Original

Diagnostic utility of combined cerebrospinal fluid interleukin-6 and procalcitonin in bacterial meningitis: Sensitivity and specificity analysis

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ABSTRACT

Background: Bacterial meningitis (BM) is a life-threatening condition requiring early diagnosis and treatment to prevent severe complications; however, traditional diagnostic methods, such as cerebrospinal fluid (CSF) analysis, Gram staining, and bacterial cultures, can be slow/nonspecific. Therefore, novel biomarkers are needed. IL-6 levels increase during inflammatory responses, whereas procalcitonin (PCT) levels specifically increase during bacterial infections. Herein, we investigated the utility of CSF IL-6 and PCT levels to differentiate BM from other central nervous system (CNS) diseases.

Methods: CSF samples were collected from 70 patients (mean age, 37.5 years; SD, 17.8 years; male/female, 36/34) treated at Kawaguchi Municipal Medical Center between September 2022 and 2023. Blood samples were additionally collected from 53 patients. BM was diagnosed based on clinical symptoms, culture results, and antibiotic responses. CSF IL-6 and PCT concentrations were measured using electrochemiluminescence immunoassays.

Results: CSF IL-6 and PCT levels were significantly higher in patients with BM than those with non-bacterial CNS diseases. Receiver operating characteristic analysis revealed that CSF PCT had a higher diagnostic accuracy (area under the curve = 0.887) than CSF IL-6 and cell counts. Concurrent measurement of CSF IL-6 and PCT levels improved the specificity of BM diagnosis from 0.71 to 0.95.

Conclusions: Combining CSF IL-6 and PCT measurements provides better diagnostic accuracy for BM than either marker alone. CSF IL-6 primarily reflects intrathecal production, and although a weak correlation with serum IL-6 was observed, it remains unclear whether serum IL-6 contributes to CSF levels. PCT remains highly specific to bacterial infections.Further large-scale studies are required to validate these findings and confirm the utility of these biomarkers in clinical settings.

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Key Words
Procalcitonin, Interleukin-6, Bacterial meningitis, Central nervous system diseases

I. Introduction

Bacterial meningitis (BM) is a treatable disease if diagnosed and managed early; however, delayed treatment can result in severe sequelae or death. Therefore, early diagnosis and prompt therapeutic intervention are crucial [1]. The diagnostic tests for this disease include biochemical analysis of the cerebrospinal fluid (CSF), Gram staining, bacterial culture, and neuroimaging (computed tomography and magnetic resonance imaging). Among these, the presence of bacteria in the CSF observed on Gram staining or bacterial culture is considered the gold standard method for diagnosis [1), 2)]. However, bacterial culture is time consuming, and is sometimes too slow in clinical settings. An increased CSF cell count is a key indicator for diagnosing BM. However, some rare cases present with no increases in the early stages of BM. Furthermore, cell count elevation is observed in other conditions, such as non-BM or Behçet's disease [3)], making diagnosis challenging. Therefore, the development of novel biomarkers that offer both accurate and rapid results for BM diagnosis is highly desirable in clinical practice.

Interleukin-6 (IL-6) is a glycoprotein with a molecular weight of 21,000–26,000, produced by T cells and macrophages. IL-6, a type of cytokine with diverse physiological functions in the body, increases in autoimmune diseases and infections [4)-6)]. Measuring IL-6 levels in the CSF has been reported as useful for diagnosing inflammatory diseases, such as Behçet's disease, neuromyelitis optica spectrum disorders, and acute brain injuries [7)-9)]. These reports support the notion that IL-6 levels increase in diseases in which lymphocytes and macrophages are activated. In contrast, procalcitonin (PCT), a precursor of calcitonin, is a polypeptide comprising 116 amino acids with a molecular weight of 13,000, and is synthesized in the C cells of the thyroid gland. PCT levels specifically increase during bacterial inflammation [10),11)], and are widely used in clinical settings owing to their rapid measurement. Several prior studies have revealed the usefulness of CSF PCT for diagnosing BM and intracranial infections after craniotomy [12)-15)]. While both IL-6 and PCT have been individually studied as biomarkers for meningitis, there is a lack of studies comparing their diagnostic values within the same cohort. Furthermore, differentiating between BM and non-BM remains a clinical challenge, and reliable biomarkers are required. Therefore, we aimed to measure IL-6 and PCT levels in CSF samples to assess their combined utility in distinguishing BM from other central nervous system (CNS) diseases. Consequently, we sought to elucidate the specific diagnostic advantages of CSF IL-6 and PCT compared with prior studies that have focused on each marker separately.

II. Methods

In the present study, we used CSF samples from 70 patients, with 52 paired blood samples, from patients submitted to the Department of Laboratory Medicine at the Kawaguchi Municipal Medical Center between September 2022 and September 2023. The patients' age and sex were calculated as follows: age: 37.5 years (mean age, SD: 17.8 years), sex: 36 males, 34 females. Inclusion and exclusion criteria were applied according to the study protocol.

The CSF and blood samples used in this study were residual samples after diagnostic testing was completed. CSF samples that exhibited reddish coloration or suspected blood contamination were excluded. Additionally, samples with insufficient volumes that prevented the simultaneous measurement of IL-6 and PCT levels were excluded. The BM group included patients diagnosed with BM based on positive or negative CSF culture results, CSF biochemical tests, imaging findings, clinical symptoms, and improvement after antimicrobial therapy. Other CNS diseases with increased CSF cell counts were diagnosed based on neurological findings, imaging (computed tomography and magnetic resonance imaging) tests, electrophysiological tests, and clinical course. Participants were classified into three groups based on their diagnosis: non-CNS diseases (non-CNS), BM, and non-bacterial CNS diseases (non-BM).

After collecting CSF samples, the CSF cell count, glucose concentration, protein concentration, CSF IL-6 concentration, and CSF PCT concentration were measured. Additionally, IL-6 and PCT concentrations were measured in blood samples collected on the same day. IL-6 and PCT concentrations in both the CSF and blood were measured using the electrochemiluminescence immunoassay method with the Cobas Pro e801 analyzer (Roche Diagnostics Co., Ltd.).

Comparisons between groups were performed using the Steel-Dwass test. Correlations were examined using Spearman's rank correlation coefficients. The normality of the distribution of continuous data was assessed using the Shapiro–Wilk test, with results confirming that the data were not normally distributed. Therefore, the data are presented as medians and interquartile ranges. Statistical analysis was performed using JMP Pro Ver.17, with a two-tailed p-value of <0.05 considered statistically significant. This study was approved by the Ethics Committee

of the Kawaguchi Municipal Medical Center (2021-13).

III. Results

1. Comparison of IL-6 and PCT levels in bacterial and non-bacterial CNS diseases

Concentrations of IL-6 and PCT in the BM group were significantly higher than those in the non-BM group (**Table 1**). The PCT concentration in the non-CNS group was significantly lower in the CSF than in the blood (**Fig. 1**). In non-BM cases, CSF IL-6 levels above the cutoff value were observed in six cases from the non-CNS group and 12 cases from the non-BM group. CSF PCT levels above the cutoff value were observed in four patients from the non-CNS group and five patients from the non-BM group.

2. Diagnostic accuracy of CSF IL-6, PCT, and cell count in BM

Receiver operating characteristic analysis was conducted to evaluate the diagnostic capabilities of CSF IL-6, PCT, and cell counts for the diagnosis of BM. The areas under the curve (AUCs) were calculated for each parameter. The results showed an AUC of 0.881 for CSF IL-6, 0.887 for CSF PCT, and 0.824 for CSF cell count. The CSF PCT level showed the highest diagnostic ability for BM (**Fig. 2**).

3. Correlations between serum and CSF IL-6 and PCT levels

Subsequently, the correlations between the serum and CSF levels of IL-6 and PCT were examined. A weak positive correlation was identified between CSF and serum IL-6 levels, suggesting that serum concentration affects CSF IL-6 levels. No significant correlations were observed between the CSF and serum PCT levels (**Fig. 3**).

4. Combined use of CSF IL-6 and PCT for improved diagnosis of BM

Based on these findings, CSF IL-6 and PCT levels showed a higher diagnostic accuracy for BM than CSF cell count. Consequently, we investigated whether the simultaneous measurement of CSF IL-6 and PCT levels could improve the diagnostic capability for BM compared with each marker measured individually. When the cutoff values for BM were set at 15.4 pg/mL for CSF IL-6 and 0.173 ng/mL for CSF PCT, the specificity for diagnosing BM increased from 0.71 (when measuring only CSF IL-6 concentration) to 0.95 (when both CSF IL-6 and PCT exceeded their respective cutoff values). However, the sensitivity for diagnosing BM when both biomarker exceeded the cutoff value decreased from 1.00 to 0.88 (**Fig. 4** and **Table 2**). The corresponding cutoff values for serum IL-6 and PCT are presented in Supplementary **Figure 1**. The AUC values for serum IL-6 and PCT were 0.6702 and 0.644, respectively. These results indicate that serum IL-6 and PCT alone do not provide sufficient diagnostic performance to reliably distinguish BM from non-BM cases (Supplementary **Fig. 1**).

IV. Discussion

In the present study, we evaluated the diagnostic capability of CSF IL-6 and PCT concentrations as quantitative biomarkers of BM. We confirmed that the CSF concentrations of these biomarkers were significantly higher in patients with BM than in those without BM. Additionally, the combination of CSF IL-6 and PCT measurements showed potential as biomarkers with high sensitivity and specificity, particularly in patients with BM.

Regarding CSF IL-6, previous studies have shown its utility for the diagnosis of BM [16),17)]. Consistent with these reports, our findings confirmed the usefulness of CSF IL-6 in the diagnosis of BM (**Fig. 1(a)**). Based on our results, CSF IL-6 appears to have a relatively high sensitivity for diagnosing BM. CSF IL-6 primarily reflects intrathecal production, and although a weak correlation with serum IL-6 was observed, it remains unclear whether serum IL-6 contributes to CSF levels. (**Fig. 3(a)**). Furthermore, even in the non-BM group, the CSF IL-6 levels tended to increase (**Fig. 1(a)**). This

Table 1 Patient characteristics

	Non-CNS (N=36)	BM (N=8)	Non-BM (N=26)
Age	29.3 ± 33.6	40.8 ± 38.6	44.1 ± 30.6
Male/Female	17/19	5/3	14/12
CSF IL-6 (pg/mL)	12.6 ± 21.4	1146.5 ± 2388.1	572.5 ± 2541.5
IL-6 (pg/mL)	66.9 ± 140.5 (n=25)	58.84 ± 55.0 (n=5)	44.6 ± 59.2 (n=22)
CSF PCT (ng/mL)	0.131 ± 0.070	1.031 ± 2.006	0.132 ± 0.069
PCT (ng/mL)	0.356 ± 0.914 (n=25)	1.451 ± 2.902 (n=5)	0.776 ± 3.111 (n=22)
CSF cells (cell/μL)	1.4 ± 0.9	45.6 ± 89.8	30.7 ± 70.0

CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin; BM, bacterial meningitis; non-CNS, non-central nervous system diseases; non-BM, non-bacterial central nervous system diseases

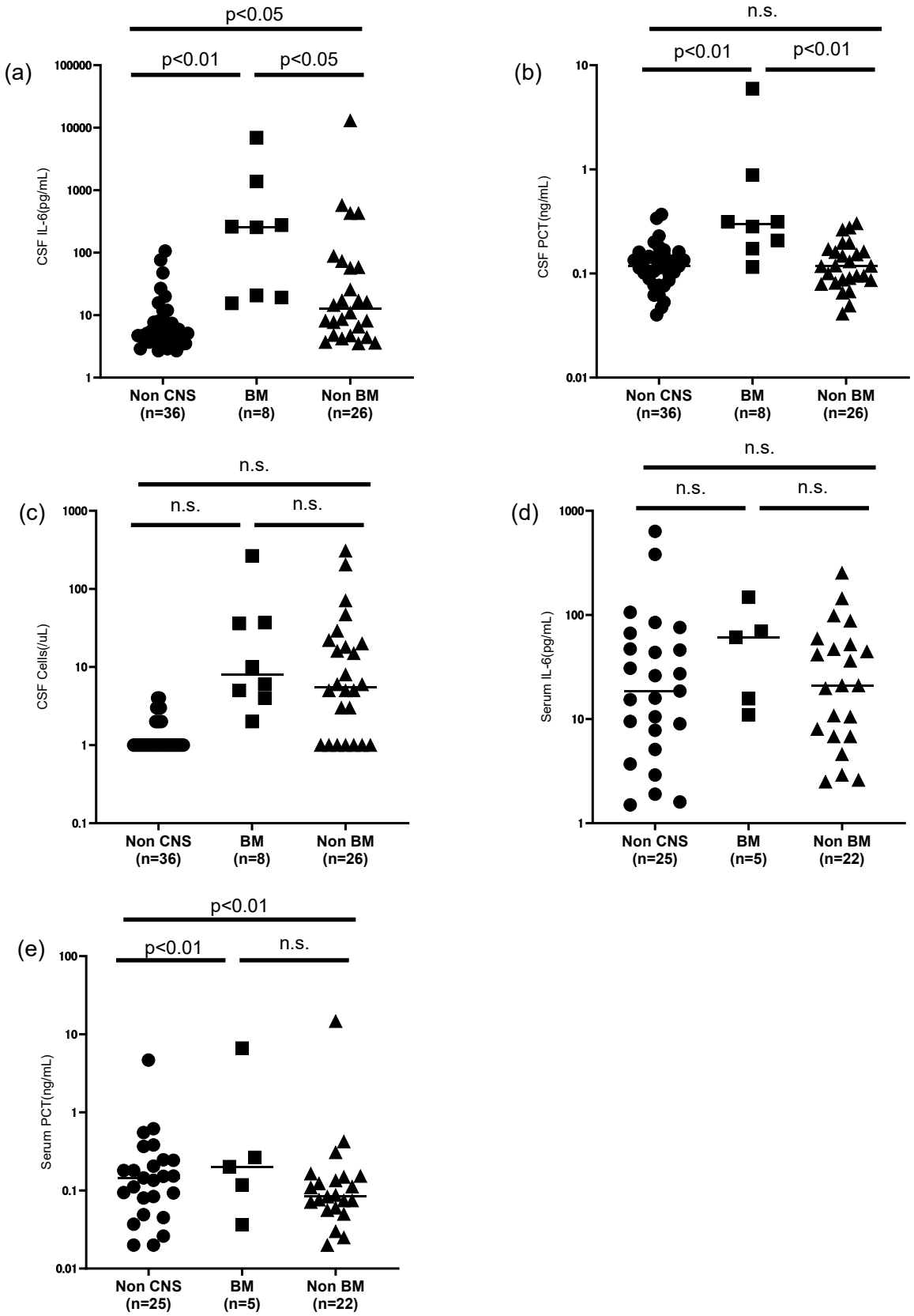

Figure 1 Comparison of IL-6 and PCT concentrations among the non-CNS, BM, and non-BM groups. CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin; BM, bacterial meningitis; non-CNS, non-central nervous system diseases; non-BM, non-bacterial central nervous system diseases.

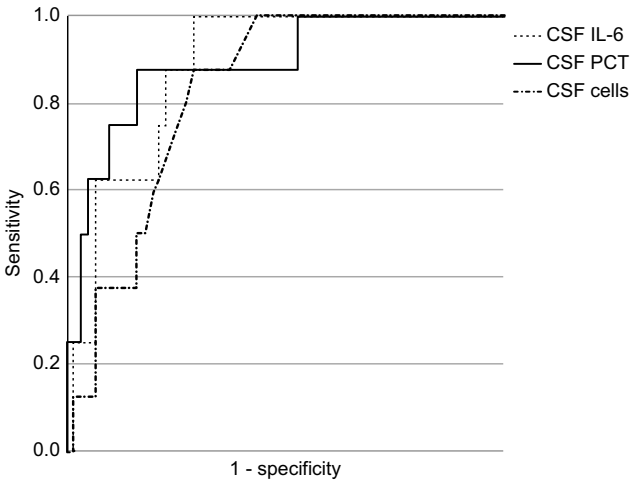

Figure 2 ROC analyses examining the ability of CSF IL-6 and PCT levels to diagnose BM.
ROC analyses were conducted to investigate the use of IL-6 and PCT levels in the CSF to discriminate between the BM and non-BM groups.
CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin; BM, bacterial meningitis; ROC, receiver operating characteristic; non-BM, non-bacterial central nervous system diseases.

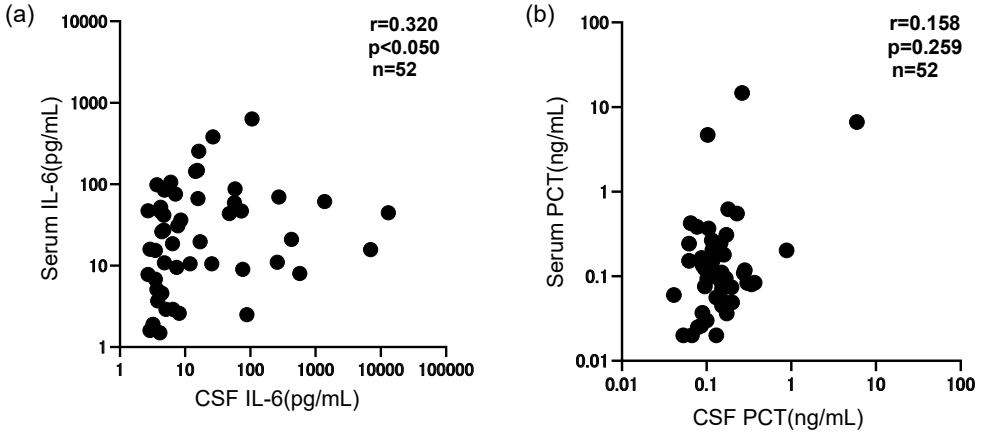

Figure 3 Correlations between IL-6 or PCT concentrations in the CSF and serum. Correlations between IL-6 or PCT concentrations in the CSF and serum are shown (n=52).
CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin.

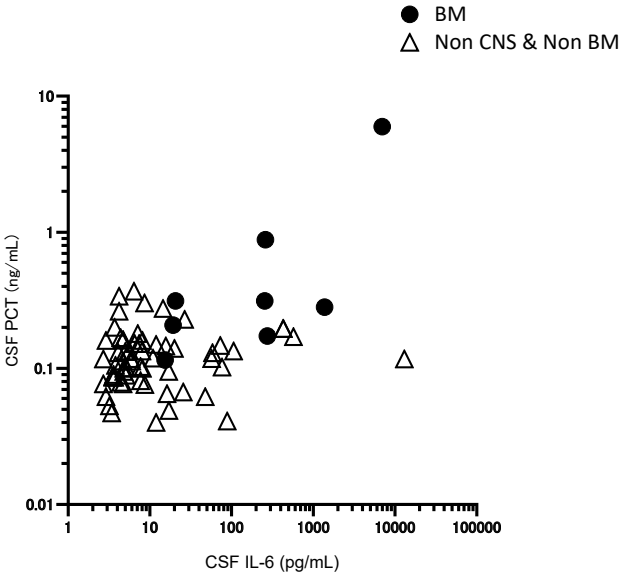

Figure 4 Distribution of participants according to the IL-6 and PCT concentrations in the CSF.
The distribution of participants in the BM group (n=70) according to their CSF IL-6 and CSF PCT concentrations are shown.
CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin; BM, bacterial meningitis; non-BM, non-bacterial central nervous system diseases

result is consistent with that of the study on the differentiation between BM and aseptic meningitis by Pinto Junior et al. [18]. Diseases other than BM in which elevated CSF IL-6 levels have been reported include viral meningitis, encephalitis, encephalopathy, and cerebral infarction [18),19)-22)]. In the present study, the non-BM group included three cases of viral meningitis, five cases of encephalitis /encephalopathy, and three cases of cerebral infarction, which likely contributed to the observed elevation. (Supplementary **Table1**) The increase in CSF IL-6 levels is thought to be due to an inflammatory response.

In recent years, several studies have investigated the role of CSF PCT and IL-6 in the diagnosis of neonatal and pediatric meningitis. For example, Borowiak et al. reported that CSF PCT and lactate levels have significant diagnostic utility in neonatal meningitis [23]. Similarly, Babenko et al. demonstrated that PCT and C-reactive protein measurements could aid in effectively differentiating BM from enteroviral meningitis in children, using a decision tree approach [24]. Rajial et al. further evaluated the utility of serum and CSF PCT for diagnosing neonatal meningitis, emphasizing its role in differentiating bacterial etiologies from viral etiologies [25]. Furthermore, Kruthika et al. conducted a systematic review of IL-6 as a biomarker for diagnosing tuberculous meningitis, highlighting its potential application in bacterial infections [26]. These findings support the relevance of CSF IL-6 and PCT in various types of meningitis and suggest that their combined measurement may improve the diagnostic accuracy. The low specificity of CSF IL-6 for diagnosing BM compared with other biomarkers (**Table 2**) is likely because of its lack of disease specificity. Although elevated CSF IL-6 concentration alone may lack specificity, it could still be useful as a screening marker for CNS diseases.

To supplement the specificity of CSF IL-6, we focused on PCT, a biomarker known to specifically increases during bacterial inflammation. Previous studies have shown the utility of CSF PCT for diagnosing BM [12)-15)]. In our study, we confirmed the usefulness of CSF PCT levels in patients with BM (**Fig. 1(b)**). CSF PCT levels were not significantly correlated with serum PCT levels (**Fig. 3(b)**), indicating that CSF PCT may have a different dynamic to serum PCT. However, Reshi et al. suggested that during infection, the blood–brain barrier may be disrupted, allowing serum PCT to enter the CSF; therefore, this possibility must be considered. The sensitivity and specificity of CSF PCT levels alone were consistent with those reported by Reshi et al., who reported a sensitivity of 0.92 and specificity of 0.87 [27]. Additionally, the AUC for CSF PCT was higher than that for CSF IL-6 or CSF cell counts for diagnosing BM (**Fig. 2**). The significant difference between the BM and non-BM groups (**Fig. 1(b)**) suggests that the CSF PCT has a high sensitivity for diagnosing BM. This is likely because IL-6 levels increase nonspecifically in inflammatory diseases, whereas PCT levels increase specifically in bacterial inflammation. The elevated CSF PCT levels in patients with BM may be because of the release of PCT from bacteria or leukocytes in the CNS. However, in the present study, elevated CSF PCT levels were also observed in the non-BM group. Raddant and Russo further reported that PCT can be produced by the trigeminal nerve or glial cells during inflammation, leading to a localized increase in the CSF levels [28]. Although we could not elucidate the reason for the elevated CSF PCT levels in the non-BM group, this must be considered when using CSF PCT as a biomarker.

Next, we examined the clinical utility of simultaneous measurement of CSF IL-6 and PCT levels. As shown in **Fig. 4** and **Table 2**, compared with the sensitivity and specificity of CSF IL-6 or PCT alone, when both markers were above their respective cutoff values, the sensitivity was similar or slightly decreased; however, the specificity was significantly improved. In the present study, 26 patients had CSF IL-6 levels above the cutoff, of whom 20 were from groups other than the non-CNS group. Pre-

Table 2 Sensitivity and specificity results of the different parameters

	Sensitivity	Specificity
CSF IL-6	1.00	0.71
CSF PCT	0.88	0.82
CSF cells	0.75	0.74
CSF IL-6 and CSF PCT	0.88	0.95
CSF IL-6 and CSF cells	0.88	0.89
CSF cells and CSF PCT	0.75	0.95

CSF, cerebrospinal fluid; IL-6, interleukin-6; PCT, procalcitonin

vious reports have indicated that patients with CSF IL-6 levels above the cutoff are highly likely to have some form of inflammatory response within the CNS [18]. This is likely the reason for the reduced specificity for diagnosing BM. Of the 26 patients with CSF IL-6 levels above the cutoff, 10 had CSF PCT levels above the cutoff, of which 7 were patients with BM. In one case within the BM group, both CSF IL-6 and CSF PCT levels did not exceed the respective cut-off values. This patient had postoperative meningitis and had received antibiotic therapy prior to CSF sampling, which may have influenced the biomarker concentrations.Conversely, three cases outside the BM group showed biomarker levels above the cut-off values: two cases of encephalitis/encephalopathy and one case of crowned dens syndrome. Because the number of these cases was limited, we were unable to further analyze the underlying reasons for the elevated values.

These results suggest that simultaneous measurements of CSF IL-6 and PCT levels can help identify the presence of CNS disease via CSF IL-6 levels and determine whether the disease is bacterial in origin via CSF PCT levels. This combination compensated for the shortcomings of each marker, resulting in a significant improvement in specificity, although the sensitivity was slightly decreased.

Although the number of patients with BM in this study was small, the above results suggest that the combination of CSF IL-6 and PCT measurements may serve as a useful quantitative biomarker for detecting BM in clinical settings. Further prospective studies with larger patient populations are required to validate the usefulness of these biomarkers, as this study has several limitations. First, as this was a single-center study, there was an inherent risk of bias related to the study design, including the patient selection criteria and data collection methods. Second, the relatively small sample size, particularly the limited number of CSF culture-positive cases in the BM group, may have introduced selection bias, potentially influencing the generalizability of our findings. Moreover, regression analysis could not be performed owing to the small sample size and limited available resources. Third, the study population was limited to patients from a specific medical institution, which may restrict the applicability of our results to different populations, including those from different geographic regions and those with varying disease prevalence rates. Furthermore, measurement of IL-6 and PCT in CSF is currently not covered by the healthcare insurance system in our country. Although there are cost limitations, we believe that their utility as rapid, minimally invasive biomarkers for distinguishing BM from non-CNS conditions justifies consideration, particularly when early differentiation is clinically crucial. Moreover, we hope that similar studies at other institutions, inspired by our research, will help to further validate and enhance the clinical utility of these biomarkers.

V. Conclusion

In conclusion, the combination of CSF IL-6 and PCT measurements provides superior diagnostic accuracy for BM than either marker alone. To further enhance the reliability of these findings, future studies should incorporate regression analyses to adjust for potential confounding factors and to better understand the independent contributions of CSF IL-6 and CSF PCT in BM diagnosis. Additionally, large-scale, multicenter, prospective studies are required to confirm these results across diverse populations and clinical settings. Investigating the impact of different clinical parameters, such as underlying conditions or disease severity, on biomarker performance will also be important for optimizing their clinical application.

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Authors' contributions

Takuya Shimura: Conceptualized the research theme, designed the study protocol, conducted the research, and wrote the manuscript. Led most aspects of the study; Hitomi Sakata: Conceptualization, Supervision, Writing - Review & Editing; Masahiro Yamamoto: Writing - Review & Editing; Ryunosuke Ohkawa: Writing - Review & Editing; Akira Yoshimoto: Writing - Review & Editing; Tomonori Suzuki: Writing - Review & Editing; Masato Nishioka: Conceptualization, Supervision, Writing - Review & Editing.

Conflicts of interests

The authors of the study have nothing to disclose.

Data statement

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

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