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Role of Inflammatory Biomarkers in Early Diagnosis of Bacterial and Aseptic Meningitis

Eesha Tariq Bhatty[1], Mobashra Mustafa[2], Mahnoor Rao[2], Arslan Ullah Khan[3], Umer Farooq[3], Hafiz Anas Saeed[3], Zainab Yousaf[4]

Correspondence
Zainab Yousaf
zainabyousaf00@gmail.com

Affiliations
1 Department of Pharmaceutics, Akhtar Saeed College of Pharmacy, Westwood, Lahore, Pakistan
2 Institute of Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan
3 Department of Medical Laboratory Technology, Allama Iqbal Medical College, Lahore, Pakistan
4 Department of Pathology, Farooq Hospital Westwood, Lahore, Pakistan

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ABSTRACT

Background: Aseptic meningitis (AM) typically has a better prognosis than bacterial meningitis (BM) and is less severe. Procalcitonin (PCT) and high-sensitive C-reactive protein (hs-CRP) are valuable biomarkers for differentiating between these two types of meningitis.

Objective: To determine the levels of PCT and hs-CRP in patients with AM and BM for early diagnosis and differentiation.

Methods: This cross-sectional study included 90 patients aged 2 to 12 years with meningitis symptoms. Lumbar punctures were performed for cerebrospinal fluid (CSF) analysis, and blood samples were collected to assess hs-CRP and PCT levels using an automated chemiluminescence immunoassay analyzer. Data were analyzed using IBM SPSS version 25.0, with chi-square tests applied to assess associations between biomarkers and meningitis type.

Results: Positive hs-CRP (>0.70 mg/L) was found in 68.96% of BM patients and 6.25% of AM patients (p=0.328). Positive PCT (>0.05 ng/ml) was found in 75.86% of BM patients and 12.50% of AM patients, with a significant association (p=0.001).

Conclusion: PCT is a more reliable biomarker than hs-CRP for early differentiation between BM and AM, aiding in prompt and accurate diagnosis.

INTRODUCTION

Meningitis, an inflammation of the meninges, can be caused by various infectious agents, including bacteria, viruses, and fungi. It is a particularly dangerous condition in neonates and young children, where bacterial meningitis (BM) is most prevalent, especially in neonates under two months of age, who exhibit the highest incidence (1). The primary bacterial pathogens responsible for meningitis include Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and Streptococcus agalactiae. Among neonates, group B streptococcus is a leading cause of BM, which remains a significant contributor to global meningitis-related fatalities, accounting for nearly half of these deaths. Without timely intervention, BM can lead to severe complications or death, with mortality rates ranging from 5-20% in children and 20-50% in adults (2, 3).

Aseptic meningitis (AM), characterized by meningeal inflammation without an infectious cause, is identified by cerebrospinal fluid (CSF) pleocytosis exceeding five cells per mm^3. AM encompasses a broad spectrum of etiologies, including viral and non-viral infections, medications, cancer, and systemic diseases. Enteroviruses, particularly Echoviruses and Coxsackie viruses, are the most frequent viral causes of AM. Clinically, AM presents with symptoms such as headache, fever, malaise, and photophobia, with severe manifestations like seizures and brain damage being rare unless caused by non-viral infectious agents. Diagnosis of AM involves serological testing, blood, and CSF investigations, with polymerase chain reaction (PCR) techniques playing a pivotal role in the rapid and accurate identification of microbial DNA in CSF (4-6).

Prompt diagnosis and treatment of meningitis are crucial to prevent severe outcomes, including organ loss, visual impairment, seizures, brain damage, and hearing loss in survivors. Although clinical symptoms alone cannot reliably differentiate meningitis from other conditions with similar presentations, CSF examination remains the gold standard for diagnosis. However, obtaining definitive results from CSF culture can take up to two days, necessitating the use of

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additional inflammatory markers in managing meningitis (7, 8).

In recent years, acute-phase inflammatory proteins have been incorporated into the screening of febrile children, with high-sensitive C-reactive protein (hs-CRP) emerging as a valuable marker for estimating infections in this population. Conversely, procalcitonin (PCT), the precursor of calcitonin, has garnered attention as a specific marker for bacterial infections. Under normal physiological conditions, PCT is produced in the thyroid gland and rapidly cleaved into calcitonin, a hormone involved in calcium homeostasis. During bacterial infections, however, extra-thyroidal organs, such as the liver, intestines, and lungs, release PCT in response to bacterial endotoxins and inflammatory mediators like interleukin-1β and tumor necrosis factor-α, resulting in a significant increase in PCT levels (9-11). This elevation makes PCT a useful diagnostic tool for distinguishing bacterial infections from non-bacterial causes of inflammation (12).

Given the importance of early and accurate diagnosis of meningitis, the present study aims to evaluate the levels of hs-CRP and PCT in patients with AM and BM. By identifying the inflammatory biomarkers associated with these conditions, the study seeks to provide insights that could minimize treatment delays and improve patient outcomes.

MATERIAL AND METHODS

The study was a cross-sectional analysis conducted to assess the levels of high-sensitive C-reactive protein (hs-CRP) and procalcitonin (PCT) in patients diagnosed with bacterial meningitis (BM) and aseptic meningitis (AM). The study population included both male and female patients aged between 2 and 12 years who presented with symptoms suggestive of meningitis. Patients with other brain infections or those older than 12 years were excluded from the study to ensure the specificity of the findings related to meningitis.

The diagnosis of BM and AM was confirmed through a comprehensive examination of cerebrospinal fluid (CSF), obtained via lumbar puncture performed by a neurophysician on patients suspected of having meningitis. CSF samples were analyzed for cellular composition, glucose, and protein levels, and were subjected to Gram staining and culture to identify bacterial pathogens. BM was diagnosed based on positive findings in the CSF bacterial culture, Gram stain, and complete examination, while AM was diagnosed when the CSF bacterial culture was negative (14).

After the initial diagnostic procedures, venous blood samples (3-5 mL) were collected from each patient into clotted vacutainers following informed consent. The blood samples were then analyzed for hs-CRP and PCT levels using an automated chemiluminescence immunoassay analyzer. Internal and external quality controls were employed to ensure the accuracy and reliability of the test results.

Data were collected systematically, and patient information was anonymized to maintain confidentiality. The study adhered to the ethical principles outlined in the Declaration of Helsinki, and ethical approval was obtained from the relevant institutional review board before the commencement of the study. Informed consent was obtained from the parents or guardians of all participating children, ensuring that they were fully informed about the nature of the study and its potential risks and benefits.

Statistical analysis was conducted using IBM SPSS version 25.0. The data were presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. The chi-square test was utilized to assess the association between hs-CRP and PCT levels with the type of meningitis. A p-value of less than 0.05 was considered statistically significant in all analyses. The results were interpreted in the context of existing literature, with attention to the limitations and strengths of the study design and methodology (13).

RESULTS

The study included a total of 90 patients diagnosed with meningitis, of whom 40 (44.4%) were male and 50 (55.6%) were female. The age of the patients ranged from 2 to 12 years, with a mean age of 5.98 ± 2.79 years. The patients were categorized into two groups based on cerebrospinal fluid (CSF) examination: bacterial meningitis (BM) and aseptic meningitis (AM). Overall, 58 patients (64.4%) were diagnosed with BM, while 32 patients (35.6%) were diagnosed with AM.

The demographic and clinical characteristics of the patients are summarized in Table 1. Among the 58 BM patients, 26 (44.82%) were male and 32 (55.17%) were female. In the AM group, 14 (43.75%) were male and 18 (56.25%) were female. Regarding age distribution, 36 (62.06%) of the BM patients and 16 (50.0%) of the AM patients were between 2 to 6 years old, while 22 (37.93%) of the BM patients and 16 (50.0%) of the AM patients were between 7 to 12 years old. The statistical

analysis revealed no significant association between the type of meningitis and age groups (p=0.318) or gender (p=0.597).

Table 1: Demographic and Clinical Characteristics of Patients with Bacterial and Aseptic Meningitis

	Frequency (%)
Mean Age (Years)	5.98 ± 2.79
Age Groups	
2-6 Years	54 (60.0%)
7-12 Years	36 (40.0%)
Gender	
Male	40 (44.4%)
Female	50 (55.6%)
Type of Meningitis	
Bacterial Meningitis	58 (64.4%)
Aseptic Meningitis	32 (35.6%)

The levels of hs-CRP and procalcitonin were analyzed in both BM and AM patients. The results are presented in Tables 2 and 3.

hs-CRP Levels: In the BM group, hs-CRP was positive (>0.70 mg/L) in 40 patients (68.96%) and negative (<0.70 mg/L) in 18 patients (31.03%). In the AM group, hs-CRP was positive in only 2 patients (6.25%) and negative in 30 patients (93.75%). The overall mean hs-CRP level was 28.20 ± 39.35 mg/L. There was no statistically significant association between hs-CRP levels and the type of meningitis (p=0.328).

Table 2: Levels of hs C-Reactive Protein in Bacterial and Aseptic Meningitis

	Bacterial Meningitis (n=58)	Aseptic Meningitis (n=32)	p-value (Chi-square)
hs-CRP <0.70 mg/L	18 (31.03%)	30 (93.75%)	0.328
hs-CRP >0.70 mg/L	40 (68.96%)	2 (6.25%)	
Mean ± SD	28.20 ± 39.35		

Procalcitonin Levels: Procalcitonin was positive (>0.05 ng/ml) in 44 BM patients (75.86%) and negative (<0.05 ng/ml) in 14 BM patients (24.13%). Among AM patients, procalcitonin was positive in 4 patients (12.50%) and negative in 28 patients (87.50%). The overall mean procalcitonin level was 8.49 ± 14.47 ng/ml. A statistically significant association was found between procalcitonin levels and the type of meningitis These results indicate that while hs-CRP levels were not significantly different between patients with BM and AM procalcitonin levels were markedly higher in BM patients, suggesting that procalcitonin may serve as a more reliable early diagnostic biomarker for differentiating between bacterial and aseptic meningitis.

Table 3: Levels of Procalcitonin in Bacterial and Aseptic Meningitis

	Bacterial Meningitis (n=58)	Aseptic Meningitis (n=32)	p-value (Chi-square)
Procalcitonin <0.05 ng/ml	14 (24.13%)	28 (87.50%)	0.001*
Procalcitonin >0.05 ng/ml	44 (75.86%)	4 (12.50%)	
Mean ± SD	8.49 ± 14.47		

DISCUSSION

The present study sought to evaluate the levels of high-sensitive C-reactive protein (hs-CRP) and procalcitonin (PCT) in pediatric patients diagnosed with bacterial meningitis (BM) and aseptic meningitis (AM) to identify reliable biomarkers for early differentiation between these two forms of meningitis. The findings revealed that while hs-CRP levels did not significantly differ between the BM and AM groups, PCT levels were markedly elevated in BM patients, indicating that PCT might be a more sensitive and specific marker for diagnosing bacterial infections in the context of meningitis.

The lack of a statistically significant difference in hs-CRP levels between BM and AM patients is consistent

with previous studies that questioned the diagnostic utility of hs-CRP in distinguishing between bacterial and viral infections (19). Although hs-CRP is a well-established marker of inflammation, its elevation in non-bacterial conditions, such as viral infections and systemic inflammatory responses, reduces its specificity as a biomarker for bacterial meningitis. This aligns with findings from other studies, such as those conducted by Alnomasy et al., which also demonstrated that hs-CRP had a limited role in differentiating BM from AM (19). The current study supports this conclusion, suggesting that hs-CRP, despite being a useful inflammatory marker, may not be reliable for early differentiation between BM and AM.

In contrast, the significant elevation of PCT levels in BM patients observed in this study underscores the potential of PCT as a robust biomarker for bacterial infections. PCT levels were significantly higher in BM patients compared to those with AM, which is in agreement with numerous studies that have identified PCT as a valuable marker for bacterial sepsis and meningitis (12, 19). The rapid and significant increase in PCT levels in response to bacterial endotoxins and inflammatory mediators provides a pathophysiological basis for its use as an early diagnostic tool in bacterial meningitis. This study's findings are consistent with those of Castagno et al., who reported that PCT was the only laboratory test that reliably predicted BM in children (20).

The study's design, which included a well-defined pediatric cohort and the use of standardized diagnostic criteria for meningitis, adds strength to the findings. However, there were some limitations that should be acknowledged. The relatively small sample size and the single-center nature of the study may limit the generalizability of the results. Additionally, while the study focused on hs-CRP and PCT, other potential biomarkers, such as lactate or interleukins, were not assessed, which could have provided a more comprehensive understanding of the inflammatory response in meningitis. Furthermore, the study did not account for possible confounding factors, such as prior antibiotic use or the presence of co-infections, which might have influenced the levels of hs-CRP and PCT.

Despite these limitations, the study provides valuable insights into the use of PCT as an early diagnostic marker for BM. The findings suggest that incorporating PCT measurement into the clinical management of suspected meningitis could improve the accuracy of early diagnosis and help guide timely and appropriate treatment, potentially reducing the morbidity and mortality associated with bacterial meningitis. Future research should aim to validate these findings in larger, multi-center studies and explore the potential role of additional biomarkers in conjunction with PCT for a more comprehensive diagnostic approach. Additionally, studies investigating the cost-effectiveness of routine PCT testing in resource-limited settings would be beneficial, given the global burden of meningitis.

In conclusion, while hs-CRP did not show significant utility in differentiating between bacterial and aseptic meningitis, PCT emerged as a promising biomarker for early diagnosis. These findings contribute to the growing body of evidence supporting the clinical value of PCT in the management of pediatric meningitis, highlighting the need for its broader implementation in clinical practice to enhance patient outcomes.

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