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Original Article

Clinical significance of cerebrospinal fluid presepsin as adjunctive biomarker for postneurosurgical meningitis: A single-center prospective observational study

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ABSTRACT

Background: Postneurosurgical meningitis (PNM) is a serious complication in neurocritical care patients, leading to clinical deterioration and worsening outcomes. Accurate diagnosis of PNM is often difficult due to the lack of definitive diagnostic criteria. This study investigates the potential utility of cerebrospinal fluid (CSF) presepsin (PSP), blood PSP, and the CSF/blood PSP ratio as adjunctive biomarkers for the diagnosis of PNM.

Methods: We conducted a single-center prospective observational study at Nara Prefecture General Medical Center in Nara, Japan, from April 2020 to March 2022. The postoperative neurosurgical patients with suspected PNM were included in the study and divided into PNM and non-PNM groups. We evaluated the sensitivity, specificity, area under curves (AUCs), positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of PNM with CSF PSP, blood PSP, and CSF/blood PSP ratio compared in the two groups.

Results: We screened 241 consecutive patients with postoperative neurosurgery. Diagnosis of PNM was suspected in 27 patients, and the clinical diagnosis was confirmed in nine patients. The results of CSF PSP (cutoff: 736 pg/mL) for the diagnosis of PNM were sensitivity 89%, specificity 78%, PPV 67%, NPV 93%, AUC 0.81 (95% confidence interval [CI], 0.60–1.00), blood PSP (cut-off: 264 pg/mL) was 56%, 78%, 56%, and 78%, 0.65 (95% CI, 0.42–0.88), and those of CSF/blood PSP ratio (cutoff: 3.45) was 89%, 67%, 57%, and 92%, 0.83 (95% CI, 0.65–1.00).

Conclusion: Elevated CSF PSP and CSF/blood PSP ratio may be associated with PNM and could serve as valuable adjunctive biomarkers for improving diagnostic accuracy.

Keywords: Biomarker, Cerebrospinal fluid, Diagnosis, Postneurosurgical meningitis, Presepsin

INTRODUCTION

Postneurosurgical meningitis (PNM) is one of the most serious complications associated with high mortality rates, severe neurological sequelae, prolongation of hospital stay, and costs.[6,9,13] The reported incidence rates of PNM vary, depending on the predisposing neurosurgical procedure; these data are hard to interpret as definitions of PNM used by the Centers for Disease Control and Prevention are tailored for surveillance purposes and clinical definitions vary.[4] Since few high-quality randomized controlled trials of PNM management have been conducted, diagnostic and therapeutic approaches are largely based on low-quality

evidence and personal experience.[4,5] Patients who have undergone neurosurgery are quite ill, to begin with, often febrile, neurologically impaired, with multiple potential sources of infections, and multiple noninfectious conditions that can cause fever and decreased level of consciousness.[3] These conditions mask the presentation of PNM. In addition, numerous noninfectious causes of cerebrospinal fluid (CSF) findings mimicking meningitis, including hemorrhage, especially subarachnoid hemorrhage, and malignancies that cause pleocytosis, hypoglycorrhachia, and specific tumors such as dermoid and epidermoid cysts.[3] Abnormalities of CSF cell counts, glucose, and protein are often not reliable indicators of infection in patients with PNM;[17] However, in practice, due to the lack of definitive PNM diagnostic criteria or specific biomarkers, patients are treated based on CSF findings and clinical conditions. The absence of a positive CSF culture may be due to prior antibiotic therapy rather than the absence of infection.[5] Considering these clinical conditions, a negative CSF Gram stain does not exclude the presence of infection.[17] Early diagnosis and treatment of PNM are crucial both neurologically and prognostically, and a useful specific biomarker for early diagnosis of PNM is important.

On the other hand, presepsin (PSP: soluble cluster of differentiation 14 [CD14] subtype) is one of the fragments of CD14 that is produced by intracellular cathepsin D and other factors when bacteria are phagocytosed by monocytes/macrophages after bacterial infection.[10,14,15] CD14 is a glycoprotein expressed on the cell membrane of macrophages/monocytes and is a receptor for endotoxin (or lipopolysaccharide).[10,14,15] According to previous studies, blood biomarker levels in sepsis showed a significant increase in PSP, making an early and sepsis-specific adjunctive diagnostic biomarker.[7,10,14,20] The diagnostic accuracy of PSP in detecting infection is useful for early sepsis diagnosis and subsequent mortality reduction in critically ill adult patients.[7,20] Several reports evaluated the usefulness of CSF PSP for the diagnosis of bacterial meningitis[1,21] or PNM in children.[16] However, there were no studies have evaluated both CSF PSP and blood PSP or used the CSF/blood PSP ratio to diagnose PNM. This study aimed to evaluate the utility of CSF PSP, blood PSP, and CSF/blood PSP ratio as adjunctive biomarkers for the diagnostic accuracy of PNM.

MATERIALS AND METHODS

Ethical approval of the study protocol

This study was conducted following the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Nara Prefecture General Medical Center, Nara, Japan (registration number: 517). Written informed consent was obtained from all patients on their initial admission to the hospital or before surgery.

Study population

This single-center prospective observational study was conducted between April 01, 2020, and March 31, 2022, in the intensive care unit at Nara Prefecture General Medical Center in Japan. Patients were enrolled after neurosurgical treatment, including craniectomy, craniotomy, irrigation, internal or external ventricular and lumbar catheter insertion, and endovascular. The patients suspected of PNM were analyzed in this study. We retrospectively divided these patients into two groups (PNM group and non-PNM group) based on the diagnosis criteria of PNM mentioned below. The patients suspected of PNM were to be evaluated for both bacterial and aseptic meningitis.

Inclusion and exclusion criteria

We enrolled all patients of age 18 years or older who had undergone neurosurgery. Among the patients, those with fever (body temperature >38.3°C) and/or unexplained neurologic deterioration were included in this study as suspected PNM. Patients were excluded under the age of 18 years and postcardiac arrest syndrome. CSF and blood samples, including culture and PSP and serum procalcitonin (PCT), were collected at the same time when PNM was suspected. When the CSF culture was positive, the definitive diagnosis of PNM was confirmed regardless of the value of other CSF findings. When the CSF culture was negative, PNM was diagnosed based on clinical diagnosis. The criteria for clinical diagnosis of PNM in this study were defined as prolonged or new onset altered consciousness, reduction in Glasgow Coma Scale,[18] persistent fever, abnormal CSF findings (CSF cell count >300/μL,[2] CSF/blood glucose ratio <0.4,[8,19] and exclusion of other infectious diseases. The clinical diagnosis of PNM was confirmed when all of these criteria were met in this study.

Data sampling

Demographic data, clinical parameters, and laboratory findings were collected from medical records, including age, sex, medical history, laboratory results, CSF findings, surgical/intervention details, antibiotics, duration of antibiotic treatment, postoperative days, and Sequential Organ Failure Assessment scores. Clinical data were reviewed independently by two study physicians who were blinded to biomarker measurements, including CSF PSP, blood PSP, CSF/blood PSP ratio, and serum PCT. PSP levels were measured using a fully automatic immunoassay analyzer (PATHFAST, LSI Medience, Tokyo, Japan) according to the manufacturer's instructions, and the lower limit of detection was set to 20 pg/mL.

Outcome measures

Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of PSP in CSF and blood, CSF/blood PSP ratio, and serum PCT. Cutoff values were determined for each biomarker using the Youden index (corresponding to the maximum of the sum "sensibility + specificity"). Based on cutoff values, prognostic parameters (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were also calculated. Moreover, linear regression analyses were used to evaluate the correlation between blood contamination of CSF after neurosurgery.

Statistical analysis

All baseline characteristics, clinical variables, and laboratory parameters were compared between patients diagnosed with PNM and non-PNM. The distribution of each variable was compared between the two groups. Continuous variables (expressed as median [interquartile range]) were compared with the Student's *t*-test or the Wilcoxon test as appropriate. Categorical variables (expressed as the number [%]) were compared with χ^2 or Fisher's exact tests. All statistical analyses were performed with the EZR software program, version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

This study screened 241 consecutive patients after neurosurgery. A total of 27 patients with suspected PMN were included in this study [Figure 1]. Clinical diagnosis confirmed PNM in 9 patients. The baseline clinical characteristics were similar between PNM and non-PNM groups [Table 1]. The laboratory findings, including CSF cell counts, CSF cell counts including red blood cells, CSF monocyte, CSF neutrophil, CSF glucose, and CSF lactate levels, revealed significantly different between the two groups [Table 2]. These CSF results were considered for the

Table 1: Patient characteristics in the PNM group and non-PNM group.

	PNM (*n*=9)	Non-PNM (*n*=18)	*P*-value
Culture			
Blood culture, *n* (%)	0 (0)	1 (6)	1.00
Sputum culture, *n* (%)	4 (44)	9 (53)	1.00
Urine culture, *n* (%)	1 (13)	7 (42)	0.21
Cerebrospinal fluid culture, *n* (%)	0 (0)	0 (0)	NA
Complications			
Surgical site infection, *n* (%)	0 (0)	2 (11)	0.54
Aspiration pneumoniae, *n* (%)	4 (44)	4 (22)	0.38
Ventilator-associated pneumonia, *n* (%)	2 (22)	2 (11)	0.58
Catheter-related bloodstream infection, *n* (%)	0 (0)	0 (0)	NA
Catheter-associated urinary tract infection, *n* (%)	0 (0)	0 (0)	NA
Acute ischemic stroke, *n* (%)	1 (13)	0 (0)	0.33
Intracranial hemorrhage, *n* (%)	0 (0)	0 (0)	NA
Major hemorrhage, *n* (%)	0 (0)	0 (0)	NA
Major thrombosis, *n* (%)	0 (0)	0 (0)	NA

IQR: Interquartile range, NA: Not applicable, PNM: Postneurosurgical meningitis

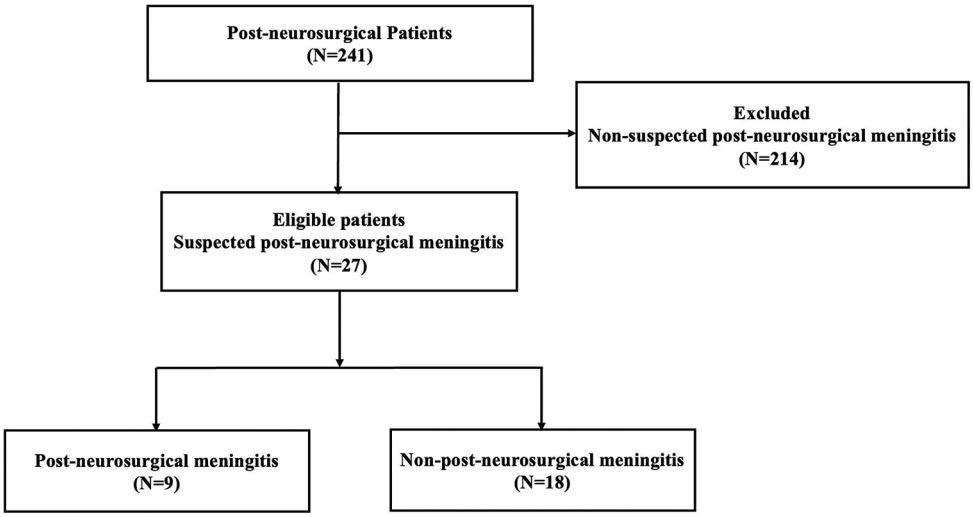

Figure 1: Patient enrollment and classification postneurosurgery.

Table 2: Correlation of laboratory findings of the patients in the PNM group and non-PNM group.

	PNM (*n*=9)	Non-PNM (*n*=18)	*P*-value
Background			
Age (years), median IQR	61 (51–66)	69 (46–78)	0.59
Sex, men, *n* (%)	4 (44)	8 (44)	1.00
Smoke, *n* (%)	5 (56)	7 (39)	0.45
Alcohol, *n* (%)	4 (44)	5 (28)	0.42
Hypertension, *n* (%)	8 (89)	11 (61)	0.20
Diabetes mellitus, *n* (%)	1 (11)	4 (22)	0.64
Dyslipidemia, *n* (%)	2 (22)	4 (22)	1.00
Coronary artery disease, *n* (%)	0 (0)	0 (0)	NA
Chronic heart failure, *n* (%)	0 (0)	2 (11)	0.54
Atrial fibrillation, *n* (%)	1 (11)	2 (11)	1.00
Chronic kidney disease, *n* (%)	1 (11)	1 (6)	1.00
Hemodialysis, *n* (%)	1 (11)	1 (6)	1.00
Ischemic stroke, *n* (%)	0 (0)	1 (6)	1.00
Intracranial hemorrhage, *n* (%)	0 (0)	0 (0)	NA
Subarachnoid hemorrhage, *n* (%)	0 (0)	0 (0)	NA
Diagnosis on admission			
Acute ischemic stroke, *n* (%)	0 (0)	2 (11)	0.54
Subarachnoid hemorrhage, *n* (%)	6 (67)	6 (33)	0.13
Intracranial hemorrhage, *n* (%)	1 (11)	3 (17)	1.00
Traumatic brain injury, *n* (%)	2 (22)	5 (28)	1.00
Brain abscess, *n* (%)	0 (0)	1 (6)	1.00
Brain tumor, *n* (%)	0 (0)	1 (6)	1.00
Surgery/Intervention			
Craniectomy, *n* (%)	0 (0)	3 (17)	0.27
Craniotomy			
Evacuation with or without ICP sensor insertion, *n* (%)	2 (22)	4 (22)	1.00
Evacuation with or without Clipping and ventricular drainage, *n* (%)	1 (11)	2 (11)	1.00
Tumor resection, *n* (%)	0 (0)	1 (6)	1.00
Endovascular treatment			
Coiling, *n* (%)	0 (0)	1 (6)	1.00
Coiling and ventricular drainage, *n* (%)	2 (22)	3 (17)	1.00
Coiling and spinal drainage, *n* (%)	1 (11)	1 (6)	0.37
Craniotomy and endovascular treatment, *n* (%)	0 (0)	1 (6)	1.00
Craniotomy and endovascular treatment and ventricular drainage, *n* (%)	2 (22)	1 (6)	0.25
Craniotomy and endovascular treatment and spinal drainage, *n* (%)	1 (11)	1 (6)	0.37
Clinical findings			
Glasgow Coma Scale (GCS)			
GCS, at the time of suspected PNM, total, median IQR	9 (6–14)	8 (3–10)	0.15
GCS, at the best time before suspected PNM, total, median IQR	13 (9–15)	11 (7–12)	0.19
GCS, the variation score between best and suspected PNM, median IQR	−2 (−3–−1)	−1 (−4–0)	0.56
SOFA score, at the day of admission, median IQR	5 (5–5)	5 (4–6)	0.67
SOFA score, at the time of suspected PNM, median IQR	4 (2–4)	4 (3–5)	0.41
Days after surgery, the median IQR	7 (6–8)	7 (4–10)	0.76
Body temperature (°C), median IQR	38.5 (37.5–38.6)	38.3 (37.9–38.9)	0.78
Antibiotics agent, *n* (%)	8 (89)	13 (72)	0.63
Antibiotics agent, days after surgery, median IQR	5 (4–7)	2 (0–6)	0.20

Median, IQR: Interquartile range, NA: Not applicable, PNM: Postneurosurgical meningitis, SOFA: Sequential organ failure assessment

diagnosis of PNM during their clinical course and were not blinded evaluations. On the other hand, CSF PSP, blood PSP, and CSF/blood PSP ratio were blinded and deserved this evaluation in this study. CSF PSP and CSF/blood PSP demonstrated significantly higher in the patients in the PNM group compared to the patients with a non-PNM

group (CSF PSP: median, 898 [851–1014] vs. 380 [242–478] pg/mL; *P*=0.02, CSF/blood PSP ratio: median, 4.05 [2.27–7.16] vs. 1.09 [0.74–2.36] pg/mL; *P*=0.006, respectively). However, there were no significant differences in blood PSP and serum PCT for the diagnosis of PNM between the two groups (Blood PSP ratio: median, 164 [114–226] vs. 268 [145–474] pg/mL; *P*=0.23, serum PCT: median 0.14 [0.09–0.21] vs. 0.11 [0.07–0.57] ng/mL: *P*=0.85, respectively) [Figure 2]. The area under curves (AUCs) for clinical diagnosis of PNM was 0.81 for CSF PSP, 0.65 for blood PSP, 0.83 for CSF/blood PSP ratio, and 0.48 for serum PCT, respectively [Figure 3]. The AUCs of CSF PSP and CSF/blood PSP ratio were higher than blood PSP or serum PCT. The results of CSF PSP (cutoff: 736 pg/mL) for the diagnosis of PNM were sensitivity 89%, specificity 67%, PPV 67%, and NPV 93%, AUC 0.81 (95% confidence interval [CI], 0.60–1.00); those of blood PSP (cutoff: 264 pg/mL) was 56%, 78%, 57%, and 78%, 0.63 (95% CI, 0.40–0.87), respectively; and those of CSF/blood PSP ratio (cutoff: 3.45) was 89%, 67%, 57%, and 92%, 0.83 (95% CI, 0.65–1.00), respectively [Figure 3].

DISCUSSION

Reliable adjunctive biomarkers with high sensitivity and specificity are needed to assist with the diagnosis of PNM. CSF PSP was reported as one of the useful adjunctive biomarkers for bacterial meningitis mentioned before; however, there was no report to evaluate the CSF/blood PSP ratio for the diagnosis of PNM. This is the first prospective study to evaluate the utility of the CSF/blood PSP ratio in patients with PNM. There were no significant differences in blood PSP between the PNM and non-PNM groups. However, the CSF PSP and CSF/blood PSP ratio at the time of PNM suspicion in the PNM group were significantly higher than in the non-PNM group. Furthermore, ROC analyses revealed that the AUCs of CSF PSP and CSF/blood PSP ratio were higher than blood PSP or serum PCT. In the previous study, the normal range for CSF PSP was 50–100 pg/mL.[1] Concerning this CSF PSP value, in the present study, CSF PSP was elevated above the normal range not only in the PNM group but also in the non-PNM group. In the present study, the validity of this normal range of CSF

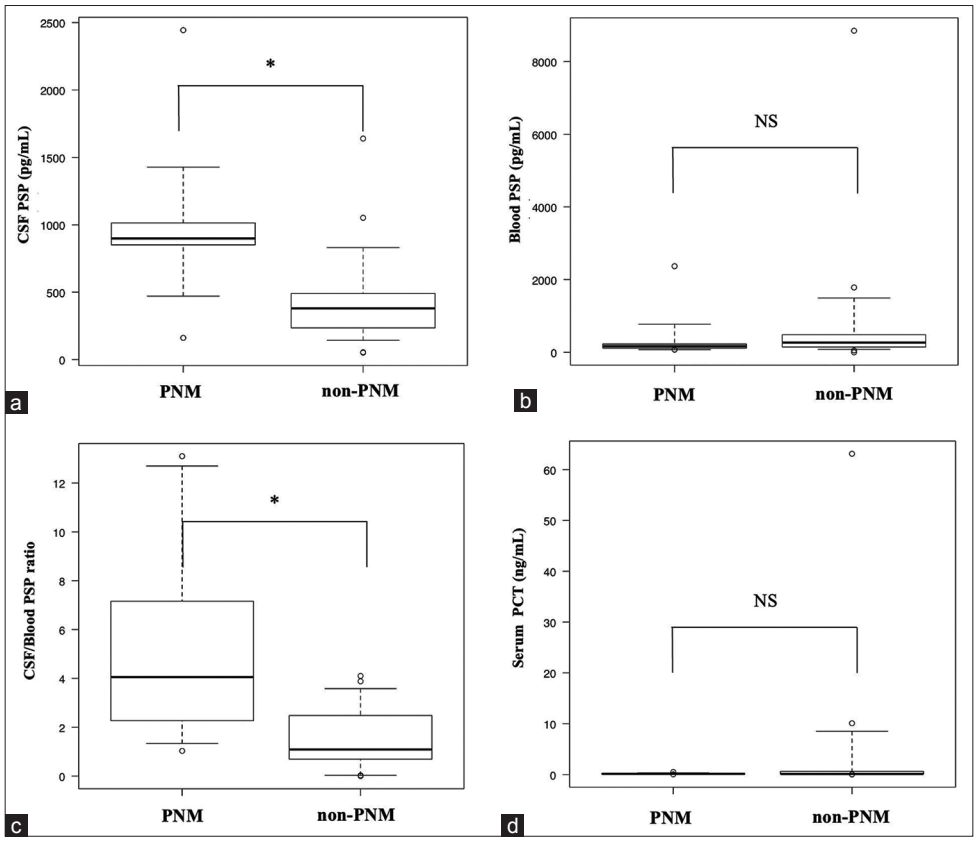

Figure 2: Median values of diagnostic markers of post-neurosurgical meningitis in each group. (a) CSF PSP. (b) Blood PSP. (c) CSF/blood PSP ratio. (d) Serum PCT. Lines denote median values; boxes represent 25th–75th percentiles, and whiskers indicate the range. *$P < 0.05$, NS: Not significant, CSF: Cerebrospinal fluid, PSP: Presepsin, PCT: Procalcitonin, PNM: Postneurosurgical meningitis.

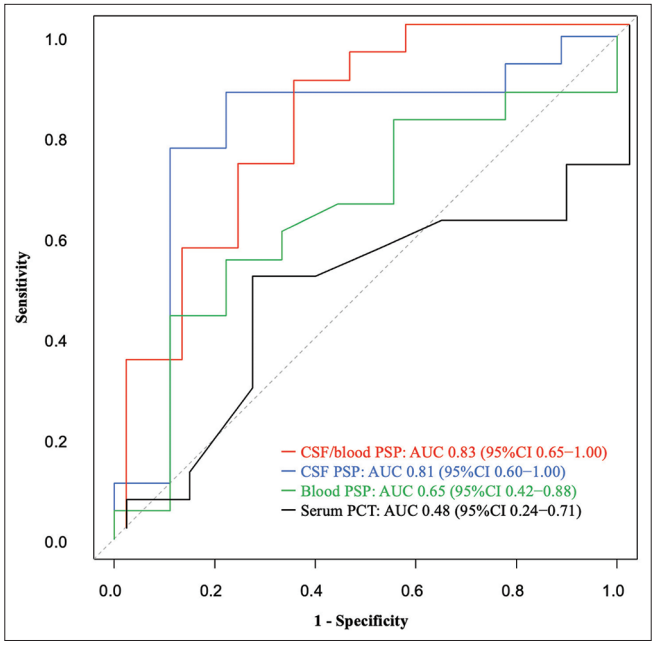

Figure 3: Receiver operating characteristic curves for diagnostic markers of post-neurosurgical meningitis comparing CSF PSP, Blood PSP, CSF/blood PSP, and serum PCT. AUC: Area under the curve, CSF: Cerebrospinal fluid, PSP: Presepsin, PCT: Procalcitonin, CI: Confidence Interval.

PSP could not be assessed due to the small number of PNM patients and the lack of multivariate logistic regression analysis. The results of the CSF PSP and CSF/blood PSP ratio analysis revealed moderate sensitivity, specificity, and AUC for diagnosing PNM [Figure 2]. Based on these findings, it was suggested that not only CSF PSP but also CSF/blood PSP ratio may be useful adjunctive biomarkers in the diagnosis of PNM. Although blood PSP and serum PCT are proven useful biomarkers in the diagnosis of sepsis,[7,20] these biomarkers could not be proven useful for their diagnostic accuracy of PNM in this study [Figures 2 and 3]. However, this does not mean that blood PSP measurement is not useful in this setting. This is because, in patients with suspected PNM, blood PSP is useful in the diagnosis of sepsis for noncentral nervous system infections commonly seen in the intensive care unit, such as ventilator-associated pneumonia, catheter-associated bloodstream infections, and catheter-associated urinary tract infections. In fact, in the comparison of complications in the present study, other coinfections cannot be ignored because bacteria were detected in various cultures measured at the same time as the CSF collection [Table 3]. For this reason, the measurement of CSF and blood PSP at the same time of suspicion of PNM and the evaluation of the combination for calculating CSF/blood PSP ratio may be useful adjunctive biomarkers for diagnosis of PNM, especially in these critical illness patients, which can be challenging to determine whether infection or not. Proper and accurate diagnosis of PNM can lead to avoiding empiric and prolonged antibiotic therapy.

It should consider the possibility of blood entering the CSF due to rupture of the vascular cavity or blood-brain barrier (BBB) in injuries related to the primary disease, such as traumatic brain injury, subarachnoid hemorrhage, intracranial hemorrhage, or neurosurgical procedures. A combination of disrupted BBB and systemic infection can be a cause of elevated levels of CSF PSP. Severe systemic infection and sepsis can also increase the level of CSF PSP in the absence of bacterial meningitis. That is because PSP synthesized in the blood can cross disrupted BBB, and mediators of systemic inflammation can stimulate glial cells for CSF PSP secretion.[1] The present study evaluated the correlation between WBC (CSF cell counts), lactate, and PSP in CSF and blood. Linear regression analysis revealed no correlation between them [Figure 4]. Several studies have shown that the CSF/blood albumin ratio is a marker of BBB impairment;[11,12] however, we could not evaluate this ratio in this study. The absence of any correlation between the CSF and blood WBC, lactate, and PSP might be explained by their different kinetics in the CSF compartment and the limited, if any, entry of the blood marker into the CSF. Based on these findings, on the contrary, if the blood PSP levels showed markedly higher than CSF PSP levels, it is reasonable to rule out PNM, especially bacterial meningitis, and consider a high probability of non-cerebrospinal infections. The results of the correlation between blood and CSF evaluation also may support the utility of a combination of CSF and blood PSP measurements at the same time.

This study has several limitations. First, there were no patients who presented a positive CSF culture, and there was the absence of microbiological evidence to support the definitive diagnosis of PNM in this study. Second, perioperative antibiotic prophylaxis was used in all patients, which might mask infection and influence the negative CSF culture results. Third, it was conducted in a single center, introducing a potential selection bias such as facility and region. Moreover, uncontrolled confounding factors may exist. Fourth, medication changes and procedures may have contributed to the outcomes in the postintervention. Fifth, we cannot exclude the possibility that changes in the patient population impacted their outcomes. For example, comorbidities were not examined in the present study. Finally, the sample size in this study was very small. Due to the low incidence of PNM in post-neurological intervention, further prospective studies in a large study population with multicenter settings are necessary to clarify the relationship between CSF PSP, blood PSP, and CSF/blood PSP in patients with PNM.

Table 3: Comparison of results of cultures and complications in the PNM group and non-PNM group.

	PNM (*n*=9)	Non-PNM (*n*=18)	*P*-value
Blood test results			
White blood count,/μL	11000 (9000–12100)	10950 (9450–16150)	0.50
Neutrophils, %	76 (70–80)	83 (79–88)	0.08
C-reactive protein, mg/dL	4.3 (3.0–15.5)	11.0 (7.9–15.7)	0.30
Procalcitonin, ng/mL	0.14 (0.09–0.21)	0.11 (0.07–0.57)	0.85
Presepsin, pg/mL	164 (114–226)	268 (145–474)	0.23
Cerebrospinal fluid results			
Cell counts,/μL	2636 (397–4801)	35 (14–203)	<0.001
Cell counts including Red blood cell,/μL	130398 (21094–935441)	5841 (220–90459)	0.02
Glucose, mg/dL	46 (29–50)	67 (59–82)	0.02
Lactate, mmol/L	4.6 (3.9–6.2)	2.9 (2.0–4.4)	0.04
Monocyte,/μL	254 (170–774)	32 (10–102)	0.001
Neutrophils,/μL	2166 (144–3467)	10 (2–84)	0.001
pH	7.49 (7.44–7.50)	7.47 (7.43–7.52)	0.91
Protein, mg/dL	95 (92–160)	73 (37–121)	0.19
Presepsin, pg/mL	898 (851–1014)	380 (242–478)	0.02
Artery blood gas analysis			
Glucose, mg/dL	144 (137–151)	127 (122–173)	0.76
pH	7.44 (7.43–7.45)	7.44 (7.42–7.46)	0.90
HCO3−, mmol/L	23.8 (23.1–24.5)	25.1 (23.3–26.3)	0.22
Lactate, mmol/L	0.70 (0.60–0.80)	0.80 (0.62–0.98)	0.34
Cerebrospinal fluid/blood ratio			
Glucose	0.29 (0.24–0.33)	0.53 (0.30–3.37)	<0.001
Lactate	6.57 (3.38–9.00)	3.76 (3.48–5.33)	0.08
Presepsin	4.05 (2.27–7.16)	1.09 (0.74–2.36)	0.006

NA: Not applicable, PNM: Postneurosurgical meningitis

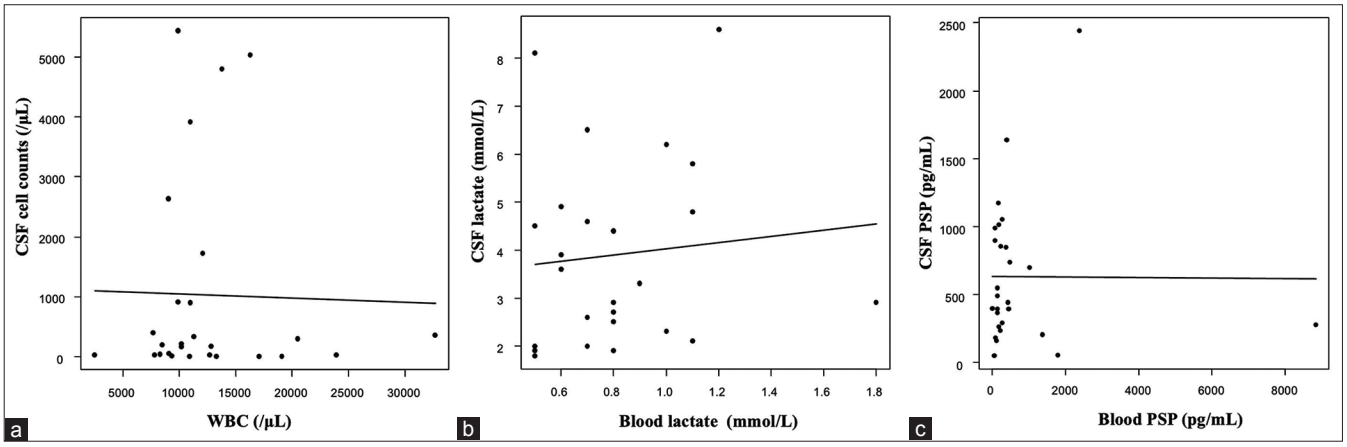

Figure 4: Correlation between blood and cerebrospinal fluid (CSF) using linear regression analyses. (a) Blood white blood cell (WBC) and CSF cell counts (r = −0.007, *P* = 0.90), (b) Blood lactate and CSF lactate (r = 0.65, *P* = 0.63), (c) Blood PSP and CSF PSP (r = 0.002, *P* = 0.97). CSF: Cerebrospinal fluid, WBC: White blood cell, PSP: Presepsin.

CONCLUSION

The CSF PSP and CSF/blood PSP ratio had a moderate to high AUC and sensitivity for the clinical diagnosis of PNM, suggesting that it might be an adjunctive biomarker for clinical diagnosis. Combining these markers with general conditions and CSF findings of previous criteria for PNM may lead to more appropriate clinical practice. Evaluating the combination of CSF and blood PSP is also useful for distinguishing whether the complex central nervous system or systemic focus infection is involved.

Data availability statement

Data requests should be made to the corresponding author.

Ethical approval

The research/study was approved by the Institutional Review Board at Nara Prefecture General Medical Center, number 517, dated March 13, 2020.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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