

The Potential for Improving the Diagnostics of Nosocomial Meningitis and Ventriculitis

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Summary

The aim of the study was to identify the most specific and sensitive criteria for diagnosing nosocomial meningitis and ventriculitis.

Materials and methods. A retrospective case-control cohort study conducted at the department of anesthesiology and intensive care of the A. L. Polenov Russian Research Neurosurgical Institute (RRNI), a branch of the V. A. Almazov National Medical Research Center (NMRC) of the Ministry of Health of Russia included 120 patients who underwent intracranial neurosurgery: the main group ($N=60$) — patients with nosocomial meningitis (NM), and the comparison group ($N=60$) — patients without NM. Inclusion criteria: age over 18 years. Exclusion criteria: severe immunosuppressive condition (HIV infection), signs of central nervous system (CNS) infection (meningitis, ventriculitis, brain abscess) on admission, extracranial surgical interventions, pre-operative cerebrospinal fluid leakage, CNS trauma, and extracranial causes of CNS infection. The US Centers for Disease Control and Prevention (CDC) and the Burdenko National Medical Research Center for Neurosurgery criteria for NM diagnosis were used in the study.

Results. External validation of the NM diagnostic criteria in the analyzed patient cohort resulted in 81.67% sensitivity and 83.33% specificity of the CDC criteria. Sensitivity and specificity of the Burdenko National Medical Research Center for Neurosurgery criteria were 81.67% and 88.33%, respectively, for probable NM, and 51.67% and 100%, for confirmed NM. The CDC criteria demonstrated the highest sensitivity for protein concentration in cerebrospinal fluid (CSF) > 0.33 g/L (83.6%), with simultaneous extremely low specificity of 21%, and the highest specificity for the CSF positive culture (100%). As for the Burdenko National Research Medical Center for Neurosurgery criteria, in probable NM the highest sensitivity was established for CSF cell count > 65 cells/ μ L (64.4%), and the highest specificity — for CSF glucose < 2.6 mmol/l (93.9%) and CSF/serum glucose ratio (CSF/SGLU) < 0.45 (96.8%). In confirmed NM, CSF cell count > 65 cells/ μ L was also the most sensitive parameter (95.2%), although with 51% specificity. The highest specificity was found for the CSF lactate > 4.2 mmol/L (92.3%). The optimal threshold values were calculated for four parameters: body temperature $> 37.7^\circ\text{C}$, CSF cell count > 245 cells/ μ L, CSF glucose < 2.0 mmol/L, and CSF lactate > 3.7 mmol/L. Using a combination of threshold values for all four parameters, we achieved a sensitivity of 90.00% and a specificity of 91.67%. CSF cell count (AUC=0.90; 95% CI 0.84–0.95), increased CSF lactate (AUC=0.85; 95% CI 0.75–0.93), total CSF protein (AUC=0.83; 95% CI 0.75–0.90) and body temperature (AUC=0.82; 95% CI 0.74–0.89) had the greatest diagnostic value. Positive CSF culture and the occipital muscle rigidity correlated with the diagnosis of NM ($r_{bp}=0.522$ and $r_{bp}=0.415$, respectively, $P=0.0001$), but did not show good predictive diagnostic capacity.

Conclusion. Fever, increase in CSF cell count and CSF lactate were identified as the most clinically significant signs of NM. A positive CSF culture traditionally used as the gold standard for diagnosis of NM showed low sensitivity of 69.2%. When taken together, the identified in the study threshold values of body temperature, CSF cell count, CSF glucose and lactate have a higher sensitivity and specificity than those used earlier.

Keywords: nosocomial meningitis; CNS infection; criteria for diagnosing nosocomial meningitis

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Nosocomial meningitis (NM) remains a life-threatening complication that increases the duration of hospital stay, causes disability, and leads to adverse outcomes. The incidence of NM among neurosurgical patients is 1.49%, and it increases to 8.4% in selective surgical interventions. The mortality rate for NM reaches 28.9% (up to 78.12% in ventriculitis, according to Corona-Nakamura A. L.), and the incidence of drainage-associated meningoventriculitis is 19.8%, or 18.3 cases per 1,000 days of drainage [1–8]. Timely diagnosis and initiation of antibiotic therapy improve the NM prognosis [9, 10].

NM probability is considered based on deviations in cerebrospinal fluid (CSF) analysis. In global clinical practice, management of ventriculitis and meningitis is based on the criteria of the Centers for Disease Control and Prevention (CDC) [11] and guidelines developed by the Infectious Diseases Society of America (IDSA) as proposed in 2017 [12].

According to the CDC criteria, the diagnosis of nosocomial meningitis is made if at least one of the following criteria is met:

1. CSF pathogen is isolated, either from CSF culture, or using other available microbiological tests.

2. The patient has at least two of the following clinical manifestations:

- fever $>38.0^{\circ}\text{C}$;
- headache;
- meningeal signs;
- signs of cranial nerve involvement;

And at least one of the following laboratory criteria:

- changes in CSF: increased leukocyte count with predominant neutrophils; increased protein concentration; decreased glucose concentration;
- serological confirmation of infection: diagnostic titer of specific IgM or a 4-fold increase in the titer of IgG antibody in paired sera.

N. N. Burdenko National Medical Research Center for Neurosurgery (NMRCN) NM diagnostic criteria (probable and confirmed) include assessment of patient's clinical status (cerebral, meningeal symptoms, fever), routine and biochemical CSF analyses, CSF cultures, hyponatremia. The N. N. Burdenko NMRCN criteria for probable NM include: a single episode of CSF cell count >65 cells/ μL , increased CSF lactate >4.2 mmol/l, decreased CSF glucose <2.6 mmol/l, CSF/serum glucose ratio (CSF/SGLU) <0.45 , or, in the absence of all above mentioned criteria, only a positive CSF culture. Additional criteria include fever $\geq 38^{\circ}\text{C}$ and plasma

sodium <135 mmol/l. NM is considered confirmed when CSF positive culture comes along with all pathological CSF tests [4].

However, as noted by N.V. Kurdyumova, clinical symptoms may not appear immediately that impedes early diagnosis [4].

Although CSF culture is considered the «gold standard», the results can be both false-positive and false-negative [13, 14]. Moreover, in 50% of cases bacteria are not detected in patients treated with antibiotics [15–17].

According to various sources, CSF leukocytosis in bacterial meningitis varies widely, from 11 cells/ mm^3 (according to the CDC) to 1,000 cells/ mm^3 [12].

The aim of the study was to determine the most specific and sensitive criteria for diagnosing nosocomial meningitis and ventriculitis.

Material and Methods

A retrospective case-control cohort study conducted at the department of anesthesiology and intensive care of A. L. Polenov Russian Research Neurosurgical Institute (RRNI), a branch of V. A. Almazov National Medical Research Center (NMRC) of the Russian Ministry of Health included 120 patients who underwent intracranial neurosurgery: the main group ($N=60$) — patients with nosocomial meningitis (NM), and the comparison group ($N=60$) — patients without NM.

Craniotomy or implantation of intracranial devices (shunts) was performed from January 2020 to January 2025.

Inclusion criteria: age over 18 years. Exclusion criteria: severe immunosuppressive condition (HIV infection), signs of central nervous system (CNS) infection (meningitis, ventriculitis, brain abscess) on admission, extracranial surgical interventions, pre-operative cerebrospinal fluid leakage, CNS trauma, and extracranial causes of CNS infection.

The following clinical features and laboratory findings were evaluated: patients' body temperature and meningeal symptoms; laboratory blood parameters, including RBC count, WBC count, concentrations of albumin and total protein; CSF parameters included cell count in 1 μL (lymphocytes, neutrophils, macrophages, plasma cells, monocytes, degenerated cells, granulocytes); RBC count, CSF glucose, protein, and lactate, CSF to serum glucose ratio (CSF/SGLU), CSF culture and microbiological examination. Presented CSF data were obtained from samples that were collected in the comparison group on the next day after surgery, and in the main group — on the day when meningitis was confirmed.

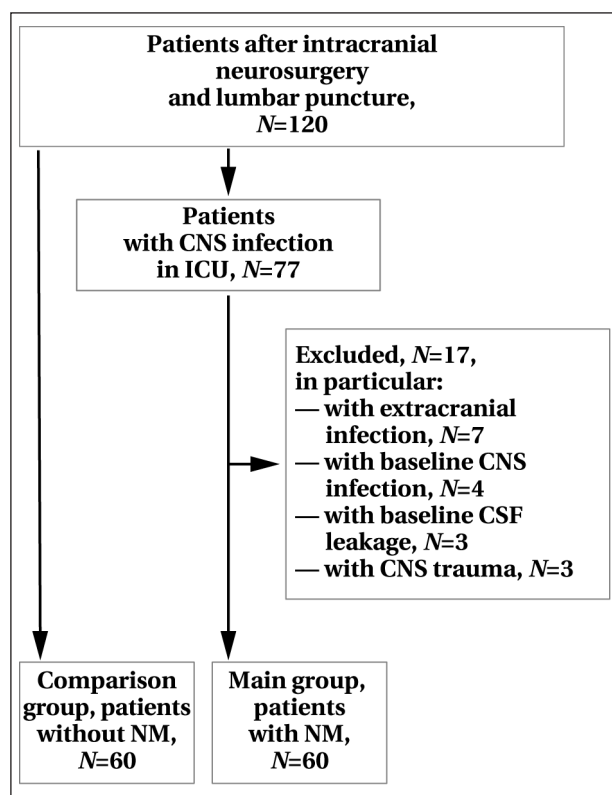


Fig. 1. Patient selection algorithm.

Notes. ICU — intensive care unit; NM — nosocomial meningitis.

The US Centers for Disease Control and Prevention (CDC) and N. N. Burdenko National Medical Research Center for Neurosurgery criteria for NM diagnosis were used in the study.

The diagnosis was based on the opinions of a neurosurgeon, an anesthesiologist-reanimatologist, and a clinical pharmacologist, following conclusions based primarily on CDC criteria. Surgical procedure in the comparison group was protected by peri-operative antimicrobial prophylaxis (lasting less than 24 hours), while in the main group, antibacterial therapy was administered in subjects with complications of extracranial infectious.

For statistical data processing, descriptive and analytical statistics were employed: the Shapiro–Wilk test was used to check the data distribution for normality and select the method for comparison of the studied groups. The t-test was used to estimate intergroup comparability for age, and the Pearson's chi-square test was employed for processing categorical variables. The standard two-sided test of significance was used with a critical threshold of $\alpha=0.05$. All comparisons, including sensitivity and specificity assessment of the features, AUROC and paired comparisons, were carried out with the assumption of a two-sided alternative hypothesis.

When calculating p-values, we used the built-in methods of Python statistical libraries, which are focused on classical two-sided testing. Collected data was used for determining sensitivity and speci-

ficity of a number of criteria. Statistical processing included correlation analysis with calculation of Spearman coefficients, point-biserial correlation, plotting of ROC curves with ROC AUC analysis, and estimation of optimal thresholds for a number of key parameters (body temperature, CSF cell count, glucose and lactate, CSF/SGLU). For determining the optimal cut-off points of a diagnostic feature, the Youden index was calculated as a summary measure of ROC analysis, using the formula:

$$J = \text{Sensitivity} + \text{Specificity} - 1.$$

The optimal threshold was determined as the point corresponding to the maximum value of the Youden index, which allowed for a balanced accounting of both sensitivity and specificity. When plotting ROC curves, we additionally calculated 95% confidence intervals (CIs) for the AUC using the DeLong algorithm; when the covariance matrix was unstable, we used bootstrapping (2000 iterations).

The following software and libraries were used for data processing: VS Code, Python programming language, and the following libraries: Pandas, NumPy, SciPy (Scipy.stats), Sklearn.metrics, and Matplotlib.pyplot.

Results

Assessment of samples representativeness showed no significant statistical differences in age ($P=0.947$) and gender ($P=1.000$) in the groups (Table 1).

The following calculated sensitivity and specificity values were obtained in the course of external validation of the CDC and N. N. Burdenko NMRCN criteria in the analyzed cohort of patients:

- CDC criteria: sensitivity — 81.67%, specificity — 83.33%;
- N. N. Burdenko NMRCN criteria:
 - probable NM: sensitivity — 81.67%, specificity — 88.33%;
 - confirmed NM: sensitivity — 51.67%, specificity — 100%.

Obtained results show that the highest diagnostic accuracy is achieved when using the N. N. Burdenko NMRCN criteria for probable NM. Meanwhile, the criteria for confirmed NM feature high specificity but low sensitivity.

Individual criteria sensitivity and specificity analysis. Sensitivity and specificity were calculated for criteria from the CDC and N. N. Burdenko NMRCN systems (Table 2).

In CDC criteria, the highest sensitivity was found for CSF protein concentration of >0.33 g/L (83.6%), although with extremely low specificity of 21%, and the highest specificity was found for CSF culture (100%).

In N. N. Burdenko NMRCN criteria for probable NM, the highest sensitivity was found for CSF cytosis

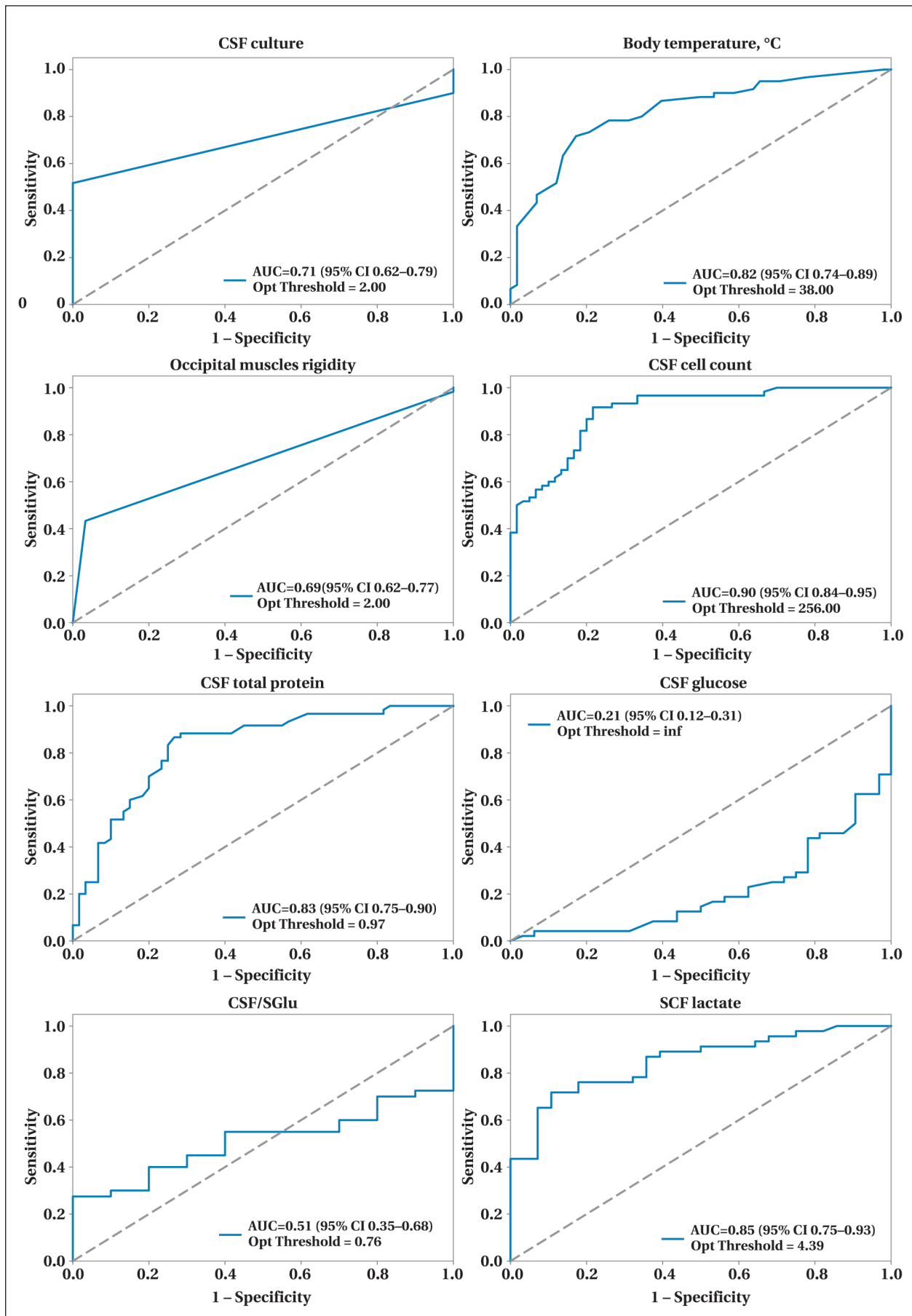


Fig. 2. ROC analysis of NM diagnostic criteria.

Table 2. Sensitivity and specificity of some diagnostic criteria.

Diagnostic criteria	Criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
CDC criteria	Positive CSF culture	69.2	100.0	79.6
	Body temperature >38°C	20.5	96.8	46.3
	Rigidity of the occipital muscles	53.6	92.6	66.8
	CSF cell count > 4 c/μl + > 50% of neutrophils	27.5	58.2	37.9
	CSF protein > 0.33 g/l	83.6	21.5	62.6
	CSF glucose < 2.8 mmol/l	34.4	91.0	53.5
N. N. Burdenko NMRCN criteria for probable NM	Body temperature >38°C	20.5	96.8	46.3
	Rigidity of the occipital muscles	53.6	92.6	66.8
	CSF cell count > 65	64.4	65.6	64.8
	CSF glucose < 2.6 mmol/l	29.5	93.9	51.2
	CSF/SGLu ≤ 0.45	29.2	96.8	52.0
	CSF lactate > 4.2 mmol/l	35.7	95.2	55.8
N. N. Burdenko NMRCN criteria for confirmed NM	Positive CSF culture	69.2	100.0	79.6
	Body temperature >38°C	20.5	96.8	46.3
	Rigidity of the occipital muscles	53.6	92.6	66.8
	CSF cell count > 65	95.2	51.1	80.3
	CSF glucose < 2.6 mmol/l	60.3	81.7	67.5
	CSF/SGLu ≤ 0.45	61.3	90.4	71.1
	CSF lactate > 4.2 mmol/l	67.7	92.3	76.0

> 65 cells/μL (64.4%), and the highest specificity — for CSF glucose < 2.6 mmol/L (93.9%) and CSF/SGLU < 0.45 (96.8%). For confirmed NM, the maximum sensitivity was established for CSF cytositis > 65 cells/μL — 95.2%, although with 51% specificity. The highest specificity (92.3%) was found for CSF lactate > 4.2 mmol/L.

ROC-analysis. The selected cut-off points were used to compare different NM diagnostic criteria, and were not used for clinical stratification of patients.

The plotted ROC curves are presented in Fig. 2.

To assess the accuracy of the diagnostic criteria, the AUC 95% CI was calculated. The increases in CSF cytositis (AUC=0.9; 95% CI 0.84–0.95), CSF lactate (AUC=0.85; 95% CI 0.75–0.93), CSF total protein (AUC=0.83; 95% CI 0.75–0.9), and body temperature (AUC=0.82; 95% CI 0.74–0.89) showed good diagnostic value, while diagnostic value of CSF culture (AUC=0.85; 95% CI 0.75–0.93) was satisfactory. The presence of occipital muscle rigidity (AUC=0.69; 95% CI 0.66–0.79) showed a low diagnostic value. The predictive diagnostic ability of CSF glucose concentration and CSF/SGLU ratio (AUC=0.35–0.37; 95% CI included values < 0.50) was low.

The AUC values are presented in Table 3.

Correlation analysis. The correlation matrix revealed statistically significant relationships between particular laboratory and clinical parameters (Fig. 3).

The following parameters demonstrated the highest positive point-biserial correlation with the presence of NM:

- Positive CSF culture ($rpb=0.522$);
- Occipital muscles rigidity ($rpb=0.415$);
- Increased body temperature ($rpb=0.415$);
- Elevated CSF lactate ($rpb=0.329$);
- Increased CSF neutrophils count ($rpb=0.249$).

A reverse point-biserial correlation was found, in particular, for the CSF/SGLU ratio ($rpb=-0.132$) and CSF lymphocyte count ($rpb=-0.242$) (Table 4).

Therefore, the most clinically significant signs of NM were: increased CSF cytositis, increased concentrations of CSF lactate and CSF total protein, and fever.

Selection of NM predictor values. In the course of correction analysis, the thresholds of key laboratory and clinical signs included in the N. N. Burdenko NMRCN diagnostic criteria were optimized. Due to insufficient sensitivity and specificity of some initial criteria, the optimal threshold values for body temperature, CSF cytositis, CSF glucose and lactate were calculated using selection on a grid of values (Grid-search) method. The following optimal criteria were obtained:

- temperature > 37.7°C;
- CSF cell count > 245 cells/μL;
- CSF glucose < 2.0 mmol/L;
- CSF lactate > 3, mmol/L.

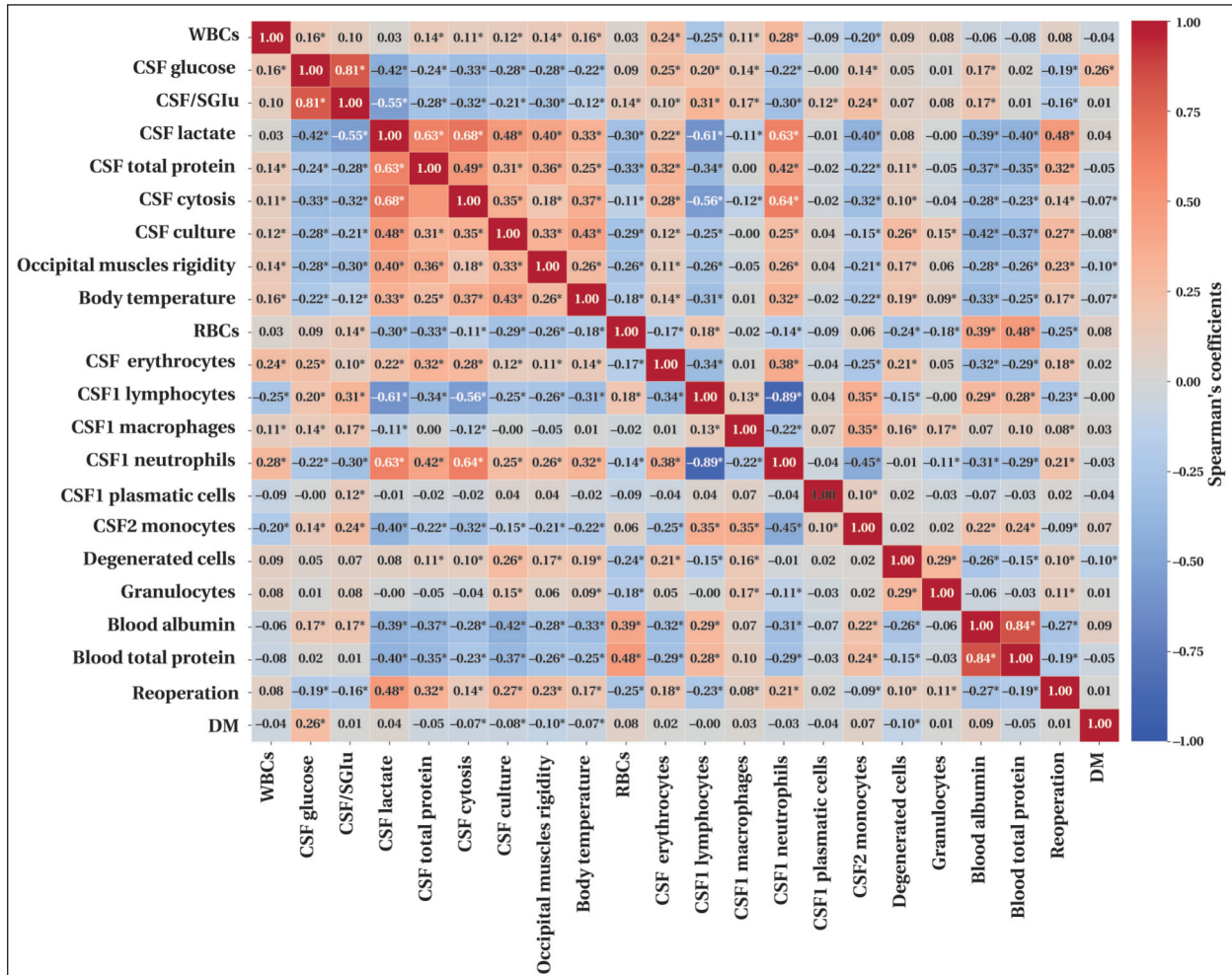
Using a combination of thresholds of all four parameters within the criteria allowed us to achieve: sensitivity: 90.00% (54 out of 60 patients with NM met the established optimal criteria), specificity: 91.67% (5 out of 60 patients without NM did not meet these criteria).

Discussion

The difficulties in diagnosing NM are due to many factors, including emergence of reactive CSF changes after intracranial surgery, the so-called «aseptic meningitis», presence of ICU specific microbial flora, recognized as the most common cause of NM, and interference of pre-analytical factors [17]. Relying on positive CSF culture — the gold standard for diagnosis — for verification of NM is not always

Table 3. Roc AUC analysis of some NM predictors.

Criteria	AUC	AUC 95% CI	AUC evaluation	Optimal value
Increased CSF cell count	0.90	0.84–0.95	Good	256
CSF lactate	0.85	0.75–0.93	Good	4.39
Total CSF protein	0.83	0.75–0.9	Good	0.97
Body temperature >38°C	0.82	0.74–0.89	Good	38
CSF culture	0.71	0.62–0.79	Satisfactory	Positive
Occipital muscle rigidity	0.69	0.62–0.77	Weak	Positive

**Fig. 3. Correlation matrix of clinical and laboratory parameters.**

Note. Spearman's coefficients; * — $P < 0.05$.

possible, as the condition necessitates initiation of antibiotic therapy within a limited timeframe, and because the culture growth can be suppressed by preceding antibiotic therapy or antibiotic prophylaxis [19]. These factors have led researchers to explore new ways to improve the diagnosis of NM.

Currently, the main indicators that should be considered in NM diagnosis have been identified, but their significance and diagnostic thresholds have not yet been definitively established [20]. According to our study, CSF cytos and lactate showed the highest sensitivity among the laboratory data. In the absence of infection in the postoperative period, the interpretation of these parameters was complicated by a wide range of values. Different

«cut-off points» for the diagnosis of NM have been described in available publications, ranging from 3.45 to 6 mmol/L for lactate concentration and from 4 to 1000 cells/ μ L for cytos [21–25].

Good diagnostic significance was established for fever among clinical symptoms, and among laboratory findings — for increased CSF neutrophil count, CSF lactate and CSF total protein concentrations. Isolated decrease in CSF glucose and of CSF/SGlu ratio, traditionally used as markers of bacterial inflammation in the CNS, did not show statistical significance. It is possible that these deviations occurred because of glucose consumption by erythrocytes extravasated into cerebrospinal fluid. According to our observations, changes in

Table 4. Point-biserial correlation of clinical and laboratory parameters with the diagnosis of NM

Parameters	Point-biserial correlation coefficient rpb	P
CSF culture	0.522	0.0001
Occipital muscles rigidity	0.415	0.0001
Body temperature >38°C	0.415	0.0001
CSF lactate	0.329	0.0001
CSF neutrophil count	0.249	0.0001
Degenerated cell count	0.192	0.0001
WBCs	0.167	0.00030
CSF total protein	0.155	0.0001
CSF erythrocyte count	0.086	0.00982
Increased CSF cell count	0.079	0.01783
Re-operation	0.061	0.06503
CSF macrophage count	0.023	0.51205
Granulocyte count	-0.030	0.40659
CSF plasmatic cell count	-0.032	0.36858
Diabetes mellitus	-0.035	0.28835
CSF glucose	-0.055	0.17817
CSF/SGLU	-0.132	0.01007
CSF monocyte count	-0.143	0.00003
CSF lymphocyte count	-0.242	0.0001
Serum total protein	-0.250	0.00009
Serum albumin	-0.332	0.0001
RBCs	-0.347	0.0001

the glucose content of CSF in bacterial meningitis occur later than changes in other parameters.

High specificity of particular criteria (CSF culture, CSF/SGLU, and CSF lactate) allows to use them not only for confirmation, but also for ruling out the NM.

Study limitations. The study focused primarily on comparing diagnostic criteria rather than creating a definitive diagnostic model. Sensitivity, specificity, and AUROC were used for comparative analysis of existing clinical diagnostic thresholds rather than for determining new thresholds. Due to the limited number of patients, there was no objective method for selecting a comparison group. The sample size

is planned to be expanded. This study was a pilot project.

Conclusion

The most clinically significant signs of NM are: elevated CSF lactate and CSF total protein, increase in CSF cell count, and fever. The «gold standard» for NM diagnosis, a positive CSF culture, showed a low sensitivity of 69.2%. When used in combination, the identified in the study threshold values of body temperature, cerebrospinal fluid (CSF) pleocytosis, CSF glucose, and CSF lactate have higher sensitivity and specificity versus previously used individual criteria.

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