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Original Article

Internal Medicine Section

Diagnostic Accuracy of Cerebrospinal Fluid Procalcitonin and Serum Procalcitonin in Adult Patients with Bacterial Meningitis: A Cross-sectional Study

MONICA KARAN[1], APARAJITA PRIYADARSHINI[2], KAVITA AGGARWAL[3], KRISHNA PADARABINDA TRIPATHY[4], PRADIP KUMAR BEHERA[5]

ABSTRACT

Introduction: Bacterial Meningitis (BM) is a serious health problem worldwide with high mortality and permanent long-term neurological sequelae. Cerebrospinal Fluid (CSF) analysis is the cornerstone for diagnosing BM, but the lack of specificity creates a difficult clinical scenario for initiating proper treatment. Empiric antibiotic use in patients with suspected meningitis at primary care settings decreases the yield of CSF culture and alters CSF cytological and biochemical findings, making it further difficult to diagnose BM. To overcome this difficulty, there is a need for other biochemical markers with higher sensitivity and specificity.

Aim: To determine the diagnostic sensitivity and specificity of Procalcitonin (PCT) in serum and CSF in patients with BM and compare its diagnostic accuracy in both sample types.

Materials and Methods: A cross-sectional study was conducted in the Department of Internal Medicine at a tertiary care centre in eastern India from September 2018 to August 2020. A total of 82 adult patients with meningitis were recruited as per the protocol, and CSF analysis was done along with estimation of PCT in serum and CSF. Receiver Operating Characteristics (ROC) curve analysis of serum and CSF PCT was used to determine sensitivity and specificity with a 95% confidence interval.

Results: Out of the 82 patients recruited, 30 (36.6%) had BM. CSF PCT with a cut-off value of >0.45 ng/mL had a sensitivity of 86.7% and specificity of 92.3%. The sensitivity of serum PCT with a cut-off value of >0.6 ng/mL was 83.3%, and specificity was 86.5%. There was no statistically significant difference in sensitivity and specificity between CSF and serum PCT in patients with BM (p-value=0.7988).

Conclusion: Both serum and CSF PCT were found to have high sensitivity and specificity as markers for diagnosing BM without any statistically significant difference between them.

Keywords: Biomarker, Diagnostic sensitivity, Diagnostic specificity, Meningoencephalitis, Pyogenic meningitis

INTRODUCTION

The occurrence of BM is a significant health problem worldwide, especially in developing countries, with high morbidity and mortality even after significant development in antibiotics and vaccines [1]. Mortality rates due to BM ranges from 10 to 20% in developed nations and can reach as high as 50% in developing countries with lower resources, where BM stands as the fourth leading cause of disability [2]. Differentiating BM clinically from viral, tubercular, or fungal meningitis is difficult but as all these conditions require different but urgent therapeutic decisions, the early and accurate diagnosis of BM is crucial to save patients [3]. The diagnosis of BM largely depends on the microbiological, cytological, and biochemical analysis of CSF [4]. Though bacterial culture and gram staining of CSF are highly specific for diagnosing BM, the accuracy rates are around 70-90% for culture and 50-90% for gram staining in untreated patients. Cases admitted to tertiary care centres are often transferred from peripheral hospitals where they may have already received antibiotics, leading to further reduced diagnostic yields from CSF gram staining or culture [5,6]. CSF cytology and biochemical analysis for leukocyte type and count, of leukocytes and CSF protein levels, serve as alternative methods for diagnosing BM, but their sensitivity and specificity are relatively low [7]. Therefore, in tertiary care settings, there is a necessity for additional biochemical markers with high sensitivity and specificity that are not influenced by prior antibiotic use.

PCT has been considered as a marker of bacterial infection due to substantial rise of serum level of PCT (as high as 1000-fold rise) in response to exposure to bacterial Lipopolysaccharide (LPS) [8]. Elevated serum PCT levels in bacterial infections have been documented in number of researches [9-12]. Serum PCT is now routinely being used in clinical settings as a marker for bacterial infections, including BM [13-15]. The diagnostic efficacy of CSF PCT in central nervous system infections like meningitis is still being evaluated, with conflicting results. Studies by Mills GD et al., Jereb M et al., and Alkholi UM et al., have reported elevated levels of PCT in CSF in cases of BM [16-18]. Ahmad M et al., also observed a similar elevation of CSF PCT in BM cases, demonstrating high diagnostic value (sensitivity 100% and specificity 96.43%) [19]. However, some researchers have reported contradictory observations. Shimetani N et al., observed no significant difference in CSF PCT levels between patients with meningitis and those with non inflammatory central nervous system diseases [20].

In another study in paediatric subjects, the CSF PCT was undetectable in both bacterial as well as viral meningitis [21]. Although many studies have been carried out, the diagnostic accuracy of CSF PCT in bacterial meningitis has not been confirmed, and the role of CSF PCT as a diagnostic marker of bacterial meningitis is yet to be established. In this study, authors investigated the CSF as well as serum PCT levels in cases of meningitis with an aim to prove whether PCT can be used as a marker in diagnosing BM and differentiating it from other non BM. The two biomarkers were compared in cases of BM to determine which one (CSF or serum PCT) has superior diagnostic accuracy.

MATERIALS AND METHODS

The present study, a hospital-based cross-sectional study, was carried out in the Department of Internal Medicine, Kalinga Institute

of Medical Sciences, Bhubaneswar, Odisha, India, from September 2018 to August 2020. The study protocol was approved by the Institutional Research as well as the Ethics Committee (Ref. no. KIMS/KIIT/IEC/134/2018).

Inclusion criteria: Adult patients aged 18 years or more admitted with a clinical diagnosis of meningitis and presence of at least two of the following clinical presentations: fever, headache, neck stiffness, mental symptoms, impaired consciousness, or seizure was minimum clinical criteria required for clinical diagnosis of meningitis [22] and were included in the study.

Exclusion criteria: Patients with contraindications to lumbar puncture, presence of any active malignancy, intracranial space-occupying lesions, immunocompromised status, or Chronic Kidney Disease (CKD) were excluded from the study. Cases with CSF findings not consistent with bacterial, tubercular, or viral meningitis were also excluded.

Sample size calculation: The sample size was calculated using the minimum sample size determination procedure for estimating a population proportion. The formula used for the purpose was as follows:

$$n=(z^2_{1-\alpha/2}P(1-P)/d^2)$$

Where n=Minimum sample size.

$z^2_{1-\alpha/2}$=value of the standard normal variant for $1-\alpha/2$ level of significance=1.96.

P=Anticipated population proportion.

Confidence level=1-∝=95%

Anticipated population proportion P=80% [23,24].

Margin of error d=0.09 (8% point).

Design effect=1 (Simple random sample).

Given these input values, the minimum sample size required was computed as 76. However, the final sample size was taken as 82.

After exercising the inclusion and exclusion criteria and receipt of signed informed consent from the patients or their legitimate guardians in cases of altered mental status, the subjects were enrolled in the study.

A thorough clinical history and detailed clinical examination findings were recorded in the predesigned case report form. Routine laboratory tests were done in all enrolled cases, and lumbar puncture was performed according to the protocol. CSF was studied for cell count, cell type, biochemical analysis, Gram staining and culture, Ziehl-Neelsen (ZN) staining, Cartridge-Based Nucleic Acid Amplification Test (CBNAT), Adenosine Deaminase (ADA), Polymerase Chain Reaction (PCR) for viral aetiologies, India ink, and CSF Procalcitonin (PCT) estimation. A blood sample for serum PCT was also simultaneously sent.

PCT levels in CSF and serum samples was estimated by I CHROMATM II PCT analyser (BodiTech Med Inc, South Korea), which employs a sandwich immunodetection method. The test results were expressed in ng/mL with a reference range of 0.5 ng/mL and a working range of 0.1-100 ng/mL.

According to the patients' clinical presentation and CSF analysis, patients were classified according to the aetiology of meningitis as BM, viral meningitis, or tubercular meningitis.

A diagnosis of BM was established based on CSF analysis meeting any of the following criteria:

i. CSF cytological analysis-cell count over 500/mm^3 with neutrophilic predominance.
ii. Positive CSF culture or
iii. Negative culture but positive Gram stain [25,26].

Similarly, a diagnosis of viral meningitis was made based on CSF analysis meeting any of the following criteria:

i. CSF cytological analysis-cell count (25-500/μL) with pleocytosis or.
ii. Positive PCR results for any viral DNA/RNA in CSF [26,27].

A diagnosis of tubercular meningitis was made based on CSF analysis meeting any of the following criteria:

i. Positive smear microscopy for acid-fast bacilli.
ii. Positive ADA or CBNAAT positive.
iii. Lymphocytic pleocytosis (cell count 10-500 cells/μL) with elevated protein (1-5 g/L) [28].

After patients were classified into three groups according to the diagnostic criteria, the epidemiological data, clinical characteristics, cytological and biochemical parameters of CSF were analysed among patients with BM and other types of meningitis. The PCT levels in CSF and serum in patients with BM were analysed for any statistical significance and for diagnostic sensitivity and specificity. The sensitivity and specificity of CSF and serum PCT in cases of BM were compared for any statistically significant difference.

STATISTICAL ANALYSIS

The collected data were scrutinised, coded, and analysed by IBM Statistical Package for Social Sciences (SPSS) version 24.0 statistical software, SPSS South Asia Pvt., Ltd. Categorical variables were studied by frequency procedure. The association of seizures and co-morbidities with the type of meningitis was assessed using the cross-tabulation procedure and the Chi-square test of independence. Comparison of CSF parameters like glucose, protein, and ADA with the type of meningitis, and duration of hospital stay with the type of meningitis were done by using one-way Analysis of Variance (ANOVA) analysis. ROC curve analysis was conducted to evaluate the diagnostic accuracy of CSF PCT and serum PCT as markers of BM with a significance level for testing the hypothesis set at <0.05.

RESULTS

A total of 82 cases of meningitis diagnosed based on CSF criteria were included in the study, with a mean age of 49.0±17.6 years. The demographic and clinical characteristics of the study population are presented in [Table/Fig-1]. According to the diagnostic criteria used

Demographic/Clinical characteristics		n (%)
Gender	Male	47 (57.3)
	Female	35 (42.7)
Age (years)	<50	40 (48.8)
	>50	42 (51.2)
Types of meningitis	Bacterial	30 (36.6)
	Viral	34 (41.4)
	Tubercular	18 (22)
Symptoms/signs	Fever	80 (97.6)
	Vomiting	78 (95.1)
	Headache	76 (92.7)
	Altered sensorium	8 (9.8)
	Seizure	17 (20.7)
	Neck stiffness	45 (54.9)
CSF findings (positiveness)	Gram staining	23 (28)
	CSF culture	20 (24.4)
	AFB staining	11 (13.4)
	CBNAT	13 (15.9)
Quarter wise Incidence of Bacterial Meningitis (BM) (n=30)	1st Quarter (Jan-March)	9 (30)
	2nd Quarter (April-June)	5 (17)
	3rd Quarter (July-Sept)	2 (6.4)
	4th Quarter (Oct-Dec)	14 (46.6)

[Table/Fig-1]: Demographic and clinical characteristics of study participants (n=82).
CSF: Cerebrospinal fluid; AFB: Acid fast bacilli; CBNAT: Cartridge-based nucleic acid amplification test

in the protocol, viral meningitis was the most common type, Upon analysing the incidence of BM in relation to seasonal variation, it was observed that most BM cases (14, 46.6%) were detected in the last quarter of the year (early winter).

The clinical, CSF, and serum characteristics of different types of meningitis have been presented in [Table/Fig-2]. Analysis of PCT levels in CSF in relation to different types of meningitis revealed that both CSF and serum PCT were significantly higher in BM compared to TB meningitis or viral meningitis. The association of co-morbidities and seizures with the type of meningitis is presented in [Table/Fig-3], indicating a higher incidence of seizures with BM.

Clinical characteristics	Bacterial meningitis (BM) (n=30)	Viral meningitis (n=34)	Tubercular meningitis (n=18)	p-value
Age in years (mean±SD)	40.6±16.6	55.9±16.6	49.9±15.8	0.002
Hospital stay in days (mean±SD)	10.2±3.1	6.0±1.3	7.8±1.8	<0.001
CSF findings				
Protien in mg/dL (mean±SD)	260.4±123.5	133.9±112.6	229.1±73.7	<0.001
Glucose mg/dL (mean±SD)	30.9±9.4	52.2±20.6	36.9±7.0	<0.001
Adenosine Deaminase (ADA) in U/L (mean±SD)	2.6±1.9	3.2±3.1	15.4±5.5	<0.001
CSF PCT in ng/mL (mean±SD)	3.9±4.3	0.64±1.36	0.49±0.19	<0.001
Serum PCT in ng/mL (mean±SD)	2.3±2.9	0.40±0.69	0.19±0.06	<0.001
Blood TLC in cells/mm^3 (mean±SD)	15243.3±2259	6247.06±4191	5001.1±2760	<0.001

[Table/Fig-2]: Clinical, CSF and serum characteristics with different types of Meningitis (n=82).

Clinical characteristics	Bacterial meningitis (BM) (n=30)	Viral meningitis (n=34)	Tubercular meningitis (n=18)	p-value
Co-morbidities in %	12 (40)	11 (32.4)	3 (16.7)	0.336
No co-morbidity in %	18 (60)	23 (67.6)	15 (83.3)	
Seizure frequency in %	10 (33.3)	2 (5.9)	5 (27.8)	0.018

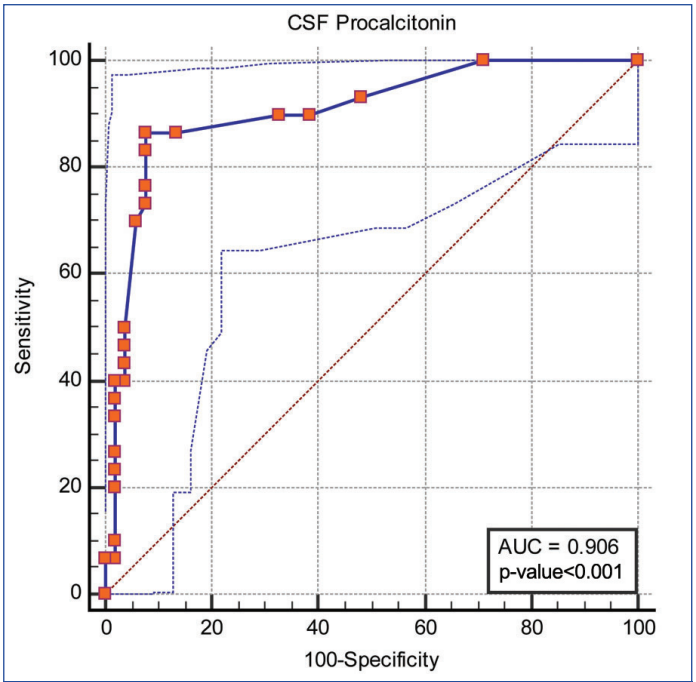
[Table/Fig-3]: Association of comorbidity and seizure with type of meningitis.

To assess the efficacy of CSF and serum PCT in diagnosing BM, the 82 subjects in the study were divided into two groups: BM and Non BM, and ROC analysis was performed. The ROC analysis of CSF PCT is shown in [Table/Fig-4]. CSF PCT had a cut-off value of >0.45 ng/mL with an Area Under Curve (AUC) of 0.906 (p-value >0.0001), indicating that CSF PCT is a very good marker of BM at this cut-off value. The ROC analysis of serum PCT as a marker of BM is presented in [Table/Fig-5]. serum PCT had a cut-off value of >0.6 ng/mL with an AUC of 0.900 (p-value >0.0001), suggesting that serum PCT is also a very good marker of BM at this cut-off value. The sensitivity and specificity of CSF and serum PCT are shown in [Table/Fig-6].

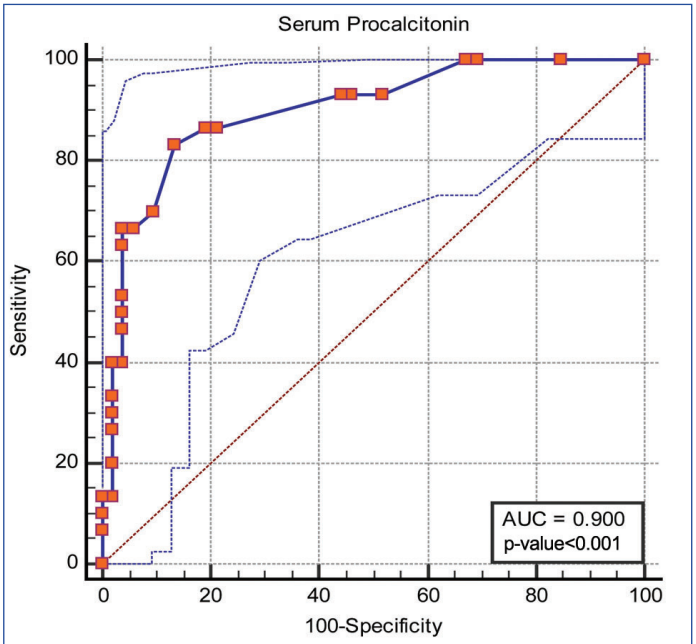
When comparing CSF and serum PCT in patients with BM, it was found that CSF PCT had slightly higher sensitivity compared to serum PCT, but the difference was not statistically significant [Table/Fig-7].

DISCUSSION

Meningitis is a devastating disease with high mortality, and survivors also suffer from significant long-term sequelae with a detrimental impact on their quality of life [29]. As a disease, meningitis is a global public health challenge, and outbreaks of meningitis warrant urgent attention. Though many different pathogens, including bacteria, mycobacteria, viruses, or fungi, can cause meningitis, bacteria are



[Table/Fig-4]: Showing the ROC analysis of CSF Procalcitonin (PCT).



[Table/Fig-5]: Showing the ROC analysis of Serum Procalcitonin (PCT).

	CSF PCT (n=30)	Serum PCT (n=30)
Area Under Curve (AUC)	0.906	0.900
95% Confidence interval	0.821 to 0.959	0.813 to 0.955
Significance level P (Area=0.5)	<0.0001	<0.0001
Associated criterion	>0.45	>0.6
Sensitivity (95% CI)	86.7	83.3
Specificity (95% CI)	92.3	86.5

[Table/Fig-6]: ROC analysis of CSF and serum PCT by in BM (n=30).

CSF Procalcitonin (PCT) VS Serum Procalcitonin (PCT)	
Difference between areas	0.00609
Standard error	0.0239
95% confidence interval	-0.0407 to 0.0529
Z Statistics	0.255
Significance level	p-value=0.7988

[Table/Fig-7]: Pair wise comparison of ROC curves of CSF and serum PCT in cases of Bacterial Meningitis (BM) (n=30).

responsible for the highest burden of acute meningitis worldwide [30]. Due to similar symptoms and signs, clinicians mostly rely on CSF cytological and biochemical findings, which are neither too sensitive nor specific and leave the treating physician in a dilemma. CSF gram stain and culture are the gold standard, and although the sensitivity and specificity have increased in recent times due to newer techniques in microbiology labs, the culture positivity is still low in meningitis. In such scenarios, elevated serum PCT has been used as a surrogate marker of BM [31]. However, CSF PCT, although studied by some researchers [32,33], is still not in clinical use due to a lack of sufficient data, the rise of PCT in some non infectious conditions like increasing age or age-related degenerative neurological conditions [34,35], and the lack of standardised cut-off levels for CSF PCT in large studies. Additionally, there are only a few studies comparing head-to-head the diagnostic accuracy of CSF and serum PCT in cases of BM [27,35]. In this study, authors have attempted to determine the sensitivity and specificity of both CSF and serum PCT for the diagnosis of BM and have also compared their diagnostic accuracy.

In the present study, serum PCT was significantly higher in patients with BM compared to viral or tubercular meningitis (p-value <0.001). A similar observation was also noted by Shen HY et al., and Saproo N and Singh R [35,36]. Konstantinidis T et al., in their study, observed that CSF PCT levels in BM were significantly higher compared to viral meningitis and control groups with sensitivity of 100% and specificity of 96.43% [37]. Shen HY et al., in their study, also noted that both CSF and serum PCT were high in BM than the Non BM group [35]. Li Y et al., in their study on post-neurosurgical BM, observed CSF PCT being high in BM patients with sensitivity and specificity of 68% and 72.7% [38]. In this study, similar observation were observed with both CSF and serum PCT being significantly higher in BM than in viral or tubercular meningitis patients with very high sensitivity and specificity (86.7% and 92.3%, respectively).

Li W et al., in their study, observed the median CSF PCT value in BM patients to be 0.22 (0.13-0.54) ng/mL, and with a cut-off value of 0.15 ng/mL, the sensitivity was 69.39 (95% CI) and specificity 91.49 (95% CI) [27]. In a meta-analysis by Kim H et al., the subgroup analysis regarding the cut-off value of CSF PCT among various studies, half of the included studies (n=9) had considered a CSF cut-off value of <0.5 ng/mL, and in the rest half of the studies, the cut-off was >0.5 ng/mL [39]. In the present study, the CSF PCT cut-off has been found to be >0.45 ng/mL with a sensitivity of 86.7 with 95% CI and specificity of 92.3 with 95%CI. The pooled sensitivity and specificity with a cut-off level <0.5 ng/mL was 0.899 (95% CI) and 0.844 (95% CI) [39], which was similar to the findings in the present study.

CSF PCT has been compared with serum PCT by some studies, with results showing disagreements among researchers. In their study to assess the diagnostic accuracy of CSF and serum PCT, Shen HY et al., concluded that serum PCT was superior to CSF PCT and could be a reliable marker to differentiate BM from viral meningitis [35]. They also observed a positive correlation between serum and CSF PCT, and as the serum PCT was higher than CSF PCT, they opined that because of a breach in the blood-brain barrier in meningitis, the serum PCT has entered into the CSF with a resultant rise in CSF PCT. However, Li W et al., in their study found that CSF PCT was the only marker that was not affected by pretreatment with antibiotics in their patients and was a superior biomarker in terms of diagnostic accuracy, whereas serum PCT was low and failed as a biomarker [27]. The authors explained this finding in terms of non entry of antibiotics into CSF due to an intact blood-brain barrier. In this study, authors also observed a higher PCT level in CSF compared to serum in cases of BM, as most of the patients are referred from peripheral health facilities where they receive at least some antibiotics, including 3rd generation cephalosporins. Another explanation for high CSF PCT compared to serum may be the local production of PCT in the CSF, as the inflammation is focal and restricted to the subarachnoid space.

But in contrast to the observations of Li W et al., present study observed serum PCT to be a good marker of BM with sensitivity and specificity of 83.3% (95% CI) and 86.5% (95% CI). When CSF PCT and serum PCT were compared, there was no statistically significant difference between the two in terms of superiority as biomarkers (p-value=0.7988) [27]. Present study observation was against the findings of Shen HY et al., who, by ROC curve analysis, compared the diagnostic accuracy of serum and CSF PCT and observed a higher AUC for serum PCT and concluded that serum PCT is superior to CSF PCT as a diagnostic marker [35]. Similar studies from the literature have been compared in [Table/Fig-8] [27,35-38].

Authors name and year	Place of study	Number of subjects	Parameters assessed	Conclusion
Konstantinidis T et al., 2015 [37]	Greece	58	CSF Procalcitonin (PCT)	CSF PCT significantly higher in BM as compared to controls
Li Y et al., 2015 [38]	Beijing, China	178	CSF PCT and Lactate	CSF PCT higher in BM patients as compared to non BM patients (p-value <0.001)
Shen HY et al., 2015 [35]	Shanghai, China	150	Serum and CSF PCT	Both CSF and serum PCT significantly elevated in BM than non BM patients
Li W et al., 2017 [27]	Xian, China	135	CSF and Serum PCT	CSF PCT was significantly higher in BM patients where as serum PCT elevation was not statistically significant
Saproo N and Singh R 2021 [36]	Jammu, India	100	CSF and Serum PCT	Serum PCT elevated significantly but not CSF PCT in BM patients as compared to non BM patients
Present study, 2024	Bhubaneswar, India	82	CSF and Serum PCT	Both CSF and serum PCT significantly elevated in BM than non BM patients

[Table/Fig-8]: Comparison of similar studies in respect to conclusion [27,35-38].

Limitation(s)

Though the subjects in the present study were mostly referred cases having received antibiotics before they were enrolled, and the subjects were not segregated as with or without antibiotic treatment, which may influence the PCT level in serum or CSF. A study with similar objectives but in groups with antibiotic and no antibiotic use will shed light on the influence of pretreatment antibiotics on serum and CSF PCT. The combined diagnostic accuracy of CSF PCT and other CSF parameters markers needs to be evaluated.

CONCLUSION(S)

From the present work, it can be concluded that both CSF and serum PCT can be good biomarkers in the diagnosis of BM and will help clinicians in differentiating bacterial from non BM. When questioning about superiority among the two, both CSF and serum PCT were of equal sensitivity and specificity for diagnosing BM in adult patients without any statistical significance.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Neurology, IMS and SUM Hospital, Bhubaneswar, Odisha, India.
2. Associate Professor, Department of Physiology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
3. Professor, Department of Biochemistry, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
4. Professor, Department of Internal Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
5. Professor, Department of Internal Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Pradip Kumar Behera,
Flat No. B 202, Elegance Apartment, Kalara Hanga, PO KIIT, Dist. Khurda,
Bhubaneswar-751024, Odisha, India.
E-mail: drpradip76@gmail.com

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