

脳神経外科術後の髄膜炎

(髄液所見による”細菌性”髄膜炎の鑑別に関する話題)

• 感染性

細菌、ウイルス、真菌、寄生虫、原生生物 …

• 非感染性

血液溶解産物、悪性腫瘍、骨片、インプラント

薬剤性、サルコイドーシス、SLE、Behcet病、類表皮嚢胞・類皮嚢胞 …

表 27 髄液所見からの主要髄膜炎、ウイルス脳炎の鑑別要点

各種髄膜炎	髄液所見				
	外観	圧 (側臥位) (mmH ₂ O)	細胞数 (/μL)	蛋白 (mg/dL)	糖 (血糖の 1/2 ~ 2/3) (mg/dL)
正常	水様透明	70 ~ 180	5 以下	15 ~ 45	50 ~ 80
細菌性髄膜炎	混濁, 化膿	200 ~ 600	200 以上 多核白血球	100 ~ 700	0 ~ 20
結核性髄膜炎	水様, 時にキサントクロミー	200 ~ 600	30 ~ 500 リンパ球, 単球	50 ~ 500	40 以下
真菌性髄膜炎	水様, 時にキサントクロミー	200 ~ 600	30 ~ 500 リンパ球, 単球	50 ~ 500	40 以下
ウイルス性またはマイコプラズマ性髄膜炎, 脳炎	水様 (時に日光微塵)	正常 ~ 300	30 ~ 300 リンパ球, 単球	50 ~ 100	50 ~ 80

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Predictive Value of Cerebrospinal Fluid (CSF) Lactate Level Versus CSF/Blood Glucose Ratio for the Diagnosis of Bacterial Meningitis Following Neurosurgery

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The value of cerebrospinal fluid (CSF) lactate level and CSF/blood glucose ratio for the identification of bacterial meningitis following neurosurgery was assessed in a retrospective study. During a 3-year period, 73 patients fulfilled the inclusion criteria and could be grouped by preset criteria in one of three categories: proven bacterial meningitis ($n = 12$), presumed bacterial meningitis ($n = 14$), and nonbacterial meningeal syndrome ($n = 47$). Of 73 patients analyzed, 45% were treated with antibiotics and 33% with steroids at the time of first lumbar puncture. CSF lactate values (cutoff, 4 mmol/L), in comparison with CSF/blood glucose ratios (cutoff, 0.4), were associated with higher sensitivity (0.88 vs. 0.77), specificity (0.98 vs. 0.87), and positive (0.96 vs. 0.77) and negative (0.94 vs. 0.87) predictive values. In conclusion, determination of the CSF lactate value is a quick, sensitive, and specific test to identify patients with bacterial meningitis after neurosurgery.

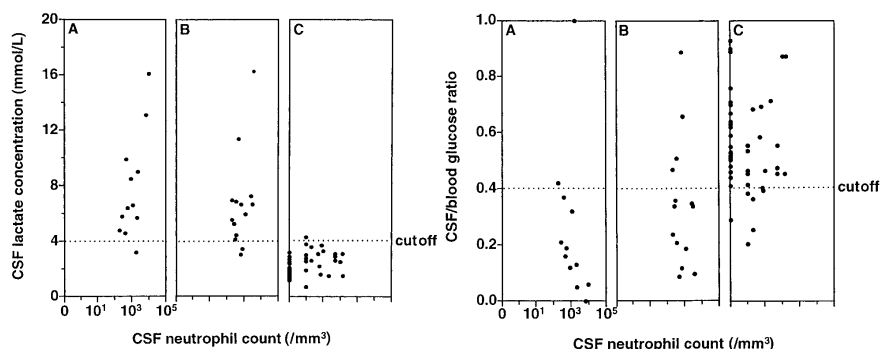
Table 2. Summary and predictive values of CSF lactate levels and CSF/blood glucose ratios in patients after neurosurgery.

Variable	CSF lactate level: mean \pm SD	CSF/blood glucose ratio: median (range)
Proven bacterial meningitis ($n = 12$)	7.8 \pm 3.6 mmol/L	0.17 (0-1)
Presumed bacterial meningitis ($n = 14$)	6.7 \pm 3.3 mmol/L*	0.34 (0.1-0.9) [†]
Nonbacterial meningitis syndrome ($n = 47$)	2.3 \pm 0.8 mmol/L	0.54 (0.9-0.2)
Sensitivity	88%	77%
Specificity	98%	87%
Positive predictive value	98%	77%
Negative predictive value	94%	87%

NOTE. Cutoff values were 4 mmol/L for lactate level and 0.4 for CSF/blood glucose ratio.

* $P =$ NS vs. proven bacterial meningitis; $P < .0001$ vs. nonbacterial meningitis syndrome.

[†] $P =$ NS vs. proven bacterial meningitis; $P < .0003$ vs. nonbacterial meningitis syndrome.



A: patients with proven bacterial meningitis
 B: patients with presumed bacterial meningitis
 C: patients with non-bacterial meningitis

Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: A meta-analysis[☆]

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Summary Objectives: Cerebrospinal fluid (CSF) lactate is produced by bacterial anaerobic metabolism and is not affected by blood lactate concentration, an advantage over CSF glucose in differentiating bacterial meningitis from aseptic meningitis. However, the previous investigations have shown mixed results of the sensitivity and specificity. Our study's purpose was to assess the utility of CSF lactate in differentiating bacterial meningitis from aseptic meningitis. **Methods:** We searched MEDLINE and EMBASE for clinical studies that included CSF lactate measurement in bacterial meningitis and aseptic meningitis. Test characteristics were pooled using hierarchical summary ROC curve and random effects model.

Results: Thirty three studies were included. The pooled test characteristics of CSF lactate were sensitivity 0.93 (95% CI: 0.89–0.96), specificity 0.96 (95% CI: 0.93–0.98), likelihood ratio positive 22.9 (95% CI: 12.6–41.9), likelihood ratio negative 0.07 (95% CI: 0.05–0.12), and diagnostic odds ratio 313 (95% CI: 141–698). Pretreatment with antibiotics lowered the sensitivity 0.49 (95% CI: 0.23–0.75). CSF lactate of around 35 mg/dl (34–36 mg/dl) had higher sensitivity and specificity than those of around 27 mg/dl (26–28 mg/dl).

Conclusions: CSF lactate's high negative likelihood ratio may make it useful for ruling out bacterial meningitis though pretreatment with antibiotics reduces clinical accuracy. CSF lactate of 35 mg/dl could be optimal cut-off value for distinguishing bacterial meningitis from aseptic meningitis.

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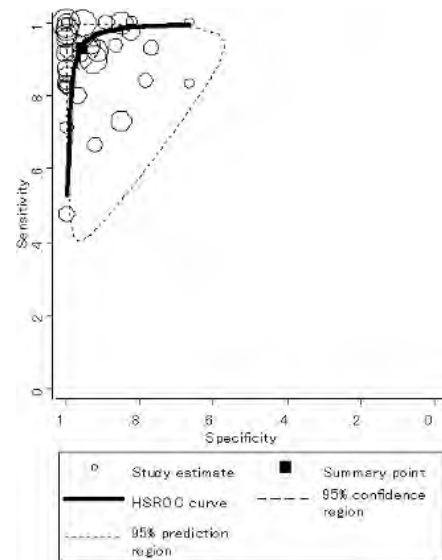


Figure 2 Hierarchical summary receiver operating characteristic (HSROC) curve of all included studies shows high sensitivity and specificity with small 95% confidence region.

	Sensitivity (95% CI)	Specificity (95% CI)
Overall analysis		
HSROC model	0.93 (0.89–0.96)	0.96 (0.93–0.98)
Random effect model	0.94 (0.92–0.96)	0.97 (0.96–0.99)
Subgroup analysis		
Bacteria proven BM ^a	0.96 (0.93–0.98)	0.97 (0.96–0.99)
Pretreated BM	0.49 (0.23–0.75)	NA ^b
Untreated BM	0.98 (0.96–1.00)	NA ^b
Cut off around 35 mg/dl	0.93 (0.89–0.97)	0.99 (0.97–1.00)
Cut off around 27 mg/dl	0.90 (0.85–0.94)	0.94 (0.90–0.98)

^a Bacterial meningitis proven by culture or gram stain.
^b Not available because of unabstractable data.

The diagnostic value of cerebrospinal fluid lactate for post-neurosurgical bacterial meningitis: a meta-analysis

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Abstract

Background: Bacterial meningitis is not rare in post-neurosurgical patients. If patients are not treated promptly, the mortality rate can reach 20 to 50 %. The concentration of cerebrospinal fluid (CSF) lactate has been reported to be helpful in the diagnosis of bacterial meningitis; however, no systematic evaluations have investigated CSF from a postoperative perspective. In this study, we performed a systematic evaluation and meta-analysis of the efficacy of using CSF lactate concentrations in the diagnosis of post-neurosurgical bacterial meningitis.

Method: We retrieved studies that investigated the diagnostic value of CSF lactate for the diagnosis of post-neurosurgical bacterial meningitis by searching PubMed, EBSCO, the Cochrane Library and ClinicalTrials.gov. All these databases were searched from inception to November 2015. We used Quality Assessment of Diagnostic Accuracy Studies (QUADAS), a tool for the quality assessment of diagnostic accuracy, to evaluate the quality of the included studies. The Meta-DiSc 1.4 and Review Manager 5.3 software programs were used to analyze the included studies. Forest plots and summary receiver operating characteristics (SROC) curves were also drawn.

Results: Five studies, involving a total of 404 post-neurosurgical patients, were selected from 1,672 articles according to the inclusion criteria. The quality of the five included studies was assessed using QUADAS, and the related results are presented in tables. The meta-analysis revealed the following diagnostic values regarding CSF lactate for post-neurosurgical bacterial meningitis: a pooled sensitivity of 0.92 (95 % CI 0.85–0.96), a pooled specificity of 0.88 (95 % CI 0.84–0.92 with significant heterogeneity), a diagnostic odds ratio of 83.09 (95 % CI 36.83–187.46), an area under the curve (AUC_{SROC}) of 0.9601, an SE(AUC) of 0.0122, a Q* of 0.9046 and an SE(Q*) of 0.0179.

Conclusion: The meta-analysis indicated that the CSF lactate concentration has relatively high sensitivity and specificity for the diagnosis of post-neurosurgical bacterial meningitis and thus has relatively good efficacy.

Keywords: Cerebrospinal fluid lactate, Post-neurosurgical bacterial meningitis, Diagnostic value, Meta-analysis

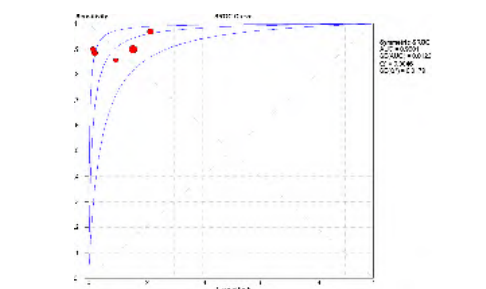


Fig. 5 SROC Curve. SROC curves were plotted. Each red point represent an included study. The AUC of the SROC curve was 0.9601, and the Q* was 0.9046. SROC: summary receiver operating characteristic; AUC: area under curve; Q*: the point on the SROC where sensitivity equals specificity.

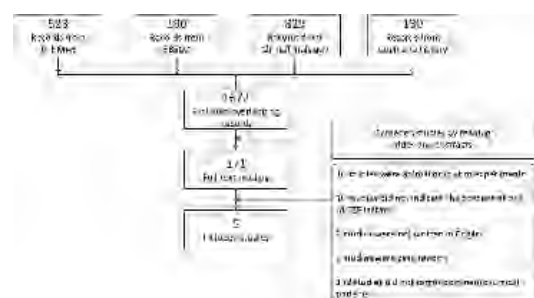


Fig. 1 Flow diagram of study screening and selection for inclusion. PRISMA flow diagram of our meta-analysis. A total of 523 studies were obtained from PubMed, 190 studies from EBSCO, 130 studies from the Cochrane Library, and 829 from ClinicalTrials.gov. After excluding overlapping literature, 1,672 studies were retrieved. We finally included 5 studies in this analysis according to the above inclusion and exclusion criteria.

Table 1 Studies included in this meta-analysis

Authors	Publication year	Type of study	Cut-off value (mmol/L)	Gold standard
Leib <i>et al.</i> [6]	1999	Retrospective	4.0	1) or 2) or 3): 1) positive bacterial CSF culture and CSF WBC > 2.5 × 10 ⁶ /L 2) CSF WBC > 1 × 10 ⁷ /L and neutrophils > 50 % 3) CSF WBC > 2.5 × 10 ⁷ /L and neutrophils > 50 % in patients treated with steroids or antibiotics at the time of LP
Tavares <i>et al.</i> [25]	2006	Prospective	5.4	positive bacterial CSF culture or Gram stain
Grille <i>et al.</i> [21]	2012	Prospective	5.2	1) or 2): 1) positive bacterial CSF culture or Gram stain 2) negative bacterial CSF culture or Gram stain and CSF WBC > 1 × 10 ⁹ /L (>50 % neutrophils) in patients treated with antibiotics at the time of lumbar puncture
Maskin <i>et al.</i> [22]	2013	Prospective	4.0	1) or 2): 1) positive bacterial CSF culture or Gram stain and CSF WBC ≥ 1 × 10 ⁵ /L or (CSF glucose < 40 mg/dL or CSF glucose/blood glucose < 0.4) 2) CSF WBC ≥ 2.5 × 10 ⁷ /L and CSF glucose/blood glucose < 0.5 if patients received antibiotics 24 h prior to CSF sampling
Li <i>et al.</i> [18]	2014	Retrospective	3.45	^a All of the below: 1) clinical symptoms 2) positive bacterial CSF culture or Gram stain 3) CSF WBC count ≥ 1 × 10 ⁹ /L and polykaryocyte percentage ≥ 75 % 4) CSF glucose < 2.5 mmol/L or CSF glucose/blood glucose < 0.4.

^a Patients who did not meet these criteria with a CSF WBC count < 5 × 10⁹/L were classified into the non-PNBM group

POLYMERASE CHAIN REACTION FOR THE RAPID DETECTION OF CEREBROSPINAL FLUID SHUNT OR VENTRICULOSTOMY INFECTIONS

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OBJECTIVE: Infection after cerebrospinal fluid (CSF) shunts or ventriculostomies is a common complication associated with significant morbidity and mortality. Polymerase chain reaction (PCR) is a powerful molecular technique that allows rapid and precise amplification of bacterial deoxyribonucleic acid (DNA) and has proven a powerful tool in the detection of a wide variety of clinically important infectious diseases. We analyzed specimens of CSF derived from ventriculoperitoneal shunts or external ventricular drains by using both conventional cultures and PCR and report herein our preliminary results.

METHODS: We selected 86 CSF samples from adult patients who underwent either shunt tap or routine surveillance cultures of their ventriculostomy. These specimens were chosen from a larger group of 300 specimens that were routinely collected (many serially) in our clinical practice. They were chosen because clinical suspicion of infection was increased because of either patient signs and symptoms (fever, stiff neck, lethargy, worsening neurological examination) or preliminary laboratory analysis of CSF data (increased white blood cell count, increased protein level, decreased glucose). We considered this subgroup optimal to efficiently initiate our investigation of the correlation of PCR and culture results. CSF was increased by using standard culture techniques and by using PCR. Samples of CSF that were to undergo PCR had DNA extracted, purified, and amplified for 16S rRNA using primers 16S-Forward and 16S-Reverse of conserved sequence regions of all bacteria. DNA was PCR-amplified for 30 cycles. One microliter of the first PCR product was subjected to nested PCR using primers specific for gram-positive and gram-negative bacteria. Samples were also subjected to PCR amplification for specific detection of *Propionibacterium acnes*, *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus* using specific primers for 16S rRNA *Propionibacterium*, nuclease gene of *Staphylococcus*, and *Mec* gene of methicillin-resistant *Staphylococcus aureus*.

RESULTS: For 18 of 86 specimens (21%), both the culture and PCR were positive. For 30 of 86 specimens (35%), both the PCR and culture results were negative. For 42 of 86 specimens (49%), cultures were negative and PCR was positive. There were no positive culture results with negative PCR results. Most negative culture/positive PCR cases occurred after prolonged intravenous antibiotics. Of the 56 PCR-positive specimens, 30 were positive for *Propionibacterium acnes*, whereas 40 were positive for *Staphylococcus aureus*. Of the *Staphylococcus aureus*-positive specimens, two were positive for methicillin resistant-*Staphylococcus aureus*. Among the 56 PCR-positive specimens, 30 were positive for both *Propionibacterium acnes* and *Staphylococcus aureus*; gram-negative organisms were not detected by any method in these specimens.

CONCLUSION: These preliminary data suggest that PCR is a highly sensitive, rapid, and potentially promising modality for the detection and treatment of CSF shunt ventriculostomy infection.

KEY WORDS: Cerebrospinal fluid, Complications, Diversion, Infection, Surgery, Tests

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TABLE 2. Distribution of patient samples^a

Grouping	No. of patients	Positive culture/ positive PCR	Negative culture/ positive PCR	Negative culture/ negative PCR	Total samples
Single sample/patient	11	1	4	6	11
No. of serial samples/patient					
2	6	2	4	6	12
3	4	2	5	5	12
4	3	5	4	2	12
>4	4	8	26	5	39
Total specimen results		18	43	24	86

^aPCR, polymerase chain reaction.

TABLE 3. Summary of PCR and culture correlation^a

	Positive	Negative
PCR (+)	18/86	43/86
PCR (-)	0/86	24/86

^aPCR, polymerase chain reaction.

Procalcitonin in cerebrospinal fluid in meningitis: a prospective diagnostic study

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TABLE 2 Results of cell counts, glucose, protein and PCT in CSF and PCT in plasma per group

	Bacterial meningitis (n = 26)	CAM (n = 16)	PNM (n = 10)	Viral meningitis (n = 14)	Non-infectious (n = 14)
CSF leukocyte count × 10 ⁶ per liter ave	5,998	7,551	3,514	267	1
Polynuclear cells × 10 ⁶ per liter ave	5,589	7,428	2,832	28	0.1
Mononuclear cells × 10 ⁶ per liter ave	616	576	677	239	0.7
Erythrocytes × 10 ⁶ per liter ave	23,649	12,892	408,597	180	287
CSF glucose mmol L ⁻¹ ave	1.6	1.0	2.6	3.5	3.4
CSF protein g L ⁻¹ ave	3.3	3.9	2.4	1	0.4
PCT in CSF ng mL ⁻¹ Average (95% CI)	0.61 (0.29–0.90)	0.81 (0.31–1.31)	0.29 (0.10–0.45)	0.10 (0.08–0.12)	0.08 (0.05–0.09)
PCT in plasma ng mL ⁻¹ Median (IQR)	0.5 (4.36)	1.28 (6.82)	0.05 (0.08)	0.02 (0.02)	–
PCT ratio CSF:plasma Median (IQR)	0.86 (2.79)	0.18 (0.27)	5.18 (4.69)	3.00 (1.38)	–
Mean difference PCT in CSF versus non infectious (95% CI)	0.74 ng mL ⁻¹ (0.20–1.28)	0.73 ng mL ⁻¹ (0.20–1.27)	0.21 ng mL ⁻¹ (0.05–0.37)	0.30 ng mL ⁻¹ (–0.001 to 0.05)	–
Mean difference PCT in CSF versus Viral meningitis (95% CI)	0.73 ng mL ⁻¹ (0.19–1.27)	0.71 ng mL ⁻¹ (0.18–1.25)	0.18 ng mL ⁻¹ (0.02–0.34)	–	–

CAM, community-acquired meningitis; PNM, postneurosurgical meningitis; CSF, cerebrospinal fluid; PCT, procalcitonin.

Abstract

Objectives: Bacterial meningitis is a severe but treatable condition. Clinical symptoms may be ambiguous and current diagnostics lack sensitivity and specificity, complicating diagnosis. Procalcitonin (PCT) is a protein that is elevated in serum in bacterial infection. We aimed to assess the value of PCT in cerebrospinal fluid (CSF) in the diagnosis of bacterial meningitis.

Methods: We included patients with bacterial meningitis, both community acquired and post neurosurgery. We included two comparison groups: patients with viral meningitis and patients who underwent lumbar punctures for noninfectious indications. We calculated mean differences and 95% confidence intervals of procalcitonin in CSF and plasma in patients with and without bacterial meningitis.

Results: Average PCT concentrations in CSF were 0.60 ng mL⁻¹ (95% CI: 0.29–0.92) in the bacterial meningitis group (n = 26), 0.81 (95% CI: 0.33–1.28) in community-acquired meningitis (n = 16) and 0.28 (95% CI: 0.10–0.45) in postneurosurgical meningitis (n = 10), 0.10 ng mL⁻¹ (95% CI: 0.08–0.12) in the viral meningitis group (n = 14) and 0.08 ng mL⁻¹ (95% CI: 0.06–0.09) in the noninfectious group (n = 14). Mean difference of PCT-CSF between patients with community-acquired bacterial meningitis and with viral meningitis was 0.71 ng mL⁻¹ (95% CI: 0.17–1.25) and 0.73 ng mL⁻¹ (95% CI: 0.19–1.27) for community-acquired bacterial meningitis versus the noninfectious group. The median PCT CSF: plasma ratio was 5.18 in postneurosurgical and 0.18 in community-acquired meningitis (IQR 4.69 vs. 0.28).

Conclusion: Procalcitonin in CSF was significantly higher in patients with bacterial meningitis when compared with patients with viral or no meningitis. PCT in CSF may be a valuable marker in diagnosing bacterial meningitis, and could become especially useful in patients after neurosurgery.

KEYWORDS

bacterial meningitis, cerebrospinal fluid, diagnostic marker, external ventricular drain, meningitis, neurosurgical intervention, procalcitonin

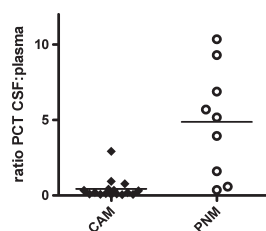


FIGURE 3 Scatter plots of procalcitonin plasma: cerebrospinal fluid ratio. Horizontal bar represents the mean value of a group, logarithmic scale

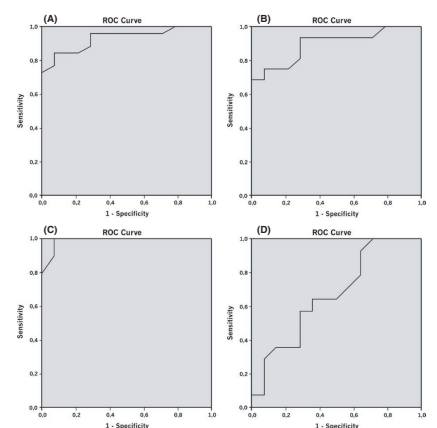


FIGURE 4 Receiver-operator curves for Procalcitonin in cerebrospinal fluid compared to noninfectious patients for (A) all bacterial meningitis patients, AUC 0.93, (B) community-acquired meningitis, AUC 0.90, (C) post-neurosurgical meningitis, AUC 0.98, (D) viral meningitis, AUC 0.67

Diagnostic accuracy of routine blood examinations and CSF lactate level for post-neurosurgical bacterial meningitis

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of routine blood examinations and Cerebrospinal Fluid (CSF) lactate level for Post-neurosurgical Bacterial Meningitis (PBM) at a large sample-size of post-neurosurgical patients.

Methods: The diagnostic accuracies of routine blood examinations and CSF lactate level to distinguish between PAM and PBM were evaluated with the values of the Area Under the Curve of the Receiver Operating Characteristic (AUC_{ROC}) by retrospectively analyzing the datasets of post-neurosurgical patients in the clinical information databases.

Results: The diagnostic accuracy of routine blood examinations was relatively low (AUC_{ROC} < 0.7). The CSF lactate level achieved rather high diagnostic accuracy (AUC_{ROC} = 0.891; CI 95%, 0.852–0.922). The variables of patient age, operation duration, surgical diagnosis and postoperative days (the interval days between the neurosurgery and examinations) were shown to affect the diagnostic accuracy of these examinations. The variables were integrated with routine blood examinations and CSF lactate level by Fisher discriminant analysis to improve their diagnostic accuracy. As a result, the diagnostic accuracy of blood examinations and CSF lactate level was significantly improved with an AUC_{ROC} value = 0.760 (CI 95%, 0.737–0.782) and 0.921 (CI 95%, 0.887–0.948) respectively.

Conclusions: The PBM diagnostic accuracy of routine blood examinations was relatively low, whereas the accuracy of CSF lactate level was high. Some variables that are involved in the incidence of PBM can also affect the diagnostic accuracy for PBM. Taking into account the effects of these variables significantly improves the diagnostic accuracies of routine blood examinations and CSF lactate level.

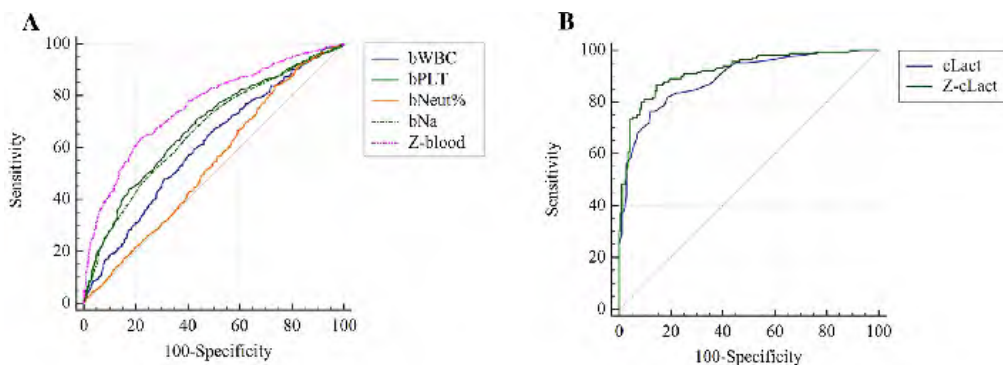
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Table 2

The AUC_{ROC} values, cut-off values and according sensitivities, specificities and Youden indices of blood examinations, CSF lactate and algorithms to diagnose PBM.

Examinations	PBM Diagnosis Accuracy AUC _{ROC} (CI 95%)	Cut-off values	Sensitivity (%)	Specificity (%)	Youden index
Blood WBC Counts (bWBC, 10 ⁹ /L)	0.607 (0.581–0.633)	>13.85	67.15	50.23	0.1738
Blood Neutrophil Proportions (bNeut%, %)	0.538 (0.511–0.564)	>81.1	83.82	26.38	0.1020
Blood Platelet Counts (bPLT, 10 ⁹ /L)	0.680 (0.655–0.704)	>247	71.48	56.11	0.2759
Blood Sodium Concentration (bNa, mmol/L)	0.668 (0.643–0.692)	<134	64.8	60.02	0.2482
CSF Lactate Level (cLact, mmol/L)	0.891 (0.852–0.922)	>3.6	76.36	87.79	0.6476
Algorithm 1 (Z-Blood)	0.760 (0.737–0.782)	>0.181	64.00	78.00	0.4200
Algorithm 2 (Z-cLact)	0.921 (0.887–0.948)	>−0.336	86.67	85.47	0.7213

The diagnostic accuracy of each examination was evaluated based on the AUC_{ROC} value. The diagnostic accuracy was classified as follows: 0.90 to 1.00 AUC_{ROC} value = excellent, 0.80 to 0.89 = good, 0.70 to 0.79 = fair, 0.60 to 0.69 = poor and 0.50 to 0.59 = failure.



$$\text{Algorithm 1: Z-Blood} = 0.009 \times \text{age} + 0.06 \times \text{OD} + 0.03 \times \text{bWBC} + 0.017 \times \text{bNeut\%} + 0.006 \times \text{bPLT} + 0.11 \times \text{POD} - 0.062 \times \text{bNa} + 3.467$$

$$\text{Algorithm 2: Z-cLact} = 0.145 \times \text{OD} + 0.423 \times \text{cLact} + 0.085 \times \text{POD} - 3.089$$

Figure 1. Receiver Operating Characteristic curves of the examinations and algorithms.

A. The Receiver Operating Characteristic curves of routine blood examinations and algorithm 1 (Z-Blood) for PBM diagnosis. B. The Receiver Operating Characteristic curves of CSF lactate level and algorithms 2 (Z-cLact) for PBM diagnosis. Algorithms were constructed with Fisher discriminant analysis to integrate the values of the variables of patient age, operation duration and postoperative days with the measurements of routine blood examinations or CSF lactate level. bWBC: blood WBC counts, bNeut%: blood neutrophil proportions, bPLT: blood platelet counts, bNa: blood sodium concentration, cLact: CSF lactate level, OD: operation duration, POD: postoperative days.