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# The diagnostic value of cerebrospinal fluids procalcitonin and lactate for the differential diagnosis of post-neurosurgical bacterial meningitis and aseptic meningitis ☆

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ABSTRACT

**Objectives:** Distinguishing between post-neurosurgical bacterial meningitis (PNBM) and aseptic meningitis is difficult. This study aims to evaluate the combined diagnostic value of CSF procalcitonin and lactate as novel PNBM markers in hospitalized post-neurosurgery patients.

**Design and methods:** This study was performed using CSF samples, collected by lumbar puncture, from 178 PNBM-suspected patients enrolled in a retrospective clinical study. The levels of CSF procalcitonin and lactate were appropriately assayed and the combined diagnostic value of these markers was assessed using receiver operating characteristic (ROC) curves, a two by two table, and non-parametric tests.

**Results:** Fifty of the 178 patients were diagnosed with PNBM, based on the clinical symptoms and laboratory results. These PNBM patients showed significantly elevated levels of CSF procalcitonin and CSF lactate compared with the non-PNBM group ($p < 0.001$ for both). It was revealed that the cut-off values for the diagnosis of PNBM were: 0.075 ng/mL (sensitivity, 68%; specificity, 73%) for procalcitonin and 3.45 mmol/L (sensitivity, 90%; specificity, 85%) for lactate. A serial test combining the levels of these two markers showed decreased sensitivity (64%) and increased specificity (91%), compared with either marker alone. In contrast, a parallel test combining the levels of these both markers showed increased sensitivity (96%) and decreased specificity (65%), compared with either marker alone.

**Conclusion:** Our study shows that the combined use of CSF procalcitonin and lactate can reliably distinguish between PNBM and non-PNBM and can be included in the design of diagnostic approaches to circumvent the shortcomings of conventional methods.



## Introduction

Bacterial meningitis after neurosurgical procedures is relatively uncommon with a low incidence of about 0.3%–1.5% [1], but it is a severe and life threatening infection with a high mortality that ranges from 20 to 50% [2]. At present, post-neurosurgery bacterial meningitis (PNBM) is diagnosed based on the criteria proposed by the Center for Disease Control and Prevention (CDC) [3], the Massachusetts General Hospital (MGH) [4], the Infectious Diseases Society of America (IDSA) and our local criteria. Our criteria included clinical symptoms, various biochemical parameters of the cerebrospinal fluid (CSF) and the blood, and the CSF bacterial culture, which constitutes the golden standard for the diagnosis of bacterial meningitis. However, the low level of the various blood and CSF biochemical parameters does not always rule out bacterial meningitis and should be used with caution. Actually, PNBM and aseptic meningitis share some clinical symptoms and physical signs, including headache, fever, neck stiffness, and vomiting [5]. In addition, hemorrhage, surgical procedure, trauma, and bone dust all appear to trigger an inflammatory response that mimics the bacterial meningitis CSF changes and fail to demonstrate a high diagnostic accuracy [5,6]. Moreover, the time-consuming nature and propensity to contamination of the CSF bacterial culture contribute to the low detection rate of positive culture, reported to be about 6–9% [7–9]. Given all these influencing factors, it is necessary to introduce novel diagnostic

*Abbreviations:* PNBM, post-neurosurgery bacterial meningitis; CSF, cerebrospinal fluid; WBC, white blood cell; ROC, receiver operator curve; AUC, area under curve; PPV, positive predictive value; NPV, the negative predictive value; PLR, the positive likelihood ratio; NLR, the negative likelihood ratio.

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markers to assist in the diagnosis of PNBM in order to offer more diagnostic options and to evaluate the utility of antibiotic drugs.

It has been established that the production of the CSF lactate by the astrocytes is triggered by bacterial infection. Recently, the CSF lactate has been shown to be correlated with bacterial infection and was suggested as a potential marker for distinguishing between infection and inflammation, as well as a biomarker for PNBM for its excellent discriminatory power [10,11].

Serum procalcitonin has also been proposed as a novel biomarker with high sensitivity and specificity for both diagnostic and prognostic values in various severe infections [12–14]. Although this biomarker has been studied as an aid to classify infections according to severity and to guide therapy durations the clinical value of CSF procalcitonin in the differential diagnosis of PNBM is rarely investigated. Thus, whether the combined use of CSF procalcitonin and lactate as biomarkers could improve the diagnostic efficacy is still unclear.

## Method

### *Patients*

The current study retrospectively analyzed 178 patients who underwent neurosurgery at our institute between October 2013 and March 2014. This study was approved by our Institutional Review Board and written informed consent was obtained from all the patients enrolled. Patients who showed clinical symptoms of bacterial meningitis such as fever, headache, neck stiffness, and disturbance of consciousness, within 48 to 72 h after surgery were subjected to lumbar puncture in order to collect CSF samples for diagnostic analysis, which included protein content, glucose, chloride, WBC count, etc. The residual CSF samples were used to assay levels of procalcitonin and lactate. The diagnosis of bacterial meningitis was based on the following criteria [15]: 1) clinical symptoms including headache, fever (>38.5 °C), meningeal irritation sign, and disturbance of consciousness; 2) positive bacterial CSF culture or Gram stain; 3) CSF WBC count ≥1000/μL and polykaryocyte percentage ≥75%; and 4) CSF glucose <2.5 mmol/L or when the ratio of CSF glucose to blood glucose was lower than 0.4. Patients who did not meet the above criteria and with a WBC count <500/μL were classified into the non-PNBM group.

### *Measurements*

After CSF samples were collected the levels of glucose, protein, chloride, procalcitonin, lactate, as well as the WBC count, and polykaryocyte percentage were determined immediately. The procalcitonin concentration was measured using a commercially available enzyme-linked fluorescent assay (VIDAS® B.R.A.H.M.S procalcitonin, Berlin, Germany), which has a lower detection limit of 0.05 ng/mL; when the CSF procalcitonin level of the patients was below this detection limit we regarded it as 0 ng/mL. The lactate concentration in the CSF was measured using a VITROS chemistry products lactate slides (Ortho-Clinical Diagnostics, Inc., New York, USA), which has a lower detection limit of 0.50 mmol/L. The CSF lactate and other biomarkers, including polykaryocyte percentage, WBC count, CSF protein, CSF chloride, and CSF glucose were assessed quantitatively on the VITROS 5,1 FS Automatic Chemistry Analyzer device using the velocity method. The positive result of the serial test was confirmed when all the included sub-tests were positive. While the positive result of the parallel test was defined as that in which at least one sub-test was positive.

### *Statistical analysis*

Since neither the procalcitonin nor the lactate data followed a normal distribution (Kolmogorov–Smirnov, $p < 0.05$), the non-parametric test (Mann–Whitney test) was used to compare the medians of the CSF procalcitonin and lactate levels to ascertain whether there was a relevant relationship between the PNBM and non-PNBM groups. The optimal cut-off value was calculated using the receiver operator curve (ROC) analysis for procalcitonin and lactate in CSF. Two-by-two tables were created based on the cut-off values and were used to calculate the positive and negative predictive values, the positive and negative likelihood ratio, the accuracy, and the diagnostic index. Subsequently, the serial and parallel tests were applied to determine the diagnostic accuracy of the combined procalcitonin and lactate levels in CSF. All the analyses were done using IBM SPSS Statistics, version 19.0 (IBM, Armonk, NY, USA).

## Results

The 178 patients enrolled in this study were divided into 50 patients to the PNBM group and 128 to the non-PNBM group. The values for each of the various parameters were not normally distributed when examined by category. The medians of the parameters for diagnosis (age, sex, CSF procalcitonin, CSF lactate, CSF WBC count and polykaryocyte percentage, CSF protein, CSF chloride, and CSF glucose) were compared and the comparison results are given in Table 1. In the PNBM group, the median of the CSF procalcitonin levels was 0.2 ng/mL, ranging from 0 ng/mL to 3.1 ng/mL, and the median of the CSF lactate levels was 5.3 mmol/L, ranging from 2.2 mmol/L to 10.6 mmol/L.

The performance of the procalcitonin and the lactate tests in the diagnosis of PNBM is summarized in Table 2. The difference in the CSF procalcitonin levels between the PNBM and the non-PNBM groups was statistically significant ($p < 0.001$) (Fig. 1). Similarly the CSF lactate levels for the PNBM and the non-PNBM groups also showed significant difference ($p < 0.001$) (Fig. 2). The ROC curve analysis of the CSF procalcitonin and lactate data revealed that the cut-off values were: 0.075 ng/mL (AUC = 0.746, $p < 0.001$, sensitivity, 68.0%; specificity, 72.7%) for the CSF procalcitonin; and 3.45 mmol/L (AUC = 0.943, $p < 0.001$, sensitivity, 90.0%; specificity, 84.4%) for the CSF lactate (Fig. 3). Together these ROC curve analysis results suggest that CSF lactate and procalcitonin hold significant diagnostic value for PNBM. In addition, the accuracy, the diagnostic index, the positive predictive value (PPV), the negative predictive value (NPV), the positive likelihood ratio (PLR), and the negative likelihood ratio (NLR) of CSF procalcitonin, CSF lactate, serial test and parallel test of CSF procalcitonin and lactate were determined. The diagnostic power of the CSF procalcitonin plus lactate was also determined by using the serial and the parallel tests. When combined for the diagnosis of PNBM, the diagnostic criteria of the CSF procalcitonin and lactate, together, showed lower sensitivity (64.0%) and higher specificity (91.4%) compared with the result of either marker alone. When the parallel test of the CSF procalcitonin and lactate was applied, there was a higher sensitivity (96.0%) and a lower specificity (64.8%) in comparison with the result of either marker alone.

The relationship between procalcitonin, lactate and conventional laboratory indicators including polykaryocyte percent, WBC count, protein level and glucose level is shown in Table 3. When the values of conventional indicators were classified by the diagnostic threshold value (0.075 ng/mL) of procalcitonin estimated above, the variation trend of procalcitonin was consistent with that of the conventional markers; a

**Table 1**
CSF data of all patients.

| Parameters | PNBM | Non-PNBM |
|---|---|---|
| Age (yrs, range) | 42 (21–67) | 42 (17–69) |
| Sex (M/F) | 23/27 | 49/79 |
| WBC/μL | 2237 (1000–18,757) | 98 (1–2567) |
| Polykaryocyte percent | 90.4% (75.1–99.4%) | 41.9% (0–97.7%) |
| CSF protein (mg/dL) | 148.7 (64.3–587.5) | 72.4 (19.6–305.8) |
| CSF chloride (mmol/L) | 113.0 (102.7–129.0) | 114.0 (48.7–132.6) |
| CSF glucose (mmol/L) | 2.1 (0.3–4.3) | 3.3 (1.0–9.0) |
| Procalcitonin (ng/mL) | 0.2 (0–3.1) | 0 (0–0.5) |
| Lactate (mmol/L) | 5.3 (2.2–10.6) | 2.3 (1.2–5.4) |