenital infections. These patients, even though their fever was not from a CNS infection, only had fever and headache without any other prominent symptoms such as diarrhea, vomiting, sputum, or dysuria, probably making it difficult to decipher the cause of the fever initially. If an alert patient with fever and headache has no positive physical signs of CNS infection and blood test results show a NLR of ≥ 6 or CRP level of ≥ 12.7 mg/L, not only CNS infection but also other causes of fever should be considered. For such patients, it would be advisable to repeat a thorough medical history taking and physical examination for gastrointestinal infections, and to consider other tests such as chest or sinus radiography, urinalysis, and chest or abdominal computed tomography while judiciously considering a lumbar puncture.

Neutrophils are important cells in the immune defense system that control mast cells, epithelial cells, and macrophages, and play a major role in the inflammatory response. Changes in NLR have been reported in bacterial or viral infections, or inflammatory responses and have been helpful in the early diagnosis of various diseases.[7-11] Various cutoff NLRs have been proposed for the diagnosis of acute infection or inflammation. In this study, the proportion of neutrophils in WBCs and the NLR were significantly higher in the patients with negative CSF examination results than in those with CSF pleocytosis. According to the ROC analysis, the proportion of neutrophils in WBCs and NLR demonstrated AUC of 0.65 and 0.70, respectively. Although not sufficient as a predictor, NLR may help clinicians anticipate negative CSF examination results and investigate sources of fever other than CNS infection.

Serum CRP level remarkably differed between the two groups, being significantly higher in the negative than in the positive CSF examination group. The best cutoff CRP level was 12.7 mg/L, and CRP levels of ≥ 12.7 mg/L had an AUC of 0.77, with 71.4% sensitivity and 82.2% specificity in predicting negative CSF examination results. CRP levels of ≥ 44.5 mg/L had 91.1% specificity, and CRP levels of ≥ 147.2 mg/L had 100% specificity. Not a single alert patient with CRP levels higher than 147.2 mg/L had CSF pleocytosis. If an alert patient with fever and headache has a high CRP level, causes of infection other than CNS should also be suspected and investigated, even in neurologically intact patients.

In respiratory viral infections such as influenza, most of the patients have relative lymphocytopenia and monocytosis,[12-16] and a LMR of < 2 has been suggested as a reliable screening method instead of the rapid antigen test for the diagnosis of influenza.[12,17]

Considering our study results and other previous research findings, we identified interesting facts about the lymphocyte and monocyte ratio in WBCs. Considering the fact that the final diagnosis of most patients with a positive CSF examination result was aseptic meningitis (40/45, 89%), in case of CNS viral infection, the proportion of lymphocytes in WBCs seems to increase and therefore result in an increased LMR. However, in cases of respiratory viral infections, the proportion of monocytes in WBCs increased and therefore resulted in a LMR of <2. We do not understand why no monocytosis was found in the CNS viral infections unlike in the respiratory viral infections, and it is beyond the scope of this study to delineate its immunologic mechanism.

The typical symptoms of CNS infections (headache, decreased or altered mental status, fever, photophobia, and nausea) are not pathognomonic symptoms that occur only in CNS infections.[18,19] In addition, according to the study by Nakao et al.,[20] the Jolt accentuation test has a sensitivity of 21% and specificity of 82%, the Kernig test has a sensitivity of 2% and specificity of 97%, the Brudzinski sign has a sensitivity of 2% and specificity of 98%, and the nuchal rigidity has a sensitivity of 13% and specificity of 80% to detect CSF pleocytosis. When the authors performed a statistical analysis to test the ability of the hematologic parameters in predicting positive CSF examination results, none of the parameters had an AUC of >0.7 in the ROC analysis. However, the proportion of lymphocytes in WBCs of $>14.3\%$ had an accuracy of 70.3% (sensitivity 68.9%, specificity 71.4%, PPV 66.0%, NPV 74.1%, and AUC 0.69), and a LMR of >1.7 had an accuracy of 70.3% (sensitivity 84.4%, specificity 51.8%, PPV 58.5%, NPV 80.6%, and AUC 0.63) in predicting a positive CSF examination result. These results suggest that the proportion of lymphocytes in WBCs and LMR are not sufficient but are more reliable than clinical symptoms or physical examination in predicting the possibility of CSF infection. However, as no symptom or physical examination or blood test has sufficient sensitivity and NPV to predict a CNS infection,[20] a CSF examination is always necessary whenever a clinician cannot exclude the possibility of a CNS infection.

Our study has several limitations. First, because we selected our patients through a retrospective review of the medical records for alert patients with fever and headache, an unintended selection bias might have existed. Second, sometimes physical examination was not performed or documented in the medical record, and we could not rely on the physical examinations performed by different physicians. Thus, we had to exclude physical examinations for CNS infections in this study. Third, in 36% of patients who had a fever, headache, and negative CSF examination result, we were not able to either presume or confirm a diagnosis, which meant that we were not able to fully analyze the negative CSF test group. Lastly, the actual infectious agents were not identified in the positive CSF examination group.

Among the neurologically intact adult patients who underwent a CSF examination on suspicion of CNS infection, those with negative CSF examination results had a significantly higher proportion of neutrophils in WBCs, lower proportion of lymphocytes in WBCs, higher NLR, lower LMR, and higher CRP level than the positive group. If this subset of patients has a NLR of ≥ 6 or CRP level of ≥ 12.7 mg/L in their blood test, not only CNS infection but also other sources of fever should be considered and investigated.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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