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Diagnostic Performance Evaluation of Cerebrospinal Fluid Procalcitonin in Patients with Bacterial Meningitis from Sourô Sanou University Hospital, Burkina Faso

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Abstract: Procalcitonin (PCT) is a biomarker for bacterial infections. The aim of this study was to evaluate diagnostic performance of cerebrospinal fluid procalcitonin (CSF PCT) as tools for detecting bacterial meningitis. This was a prospective and descriptive study conducted at Sourô Sanou University Hospital from May to August 2022. Random sampling was carried out, including patients with suspected bacterial meningitis. Quantitative procalcitonin was determined on CSF supernatants by electrochemiluminescence. Direct real-time PCR (rt-PCR) was applied from the specimen, for species diagnosis of Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae. Fisher's exact test was used to assess associations with a significance level of 0.05%. Receiver Operating Characteristic (ROC) analysis was used to assess diagnostic performance. A total of 52 patients with a median age of 18.00 years (minimum-maximum: 0.030-87 years) were included. PCR analysis was positive in 13.46% CSF samples (7/52). A new CSF PCT cut-off value equal to 0.106 ng/mL was determined, with a diagnostic sensitivity and specificity of 100.0% [IC95%=59.0-100.0] and 40.0% [IC95%= 25.7-55.7]. The area under the curve (AUC) for CSF PCT obtained was equal to 0.597 [CI95%=0.439-0.754]. So, we can assume CSF PCT to be a fairly good tool for detecting bacterial meningitis in suspected meningitis. Further research is needed to better determine CSF PCT's diagnostic contribution in patients with tropical diseases.

Keywords: Bacterial Meningitis, Procalcitonin, Cerebrospinal Fluid

1. Introduction

Bacterial meningitis is a major cause to morbidity and mortality worldwide, with 1.2 million cases reported each year and 135,000 deaths. Member states within Africa's meningitis belt reported 19,552 new cases and 885 deaths

in 2020 [1]. Many biomarkers have been evaluated in response to the need for rapid diagnosis of bacterial meningitis [2], including procalcitonin (PCT). PCT is a protein marker with serum concentrations increasing during bacterial infection [3]. An international meeting has designated PCT as an indicator in sepsis diagnosis and its importance in diagnosis and therapeutic treatment for bacterial infections [4]. Several authors have observed an increase in serum and cerebrospinal fluid (CSF) PCT during intracranial infections [4-6]. Wang et al., (2020) showed that when cerebrospinal fluid PCT was higher than serum PCT, this could be a diagnostic indicator for intracranial infections [7]. However, studies have shown that when neurosurgery has compromised the blood-brain barrier, CSF PCT increases are no longer specific due to serum PCT influence [8, 9]. Furthermore, few studies have been carried out on bacterial meningitis in patients without neurosurgery [10]. As previously reported, no study has been carried out to determine PCT in CSF for bacterial meningitis diagnosis in Burkina Faso. This study was performed to evaluate diagnostic performance of cerebrospinal fluid procalcitonin in patients with suspected bacterial meningitis.

2. Methodology

2.1. Study Population and Sampling

This was a prospective and descriptive study conducted at Sourô Sanou University Hospital from May to August 31, 2022. Patients hospitalized in clinical departments were included. Random sampling was carried out, including patients with suspected bacterial meningitis for biochemical and cytobacteriological analysis on CSF. Patients with a previous neurosurgical intervention were not included in this study.

2.2. Data Collection and Studied Variables

Data were collected from biochemistry and bacteriology-virology department registers. Studied variables were biological (procalcitonin, CSF colour, leukocytes and red blood cells, Gram stain, culture, germ identification, antibiogram and rt-PCR result); sociodemographic (age, sex), antibiotic treatment in course, patient's clinical context.

2.3. CSF Sampling

CSF was collected by lumbar puncture during hospitalization. Two sterile dry plastic tubes were used, one for the biochemistry department and a second for the bacteriology-virology department.

2.4. Determination of Biochemical Parameters

For biochemical analysis, CSF samples were centrifuged upon receipt for 5 minutes at 4,000 rpm, once CSF aspect had been noted. Quantitative procalcitonin was determined on CSF supernatants by electrochemiluminescence using HITACHI Cobas ® 6000.

2.5. Cytobacteriological and Molecular Biology Analysis

For cytobacteriological analysis, CSF samples were received in bacteriology-virology laboratory. Analysis included cytology, Gram staining, culture, germ identification and antibiogram. For molecular biology analysis, an aliquot was stored at -20°C in a cryotube. Direct real-time PCR (rt-PCR Direct) was applied from the specimen, without extracting genetic material. PCR was used for species diagnosis of *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. After positive results for *Neisseria meningitidis*, different serogroups (A, B, C, W, X and Y) are tested.

2.6. Data Analysis

Data were statistically analyzed using XLSTAT 2016.02.27444 software. Considering PCT cut-off point 0.50 ng/ml to diagnose patients with bacterial meningitis [11], we evaluated diagnostic performance criteria. Fisher's exact test was used to assess associations with a significance level of 0.05%. Receiver Operating Characteristic (ROC) analysis was used to assess diagnostic performance, based on rt-PCR results as gold standard.

3. Results

3.1. Patient Characteristics

A total of 52 patients with a median age of 18.00 years (minimum-maximum: 0.030-87 years) were included. The sex ratio was 1.08, with male frequency 51.92% (27/52). Clinical context included meningeal syndrome (13.46%), febrile coma (5.77%) and infectious syndrome (5.77%). Probabilistic antibiotic therapy was initiated for 86.54% (45/52) (Table 1).

Table 1. *Cytobacteriological and molecular biology results.*

Patient characteristics	Number	Frequency (%)
Clinical information		
Meningeal syndrome	7	13.46
Febrile coma	3	5.77
Infectious syndrome	3	5.77
Febrile convulsion	2	3.85
Meningitis suspected	2	3.85
Convulsion+Febrile coma	1	1.92
Convulsion+Disorders of consciousness	1	1.92
Convulsion+Prostration	1	1.92
Cephalalgia+vomiting	1	1.92
Meningitis encephalitis	1	1.92
Meningitis+General deterioration	1	1.92
Cervical stiffness	1	1.92
Suspected encephalitis	1	1.92
No clinical information	27	51.92
Treatment prior to lumbar puncture		
Ceftriaxone	19	36.54
Ceftriaxone+Gentamycin	22	42.31
Gentamycin+Ampicillin	4	7.69
No antibiotic treatment	7	13.46

3.2. Cytobacteriological and Molecular Biology Results

CSF was clear (90.38%), slightly hematic (5.77%), turbid

(1.92%) or xanthochromic (1.92%). Cytology showed leukocytes or red blood cells below 01/mm^3 at 96.15 and 100% respectively. Gram staining and culture were negative. PCR analysis was positive in 13.46% CSF samples (7/52), including 1.92% for *Neisseria meningitidis* serogroup C, 11.54% for *Streptococcus pneumonia* (Table 2).

Table 2. *Cytobacteriological and molecular biology results.*

Cytobacteriological and molecular biology parameters	Number	Frequency (%)
Aspect		
Clear	47	90.38
Hematic	3	5.77
Turbid	1	1.92
Xanthochromic	1	1.92
Leukocytes/mm^3		
0	50	96.15
21	1	1.92
147	1	1.92
Red blood cells/mm^3		
0	52	100.00
Polynuclear neutrophils (%)		
0	50	96.15
95	2	3.85
Lymphocytes (%)		
0	50	96.15
5	2	3.85
GRAM staining		
Negative	52	100.00
Culture		
Negative	52	100.00
rt-PCR result		
Neisseria meningitidis serogroup C	1	1.92
Streptococcus pneumonia	6	11.54
Negative	45	86.54

3.3. Cerebrospinal Fluid Procalcitonin

PCT median value was 0.19 ng/mL [minimum-maximum= 0.04-7.42 ng/mL]. PCT values in the range [0-0.50 ng/mL] and above 0.50 ng/mL had frequencies of 69.23% (36/52) and 30.77% (16/52) respectively. PCT values were not significantly correlated with rt-PCR results at the cut-off points 0.50 ng/mL (p= 0.662) and 0.106 ng/mL (p=0.081) (Table 3).

Table 3. *CSF PCT cut-off point and molecular biology results.*

PCT cut-off	rt-PCR result		Total	p-value
	Negative (n=45)	Positive (n=7)		
PCT cut-off_ 0.106 ng/mL				0.081
[0-0.106]	18 (34.62)	0 (0.00)	18 (34.62)	
>0.106	27 (51.92)	7 (13.46)	34 (65.38)	
PCT cut-off_ 0.500 ng/mL				0.662
[0-0.50]	32 (61.54)	4 (7.69)	36 (69.23)	
>0.50	13 (25.00)	3 (5.77)	16 (30.77)	

3.4. Diagnostic Performance of CSF PCT

Based on PCT cut-off point of 0.50 ng/mL, we obtained a diagnostic sensitivity of 42.9% [IC95%=16.0-74.9] and a diagnostic specificity of 71.1% [IC95%=56.5-82.3] (Table 4). ROC curve analysis determined a new PCT cut-off point equal to 0.106 ng/mL with a diagnostic sensitivity, specificity and accuracy of 100.0% [IC95%=59.0-100.0], 40.0% [IC95%= 25.7-55.7] and 48.10% respectively.

Table 4. *CSF PCT cut-off point and measure of performance.*

Measure of performance	PCT cut-off_ 0.500 ng/mL		PCT cut-off_ 0.106 ng/mL	
	Value	IC95%	Value	IC95%
Sensitivity (%)	42.9	[16.0-74.9]	100.0	[59.0-100]
Specificity (%)	71.1	[56.5-82.3]	40.0	[25.7-55.7]
Fraction of false positives (%)	28,9	[16.2-41.6]	60.0	[46.3-73.7]
Fraction of false negatives (%)	57.1	[27.9-86.4]	0.0	[0.0-0.0]
Prevalence	13.5	[4.2-22.7]	13.5	[4.2-22.7]

Measure of performance	PCT cut-off_ 0.500 ng/mL		PCT cut-off_ 0.106 ng/mL	
	Value	IC95%	Value	IC95%
Positive Predictive Value (%)	18.8	[0.00-37.9]	20.6	[7.0-34.2]
Negative Predictive Value (%)	88.9	[78.6-99.2]	100.0	[100.0-100.0]
Positive Likelihood Ratio (LR+)	1.48	[0.56-3.91]	1.67	[1.31-2.12]
Negative likelihood ratio (LR-)	0.80	[0.41-1.57]	0.00	[0.00-0.00]

AUC obtained was equal to 0.597 [CI95%=0.439-0.754] using CSF PCT cut-off point of 0.106 ng/mL (Figure 1).

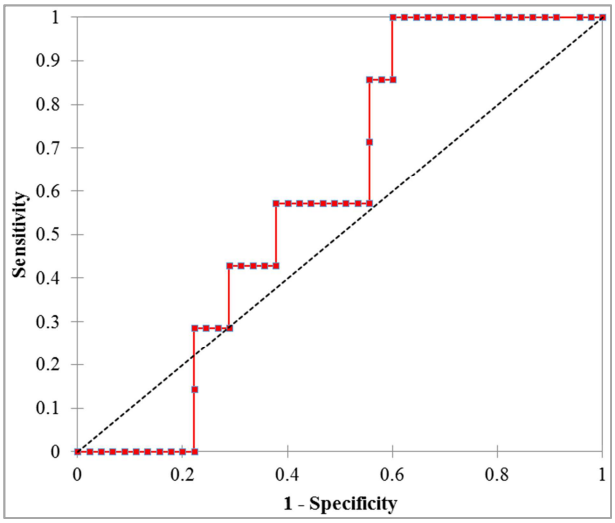

Figure 1. *Receiver operating characteristics (ROC) analysis of cerebrospinal fluid procalcitonin (CSF PCT).*

At the new cut-off point 0.106 ng/mL, CSF PCT mean value (0.429±0.343 ng/mL) obtained in patients with a positive PCR was not significantly different from mean value (0.779±1.474 ng/mL) of those with a negative PCR (p= 0.287) (Figure 2).

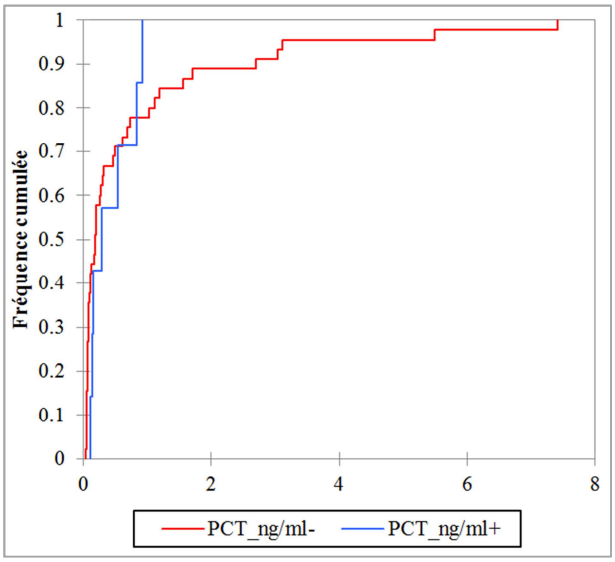

Figure 2. *CSF PCT distribution versus PCR results.*

4. Discussion

CSF analysis is a medical emergency for patients with suspected meningitis, as defined by WHO. Results obtained in cytobacteriological analyses were negative in all patients with leukocytes below 01/mm^3. No bacterial germs were found. This could be explained by antibiotics most often taken by patients. Moreover, according to WHO, meningitis is not only caused by bacteria, but can also be caused by viruses, parasites or even fungi. This would explain our results.

We used direct rt-PCR to identify bacteria responsible for bacterial meningitis. This molecular biology method seems to be a more efficient method than bacterial culturing to determine the pathogens that most commonly cause bacterial meningitis [12]. Previous study used CSF culture from an automated system (BACTEC 9050; Becton-Dickinson, San Jose, CA). Microorganisms identified were *Streptococcus pneumonia, Streptococcus agalactiae, Listeria monocytogenes, Enterococcus faecium, Staphylococcus aureus, Escherichia coli, Haemophilus influenza* and *Clostridium perfringens* [13].

PCT is generally considered an endogenous non-steroid, a glycoprotein with no hormonal activity [3]. In this study, CSF PCT was increased in 30.77% whereas cytobacteriological results were negative. Rajial et al., (2022) in India showed that high CSF PCT levels could confirm bacterial meningitis [14]. Similarly in China, Hong-Yuan et al., (2015) showed that CSF PCT is significantly elevated in patients with bacterial meningitis [15]. Hoen (2009) showed in France that PCT appears to be the first biochemical marker to accurately discriminate bacterial from viral meningitis, with a cut-off value of 0.50 ng/mL [16].

Similarly, CSF PCT values had been used in Europe to differentiate bacterial and viral meningitis, with a cut-off of 0.50 ng/mL [11].

This study was constrained by expensive kits for PCT determination, which prevented us from performing a serum PCT analysis cocomitantly. Moreover, we have noted a low cut-off point 0.106 ng/mL, likely to give higher diagnostic performance than the currently used cut-off point 0.50 ng/mL. CSF PCT diagnostic performance criteria varied according to the cut-off points considered. At cut-off of 0.2 ng/mL, CSF PCT had sensitivity of 95.2% and specificity of 96% in the diagnosis of meningitis [11]. CSF PCT with a cutoff point of 0.085 ng/mL had a sensitivity of 55.17% and a specificity of 95.83% [13].

However, with an AUC not below 0.5 and not greater than 0.7, we can therefore assume CSF PCT to be a fairly good tool for detecting bacterial meningitis. The area under ROC curve for CSF PCT was 0.76 (0.64-0.88) [13].

This CSF PCT determination is the first one performed in our region. CSF PCT mean value 0.429±0.343 ng/mL was lower than 1.00 ng/mL (0.20-2.56) obtained among bacterial meningitis patients [13]. Furthermore, compared to viral

infections, CSF PCT levels are significantly higher in bacterial infections [17].

Empiric antibiotic treatment prior to the first lumbar puncture in our hospital associated with late consultation or hospitalization could have an impact on CSF PCT levels, which were not significantly different from positive or negative PCR results.

5. Conclusion

Bacterial culture was usually negative maybe due to early antibiotic therapy. This demonstrates the importance for routine use of the PCR. We had no significant difference between CSF PCT values in patients positive or negative to PCR. Excellent diagnostic sensitivity was achieved using the new cutoff value 0.106 ng/mL, despite low diagnostic specificity and accuracy. Based on AUC obtained, we can assume CSF PCT to be a fairly good tool for detecting bacterial meningitis in suspected meningitis patients. Further studies using reference diagnostic methods for other causes of meningitis would be useful to better determine CSF PCT's diagnostic contribution.

Ethical Considerations

Informed consent was obtained from all hospitalized patients with suspected bacterial meningitis included in this study. They were alerted about bacterial meningitis and its outcomes. Their participation was completely voluntary. Cerebrospinal fluid samples were well labeled and all data were processed in anonymity.

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