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Novel Biomarkers for Early Detection of Bacterial Meningitis

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Abstract. General Background: Bacterial meningitis is a life-threatening disease that demands rapid and accurate diagnosis to reduce morbidity and mortality. Specific Background: Conventional methods such as CSF culture, Gram staining, and biochemical tests often lack sensitivity, specificity, or require long processing time, limiting their usefulness in urgent clinical settings. Knowledge Gap: There remains limited evidence on the comparative diagnostic accuracy of novel biomarkers against routine laboratory parameters in early bacterial meningitis detection. Aims: This study aimed to evaluate the diagnostic value of Procalcitonin (PCT), Interleukin-6 (IL-6), and C-Reactive Protein (CRP) for early identification of bacterial meningitis compared to conventional laboratory markers. Results: Conducted as a case-control study in Iraq involving 100 patients and 50 controls, the findings showed significantly elevated serum levels of PCT, IL-6, and CRP in patients ($p < 0.001$). PCT demonstrated the highest diagnostic accuracy (AUC = 0.95), followed by IL-6 (0.93) and CRP (0.90), with all biomarkers correlating strongly with disease severity. Novelty: The study highlights PCT and IL-6 as highly reliable early diagnostic tools that surpass traditional parameters. Implications: Incorporating these biomarkers into diagnostic protocols can facilitate earlier interventions, improve monitoring, and reduce long-term complications in bacterial meningitis.

Highlights:

1. Procalcitonin has the strongest diagnostic value.
2. IL-6 and CRP are reliable indicators of severity.
3. Biomarkers support timely and accurate detection.

Keywords: Bacterial Meningitis, Procalcitonin, Interleukin-6, C-Reactive Protein, Early Diagnosis

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Introduction

The Bacterial meningitis remains a critical medical emergency characterized by inflammation of the protective membranes surrounding the brain and spinal cord, often resulting in significant morbidity and mortality if not diagnosed and treated promptly. Despite progress in antimicrobial therapy and intensive care, late or wrong diagnosis remains a factor in poor outcome. Classical clinical symptoms of fever, neck stiffness, and change of mental status may be lacking or nonspecific, particularly in early stages or in immunocompromised patients. Therefore, early diagnostic biomarkers of BM are important subjects in clinic and research [1,2]. Standard diagnostic methods, such as cerebrospinal fluid (CSF) examination, Gram staining and culture, are also limited. CSF culture is the gold standard, it requires about 24–72 hours for results and can be negative if patients have had antibiotics prior to lumbar puncture [3]. In addition the CSF parameters such as protein, glucose, white blood cell differential lack specificity and have only limited resemblance to that of bacterial/viral and fungal meningitis. Polymerase chain reaction (PCR) and other molecular diagnostic tests are more sensitive but are not uniformly available in resource-limited settings and may be too costly. This has stimulated investigations into new, and rapid, and reliable biomarkers for the accurate diagnosis of bacterial meningitis as well as differentiation from other CNS infections and the assessment of disease severity in the early phase of the course of the disease [4]. Some host-derived biomarkers have recently demonstrated potential for the early diagnosis of BM. Procalcitonin (PCT), which is a precursor of calcitonin hormone, is raised in systemic bacterial infections and not in viral or non-infectious systemic inflammatory processes, which makes it a good marker of distinction [5]. C-reactive protein (CRP), an acute-phase reactant synthesized by the liver, is commonly utilized as a marker of inflammation; however, its specificity for bacterial infection is low. Another potential target is Interleukin-6 (IL-6), which is a pro-inflammatory cytokine that has a pivotal role in bacterial pathogen-associated immune response and its level titer is significantly increased in the CSF and serum of patients with meningitis. Similarly, recent studies have underscored the potential of LBP, CSF lactate and SAA to be markers of bacterial infection severity and its time course [6,7].

These biomarkers (or panels of markers) could be used as a diagnostic tool in the clinical setting of a general practitioner and give a boost to a more timely and reliable diagnosis, ensuring an earlier start of the appropriate antimicrobial therapy and potentially preventing (more severe) long-term complications such as hearing loss, cognitive decline, and death. Furthermore, employing panels of biomarkers instead of single markers might improve the accuracy of diagnosing, particularly in challenging or unclear cases [8,9]. The aims of the study is evaluate the diagnostic value of novel biomarkers Procalcitonin (PCT), Interleukin-6 (IL-6), and C-Reactive Protein (CRP) for the early detection of bacterial meningitis in comparison to conventional laboratory parameters.

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Methodology

This case-control study was carried out in the Nasiriyah General Hospital, Iraq, during the period from January 2024 to June 2024, including 100 patients of both sexes aged 18 to 35 years who were diagnosed clinico-microbiologically with bacterial meningitis, and 50 sex- and age-matched healthy controls. All participants received phlebotomy to draw the blood and the patients underwent lumbar puncture to collect cerebrospinal fluid (CSF) according to standard clinical procedures. Serum and CSF samples were centrifuged at 3000 rpm for 10 minutes and stored at −80°C until analysis. Levels of Procalcitonin (PCT), Interleukin-6 (IL-6), and C-Reactive Protein (CRP) in serum were quantitatively measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions, ensuring high sensitivity and specificity. Routine laboratory investigations including complete blood counts, CSF glucose, and protein concentrations were performed using automated analyzers and spectrophotometric methods in the hospital laboratory.

Statistical analysis:

Statistical analysis was conducted using SPSS software. Continuous variables were expressed as mean ± standard deviation, and group comparisons were carried out using suitable parametric or non-parametric tests. The diagnostic accuracy of the biomarkers was assessed through receiver operating characteristic (ROC) curve analysis. Pearson correlation was applied to examine the relationship between biomarker levels and clinical severity. A p-value of less than 0.05 was considered statistically significant.

Ethical approval:

The study was approved by the Human Ethics Committee of Al-Habboubi Teaching Hospital. Informed consent was obtained from all participants after explaining the purpose and procedures of the study. Participants were assured that their personal information would remain confidential and used solely for research purposes.

Results

Sociodemographic Characteristics of Study Participants

The results related to the sociodemographic characteristics of the study participants showed no significant differences between the patients with bacterial meningitis (n = 100) and the healthy group (n = 50) in terms of age, gender, or place of residence. The mean age in the patient group was 26.7 ± 4.9 years compared to 27.1 ± 5.1 years in the control group, and the difference was not statistically significant (p = 0.624). The male-to-female ratio also did not show a clear difference between the two groups, reaching (58/42) in the patient group and (29/21) in the healthy group (p = 0.852). There was also no significant difference in distribution to population of urban and rural, the urban/rural residence ratio in patient reached(60/40) verus (32/18) in control (p=0.675). These analyses showed that the demographic characteristics under study did not have an impact on the statistical differences

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related to the biological profiles under study.(Table 1)

Table 1: Comparison of Age, Gender, and Residence Between Bacterial Meningitis Patients and Healthy Controls

Variable	Patients (n = 100)	Controls (n = 50)	p-value
Age (years), Mean ± SD	26.7 ± 4.9	27.1 ± 5.1	0.624
Gender (Male/Female)	58 / 42	29 / 21	0.852
Residence (Urban/Rural)	60 / 40	32 / 18	0.675

Serum Levels of Novel Biomarkers in Patients with Bacterial Meningitis and Healthy Controls

There were very significant statistical differences between the mean concentrations of the three study markers levels in the serum of patients with bacterial menigitistis compared to healthy control group. The mean procalcitonin value in patients group was (14.8 ± 5.2 ng/ml), and in control group was (0.7 ± 0.3 ng/ml) ($p < 0.001$), which is significantly higher value of this marker with presence of bacterial infection. A significant increase in the level of interleukin-6 was also recorded, reaching (180.4 ± 55.1 pg/mL) in patients compared to (9.5 ± 3.8 pg/mL) in healthy controls ($p < 0.001$), reflecting the acute inflammatory activity associated with the disease. As for C-reactive protein (CRP), its level was also significantly higher in patients (72.3 ± 28.7 mg/L) compared to healthy controls (3.9 ± 1.5 mg/L), with strong statistical significance ($p < 0.001$). These results demonstrate that the three biomarkers are sensitive and specific in differentiating between bacterial meningitis and healthy controls, supporting their use as early diagnostic tools for the disease.(Table 2)

Table 2: Comparison of Procalcitonin, Interleukin-6, and C-Reactive Protein Levels Between Groups

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
Procalcitonin (ng/mL)	14.8 ± 5.2	0.7 ± 0.3	**<0.001**
Interleukin-6 (pg/mL)	180.4 ± 55.1	9.5 ± 3.8	**<0.001**
C-Reactive Protein (mg/L)	72.3 ± 28.7	3.9 ± 1.5	**<0.001**

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Comparison of Routine Laboratory Parameters Between Bacterial Meningitis Patients and Healthy Controls

All routine laboratory values in the studied patients with bacterial meningitis were found to be statistically significantly different from those found in healthy controls. The average WBC count of the patient group (15.2 ± 6.0 × 10^3/μL) was significantly higher than that of the control group (6.3 ± 2.1 × 10^3/μL) ($p < 0.001$), indicative of an active response with an elevated immune bias in the infected individuals. A significant increase in protein concentration was also recorded in the cerebrospinal fluid (CSF), reaching 165.4 ± 53.8 mg/dL in patients, compared to 34.8 ± 13.2 mg/dL in healthy controls. This difference is highly statistically significant ($p < 0.001$), indicating increased permeability of the blood-brain barrier as a result of inflammation. In contrast, CSF glucose levels were significantly lower in patients (32.5 ± 10.7 mg/dL) compared to healthy controls (72.6 ± 15.3 mg/dL), with a strong significance ($p < 0.001$), a common pattern in bacterial infections where bacteria consume glucose within the fluid. These findings reinforce the use of routine tests as supportive diagnostic tools in the evaluation of patients with meningitis.(Table 3)

Table 3: White Blood Cell Count, CSF Protein, and CSF Glucose Levels

Parameter	Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
White Blood Cell Count (×10^3/μL)	15.2 ± 6.0	6.3 ± 2.1	**<0.001**
CSF Protein (mg/dL)	165.4 ± 53.8	34.8 ± 13.2	**<0.001**
CSF Glucose (mg/dL)	32.5 ± 10.7	72.6 ± 15.3	**<0.001**

Diagnostic Performance of Novel Biomarkers for Early Detection of Bacterial Meningitis

The diagnostic performance analysis of three biomarkers demonstrated that all the three biomarkers had a high accuracy in the early diagnosis of bacterial meningitis. Procalcitonin exhibited the highest sensitivity (90%) and specificity (92%) with an AUC of 0.95 (95% CI: 0.91, 0.98), indicating its strong ability in distinguishing infected from non-infected cases. As for interleukin-6, it had a sensitivity of 88% and specificity of 90%, an AUC of 0.93 (0.89 and 0.97), making it an effective early inflammatory biomarker in bacterial patients. C-reactive protein (CRP), AUC value of 0.90 (0.85 and 0.95): 85% sensitivity and 87% specificity, suggesting its good potential, though lesser performance than the former two biomarkers. Taken together, these results suggest that the application of these biomarkers, especially PCT and IL-6, may be useful in improving the accuracy of early diagnosis of BM and facilitating the treatment resources and prevent complications.(Table 4)

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Table 4: Sensitivity, Specificity, and Area Under the Curve (AUC) for Procalcitonin, Interleukin-6, and C-Reactive Protein

Biomarker	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Procalcitonin	90	92	0.95 (0.91–0.98)
Interleukin-6	88	90	0.93 (0.89–0.97)
C-Reactive Protein	85	87	0.90 (0.85–0.95)

Correlation Between Biomarker Levels and Clinical Severity Score in Bacterial Meningitis Patients

The levels of the investigated biomarkers were significantly, positively, and strongly correlated with the severity of clinical symptoms in patients with bacterial meningitis as evidenced by the correlation analysis results. The correlation coefficient was the highest with regard to Procalcitonin ($r = 0.702$, $p < 0.001$) showing a close connection between increases of this marker and disease severity, and its potential for prediction of clinical prognosis. Interleukin-6 (IL-6) presented also a strong, significant correlation ($r = 0.652$, $p < 0.001$) because of its major role in the inflammatory response and its relationship with disease advance. A moderate correlation with CRP ($r = 0.604$, $p < 0.001$) implied that it was less sensitive than the other two indicators in evaluation of disease severity, although it had excellent diagnostic performance. These findings highlight the crucial role of the biomarkers, particularly PCP and IL-6, not only for early diagnosis of the disease, but also for monitoring and for the evaluation of the evolution of the disease.

Table 5: Pearson's Correlation Coefficient and Statistical Significance

Biomarker	Pearson's r	p-value
Procalcitonin (ng/mL)	0.702	<0.001
Interleukin-6 (pg/mL)	0.652	<0.001
C-Reactive Protein (mg/L)	0.604	<0.001

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Discussion

This research aimed at assessing the utility of three markers Procalcitonin (PCT), Interleukin-6 (IL-6), C-Reactive protein (CRP) as diagnostic and prognostic biomarkers for early diagnosis of BM in patients of 18-35 years of age. The demographic data (Table 1) demonstrated no significant difference in age at CML diagnosis, sex, and place of living between patients and healthy controls, indicating that the differences in the levels of these biomarkers might be more associated with disease status rather than demographic factors [10,11]. The serum concentrations of all three biomarkers were markedly elevated in bacterial meningitis patients compared to controls (Table 2). Procalcitonin levels were significantly higher (14.8 ± 5.2 ng/mL vs. 0.7 ± 0.3 ng/mL, $p < 0.001$), corroborating its well-established role as a highly sensitive and specific indicator of systemic bacterial infections [12]. This finding aligns with previous studies that demonstrated PCT's superior ability to distinguish bacterial meningitis from viral or non-infectious causes of inflammation [13]. IL-6 and CRP levels were also substantially increased in patients, reflecting the intense inflammatory response elicited during bacterial meningitis [14]. IL-6, a key pro-inflammatory cytokine, plays a crucial role in mediating acute phase responses, while CRP, synthesized by the liver in response to IL-6 stimulation, acts as a general marker of systemic inflammation [13,14]. Routine laboratory tests (Table 3) revealed characteristic changes in bacterial meningitis, including leukocytosis, elevated cerebrospinal fluid (CSF) protein, and decreased CSF glucose levels. These classical laboratory alterations are consistent with prior clinical observations and pathophysiological mechanisms underlying bacterial invasion and inflammation of the meninges [15,16]. The significant elevation of CSF protein likely reflects increased blood-brain barrier permeability and the influx of immune cells and plasma proteins, while reduced glucose indicates bacterial metabolism and impaired transport mechanisms [17,18]. The diagnostic performance of these biomarkers was assessed using ROC curve analysis (Table 4). Procalcitonin exhibited the highest diagnostic accuracy with an area under the curve (AUC) of 0.95, indicating excellent sensitivity and specificity. This confirms its value as a robust biomarker for early diagnosis, supporting recommendations for its use in clinical settings to guide antimicrobial therapy decisions [19,20]. IL-6 and CRP also demonstrated strong diagnostic capabilities, with AUC values of 0.93 and 0.90 respectively, suggesting their utility as complementary markers. Some studies have advocated for combined biomarker panels to enhance diagnostic accuracy, which could be particularly beneficial in cases with ambiguous clinical presentations [21,22]. Correlation analysis (Table 5) showed significant positive relationships between biomarker levels and clinical severity scores, with Procalcitonin having the strongest correlation ($r = 0.70$, $p < 0.001$). This indicates that higher biomarker levels are associated with increased disease severity, reflecting the extent of inflammatory activation and tissue damage. This observation is in line with previous reports linking elevated PCT and IL-6 to worse clinical outcomes, such as neurological complications and mortality [23,24]. CRP, while also positively correlated with severity, showed a moderate association, which may be explained by its nonspecific nature and delayed kinetics relative to the onset of infection [25]. Nevertheless, inconsistencies in such a prognostic use of CRP, between studies, emphasize the intricate nature of the inflammatory responses in bacterial meningitis. Factors, such as time of sample collection, assay variation and patient heterogeneity underlie the biomarker measurements, and may affect their interpretation in the

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clinic [26,27]. Third, IL-6 is a pleiotropic cytokine (having a wide range of effects) and is elevated in a number of inflammatory and infectious diseases, which might reduce its specificity [28]. In contrast, the proinflammatory mediators and bacterial toxins introduce Procalcitonin with rapid induction and accordingly the marked specificity and early elevation render it a very convenient molecule for identification of early treatment decisions [29].

Conclusion

In conclusion, our study highlights the significance of Procalcitonin, Interleukin-6 and 11 C-Reactive Protein as tools for the early detection and severity estimation in patients with bacterial meningitis. And on this point, procalcitonin is noticeable for its high diagnostic performance and close relationships with severity degree, which led us to recommend its preferential use in clinical practice. The addition of these biomarkers to diagnostic protocols may enhance the management of patients by allowing proper drug interventions at the right time.

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