**International Journal of Medical Science and Clinical Research Studies**

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 01 Issue 07 September 2021

Page No :163-170

DOI: https://doi.org/10.47191/ijmscrs/v1-i7-03, Impact Factor: 5.276

# Utility of Procalcitonin Over C-Reactive Protein and WBC as an Early and Rapid Diagnostic Marker of Bacterial Infections in Febrile Patients with or no Hemoculture Results as Gold Standard in a Malaria Endemic Zone of Cameroon

**Akwah Lilian[1,2], Hortense Gonsu Kamga[3], Emilia E. Lyonga Mbamyah[3], JP Nda Mefo'o[4,5], Mohamadou Mansour[1,2], Mbah Clarisse Engowei[1,6], Esemi Livo[1,6], Mbakop Calixte Didier[1], Essia Ngang Jean Justin[1,2], Essame Oyono Jean Louis[1]**

[1]Institutue of Medical Research and Medicinal Plant Studies, Center of Medical Research, Human Biology Laboratory, Cameroon
[2]Department of Microbiology, Faculty of Science, University of Yaoundé 1, Cameroon
[3]Department of Microbiology, Haematology, Parasitology and Infectious Diseases, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon.
[4]Clinical Biology Laboratory–Douala General Hospital
[5]Department of Biological Sciences, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Cameroon
[6]Department of Microbiology, Faculty of Science, University of Buea, Cameroon

**ABSTRACT**

**Background & objectives:** Early identification of bacterial infection in patients with fever is important for prompt and specific treatment. However, the available biomarkers such as C-reactive protein (CRP) and leukocyte counts are not specific to bacterial diagnosis. This study aimed to assess the diagnostic value of procalcitonin (PCT) over CRP and leukocyte counts for bacterial infection screening in febrile patients while awaiting their hemoculture results, which takes up to 7 Days before results are available though it is the gold standard for the diagnosis of bacterial infections.

**Methods:** Blood samples were collected from febrile patients between January and July 2020 then processed for blood cultures. PCT, CRP and WBC levels were measured. The patients were divided into two groups according to the final diagnosis: bacterial infection group (group1) and non-bacterial infection group (group 2).SPSS version 20.0 software package was used for data analysis and normally distributed variables were calculated using mean, standard deviation and ANOVA test while median and range were used for variables without a normal distribution. Significance testing was done using Kruskal-Wallis h test and Wilcoxon two sample test and the diagnostic accuracy was assessed by calculating the area (AUC) under the receiver operating characteristic curve (ROC).

**Results:** There were significant ($P<0.05$) difference in the levels of PCT, CRP and WBC among the two groups. The PCT levels of patients in the bacterial infections group were significantly higher than those in the nonbacterial infections group (27.9 vs., 11.7 $P < 0.001$). The best cut-off value to detect bacterial infections was 1.46 ng/ml for PCT. PCT, CRP and WBC had areas under the curve of 0.71, 0.66 and 0.45 respectively and sensitivity of 100%, 72.7% and 27.3% respectively.

**Interpretation & conclusions:** Our results showed that PCT was a valuable marker for the early and rapid diagnosis of bacterial infections in febrile patients in our setting when compared to CRP and WBC. However, prospective and large scale studies are warranted to confirm these findings in Cameroon.

**ARTICLE DETAILS**

**Published On:**
**06 September 2021**

**Available on:**

**Utility of Procalcitonin Over C-Reactive Protein and WBC as an Early and Rapid Diagnostic Marker of Bacterial Infections in Febrile Patients with or no Hemoculture Results as Gold Standard in a Malaria Endemic Zone of Cameroon**

**KEYWORDS:** C-reactive protein - procalcitonin – WBC - fever - infection – early and rapid diagnosis.

https://ijmscr.org

## INTRODUCTION

Millions of deaths occur each year in the tropics due to bacterial, viral, or parasitic (malarial) infections that often initially present themselves as undifferentiated fever [1]. Many febrile patients seek care at peripheral levels of the healthcare system where diagnostic capacities are minimal. Given that malaria and bacterial infections may be rapidly fatal, overtreatment with antimicrobials is common, contributing to drug resistance that threatens health care systems at a global scale [2–4]. Traditionally, fever has been associated with bacterial infection. However, in up to 50% of febrile people, fever is caused by non-bacterial infection like malaria or other inflammatory conditions, such as malignancy or auto-immune disease [5, 6]. The early identification of bacterial infection in fever is very important, since appropriate etiological treatment and avoidance of unnecessary antimicrobial therapy could not only reduce the morbidity, mortality and costs to patients, but also can reduce the emergence of antibiotic-resistant bacteria.

The traditional diagnostic tools, such as C-reactive protein (CRP),erythrocyte sedimentation rate (ESR) and leukocyte count, are not specific for differentiating bacterial infections from viral infections and systemic inflammation [7,8]. Also, microbiologic culture being the gold standard for identifying and differentiating bacteria requires at least 24-48 hours, and negative cultures do not exclude the presence of infections [9]. Moreover, only 5-10 per cent of cultures performed in hospitals show microorganisms [10]. Therefore, there is an obvious need for more specific and rapid biomarkers of bacterial infections in febrile patients. Lately, procalcitonin (PCT) has been added to the diagnostic work-up of febrile patients.

PCT is a prohormone of calcitonin hormone and is produced by C cells of the thyroid gland as well as by other cell types in response to infection. Some of the strongest inducers of PCT include inflammatory cytokines (TNF, IL-6, IL-2), bacterial endotoxins and exotoxin [11]. PCT is considered to be a specific marker of severe bacterial infection in patients with suspicious bacteremia [12, 13]. In healthy subjects serum PCT concentration is undetectable, but rises markedly under certain situations [14]. Following an infectious stimulus, it is detected in serum after 2-3 hours, peak within 6-12 hours and maintains plateau after a 24 hours or continues until appropriate treatment is initiated or the infection is under control. It has shown it relevance and usefulness in the treatment and monitoring of critically ill patients [15]. CRP and WBC are non-specific biomarker, used in detecting infections, inflammatory diseases, tissue damage and neoplasia. An increase in PCT level in bacterial infections occurs faster than with CRP and WBC. Whilst CRP and WBC also increase in viral infections, PCT is known to increases only in bacterial infections [17] and has a long half-life in blood. Therefore, it is a useful auxiliary test for bacterial infection. Chronic non-bacterial infections such as malaria, autoimmune diseases, other systemic diseases, non-infectious and neoplastic diseases do not induce PCT, thus do not increase plasma PCT concentrations [18].In Africa and Cameroon in particular, PCT is not yet frequently in use in most hospitals and the majority of our clinical laboratories lack adequate infrastructures, equipments and cannot afford to have a bacteriology unit were hemoculture can be done so as to isolate the causative bacterial responsible for the fever. Moreover, laboratories with units for hemoculture demands up to 7 days of analysis before the final diagnosis of the infection are known.

Therefore, we undertook this study to compare the diagnostic properties and assess the optimum cut-off values of PCT, CRP, and WBC in the early detection of bacterial infections in febrile patients presenting in the Douala General Hospital.

## MATERIAL AND METHODS

**Study design and settings:** The study was conducted between January and July 2020, in the laboratory of the Douala General Hospital, Cameroon. Ethical clearance was obtained from the Cameroon National Ethical Committee; N° 2019/11/57/CE/CNERSH/SP and a research authorization was also obtained from the hospital involved in the study. Written informed consent was obtained from every enrolled patient and for children the parent/guardian or caregiver gave their assent. Included in the study; were persons of all age groups with fever, hyperthermia (temperature ≥38.5°C), hypothermia (temperature ≤ 36.5°C), admitted within 24 hours and not yet on any anti-infectious treatment.

### *Data Collection*

For all patients, the following variables were collected: age, gender and temperature.

### Blood Sample Collection and Assays.

Blood was collected on the first day of admission from all febrile patients. The serum was separated, stored at -70°C, and used subsequently for assaying procalcitonin and CRP while whole blood was used for WBC and MP (malaria parasite) detection. Procalcitonin was measured using a florescence immunoassay (Finecare™ PCT Rapid quantitative test, Wondfo Biotech, Guangzhou, China). The detection limit was 0.1 ng/mL, and the assay ranged from 0.1

~100 ng/ml. The normal serum procalcitonin concentration with this assay is < 0.5 ng/mL.[19] CRP was measured using a standard latex agglutination slide test for qualitative and semi quantitative determination of C Reactive Protein (CRP) in human serum nephelometric assay (Biolabo SAS , France) and the analytical sensitivity varied between 6 mg/L (0.5 - 10.0) mg/L. The normal value is equal or < 6 mg/L. [20] WBC counts were performed using the Cell-Dyn Sapphire Hematology analyzer (Abbott Diagnostics Division, Santa Clara, CA), MP detection was done using two methods: the rapid diagnostic test method for the antigen detection of malaria ( P. falciparum, P. vivax, P.ovale and P. malariae),where the Care Start™ Malaria pf/PAN (HRP2/Pldh)Ag Combo RDT was used for the rapid diagnosis and the Giemsa staining method to confirm the rapid diagnostics test method and quantify the trophozoites, while blood cultures were processed using the BacT/Alert 3D (Biomerieux,France) automated hemoculture system.

**Group classification:**

The patients were divided into two groups according to their final diagnosis. Group 1 represented patients with bacteraemia defined by a positive blood culture and Group 2 represented patients with no bacterial infections define by a negative blood culture. The groups were comparable in age and sex.

**Statistical analysis:** Data were analyzed using SPSS version 17.0 software package (SPSS Inc., Chicago, USA).Variables with normal distribution; the mean, standard deviation and ANOVA test was calculated**.** Variables which did not fit the normal distribution were expressed as median and ranges. Univariate data analyses were used for categorical variables. Significance testing was carried out using the Kruskal-Wallis Test and Wilcoxon two sample tests. Diagnostic accuracy was assessed by calculating the areas (AUC) under the receiver operating characteristic curve (ROC). ROC curve analysis was carried out using the method of DeLong *et al [*21].An AUC > 0.9 was considered excellent; 0.8- 0.9, very good; 0.7-0.8, good; 0.6-0.7, average; < 0.6, poor [22]. The best cut-off point is the point where sum of specificity and sensitivity is maximum, when equal weight is given to both [23]. A $P < 0.05$ was considered significant.

**RESULTS**

1. **Demographic and clinical characteristic of the patients**

A total of 220 febrile patients (134 males and 86 females) were included in this study. 104 patients were from the pediatric units, 39 from the emergency unit, 17 from the reanimation unit, 7 from the burn unit, 25 from the neonatology unit, 10 from the surgical unit and 17 from the General medicine units. Demographic characteristics of patients with fever in this study are listed in Table I.1.

The mean serum PCT level in the bacteria group (24.31%) was 27.8680 ng/ml, the mean serum CRP level was 85.6816 ng/ml and the mean serum WBC was 12.0743 count/µl while for the non bacteria group; the mean serum PCT level was 11.7 ng/ml, the mean serum CRP level was 48 ng/ml and the mean serum WBC was 12.0743 count/µl as shown on Table I.2.

**Table 1.1.Demographic characteristics of the febrile patients**

| Characteristics | No. of cases [n (%)] |
|---|---|
| 0 -30 Days [ (Neonates) | 32 (14 .5 %) |
| 1 Month - 2 Years [ (Infants) | 46 (21%) |
| 3 - 12 Years [ (child) | 67 (30.5%) |
| 13- 18 Years [ (Adolescent) | 7 (3.9%) |
| 19 – 100 Years (Adults) | 80 (36.4%) |
| Male | 134 (61%) |
| Female | 86 (39.1%) |
| Temperature $\geq 38.5^0$C | 67 (30.5%) |
| Temperature $\leq 36.5^0$C | 10 (4.5%) |
| Cases with procalcitonin | 209 (95%) |
| CRP | 202 (91.8%) |
| WBC | 197 (89.5%) |
| Blood culture | 216 (98.2%) |
| Thick blood films | 131 (59.5%) |

**Table I.2. Laboratory characteristics of enrolled patients (n=220) with fever**

| Parameters | All | Group 1 ( Bacteraemia) | Group 2 ( Non bacterial infections) | No Hemoculture | p Value |
|---|---|---|---|---|---|
| Number | 220 | 35 | 109 | 76 | |
| Sex (Male vs. female) | 134: 86 | 27:8 | 67: 42 | 40: 36 | |
| Age(Yr) (median) (IQR) | 32 years (7months-9years) | 27 (1-4days) | 19 (7months-32years) | / (1day-9month) | 1,0 |
| PCT (ng/ml) Mean ( median) (IQR) | 13 (1.67)(0.05-200) | 27.9 (10)(0,163-200) | 11.7 (1.12) (0.05-123) | 6.7 (0.8) (0.2-9) | 0.001 |
| CRP (mg/l) Mean (median) (IQR) | 54.8 (105.6)(< 0.5-98.9) | 85.7 (107)( <5-88) | 48 (99.7) (<0.5-99) | 50.4 (78)(0.4-43) | 0.38 |
| WBC Mean | 12.1 | 12.1 | 12.1 | 0.0 | 0.8 |

**2. Microbiology**

Among the 220 febrile patients, hemoculture was done on 144 patients, 109 had sterile growth, and 35 had microbiological evidence of infection.

Bacteraemia was confirmed in 28 patients; among which 21 patients had Gram-negative bacteria, 7 patients had Gram-positive bacteria and in 7 patients, more than one organism was recovered while parasitic infections was diagnosed in 8 patients. Pathogens isolated from culture are shown in Table 2.The most frequently isolated pathogen was *Klebsiella pneumoniae* (7/35), followed by *Staphylococcus aureus* (5/35).

**Table 2.** Microbiological Characteristics

| Isolate | Number |
|---|---|
| **Gram-positive bacteria** | |
| *Staphylococcus aureus* | 5 |
| *Staphylococcus heamolyticus* | 2 |
| Enterococcus *fecalis* | 3 |
| **Gram-negative bacteria** | |
| *Escherichia coli* | 4 |
| *Klebsiella pneumonia* | 7 |
| *Pseudomonas aeruginosa* | 2 |
| *Enterobacter species* | 3 |
| *Acrobacter species* | 2 |
| **Contaminant** ( more than one bacteria) | 7 |
| **Parasitic infections** | 8 |
| Total | 43 |

**3. Diagnostic Value of Procalcitonin.**

Serum procalcitonin concentrations on day 1 were significantly higher (p= 0.001) in the patients with bacterial infections than those without bacterial infections as shown in Table 1.2. PCT, CRP and WBC concentrations according to pathogens in patients with bacterial infection are shown in Table 3. The ROC curves of PCT, CRP and WBC concentrations for discrimination between patients in the bacterial infection group and non-bacterial infection group are shown in Fig. 1. The best cut-off value to detect bacterial infection was 1.46 ng/ml for PCT. The AUC values for the studied biomarkers are listed in Table 5. PCT was better than CRP and WBC for detecting bacterial infection. A cutoff of 1.46 ng/ml had 100 % sensitivity and 53 % specificity for separating patients with bacterial infections from those without bacterial infections. Positive predictive value and negative predictive values were 28 % and 100 % respectively. Serum C reactive proteins and WBC concentrations were different in the two groups (Table 2). PCT concentrations were significantly elevated in gram-positive infections (62.3271ng/mL) than in those with gram- negative infections (20.9581ng/mL).

**Table 3. Diagnostic value of procalcitonin (PCT), C-reactive protein (CRP), and WBC on day 1 of fever.**

| | Bacteraemia | | Non bacterial infections | | P values |
|---|---|---|---|---|---|
| Biomarkers | Mean | Std .Deviation | Mean | Std .Deviation | |
| PCT | 27.9 | 49.1 | 11.7 | 21.8 | 0.001 |
| CRP | 85.7 | 105.3 | 47.9 | 55.7 | 0.9 |
| WBC | 11.6 | 7.8 | 12.1 | 9.3 | 0.8 |

**Table 4. Area under the curves (AUC) of the receiver operating characteristic (ROC) for procalcitonin (PCT), C-reactive protein (CRP), and WBC and the best cut-off values to detect bacterial infection in febrile patients.**

| Biomarker | AUC | Cut- off value | PPV (%) | NPV (%) | FP | FN | Sensitivity (%) | Specificity (%) | Youden's index (%) |
|---|---|---|---|---|---|---|---|---|---|
| PCT | 0.71 | 1.46 | 20% | 10% | 28 | 0.0 | 100 | 52.5 | 0.53 |
| CRP | 0.66 | 117 | 34% | 93% | 15 | 3.0 | 72.7 | 74.6 | 0.47 |
| WBC | 0.445 | 17.7 | 21% | 85% | 11 | 8 | 27.3 | 81.4 | 0.086 |

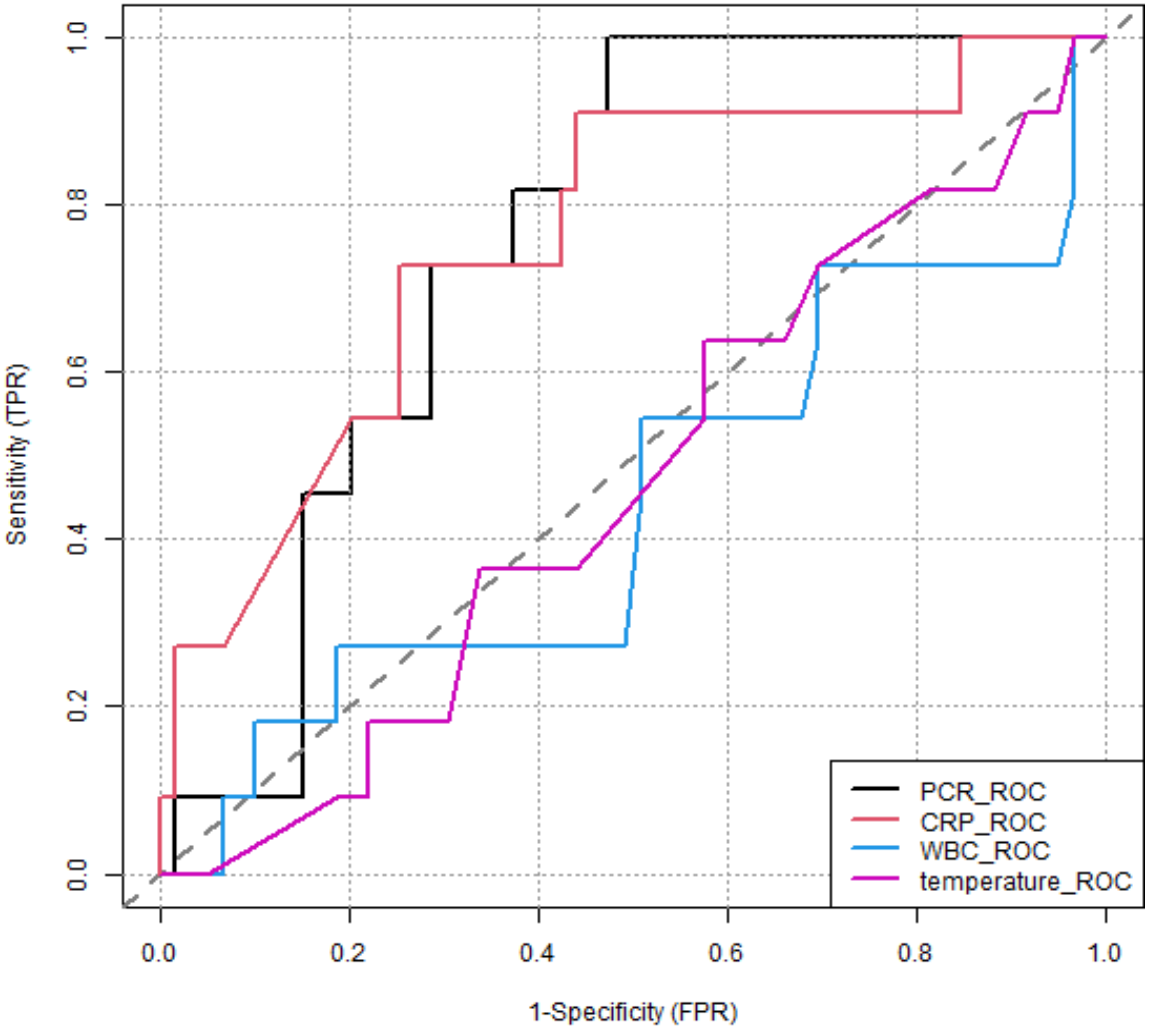


**Figure 1: Receiver operating characteristic (ROC) curve showing the diagnostic value of PCT, CRP and leukocytes for the differentiation between the bacterial infection group and non-bacterial infection group.**

Area under the curve (AUC) for PCT was 0.71 (sensitivity 100%/specificity 52.5% at cut-off 1.46 ng/mL); CRP was 0.66 (72.7%/74.6% at 117 mg %); and for leukocytes it was 0.45 (27.3%/81.4% at 17.7 giga/L), respectively

## DISCUSSIONS

The rapid detection of bacterial infections in patients with fever facilitates early implementation of therapy and identifies patients at high risk for complications. [24]. Similarly, ruling out bacterial infections in febrile patients

have substantial benefits, including reduction of the hospitalization length, antimicrobial use and facilitating clinician focus on alternative diagnostic pathways [26]**.** In this study, we have focused on the rapid diagnosis of bacterial infections in feverish patients. We assessed the diagnostic properties of the most commonly and frequently used markers like hemoculture, CRP and WBC (leukocyte counts) then compared its value with a marker like PCT not yet frequently in used in our country for the rapid diagnosis of bacterial infections in febrile patients.

Of the 220 recruited patients for our study, most were from the pediatric unit, followed by the emergency unit and the reanimation unit; all these patients need urgent medical attention. Also most of our patients were male and most had temperatures over $38^0$ C, which signals the presence of an infection and necessitated specific and rapid biomarkers of infection like PCT to compliment hemoculture which is the gold standard but requires up to 7 days to isolate the bacteria, in case the infection is cause by a bacteria. This result corroborates the work by Junyan *Qu et al.,* 2015 [32], who also had more males than females patients with temperatures $> 38^0$ C.

*Klebsiella* (7 %) and *Staphylococcus aureus* (5%) were the most frequent causal pathogens among the Gram-negative and gram-positive bacteria's respectively. This was similar to the work by Helena *et al*, 2012 [30], who identified *Staphylococci* (33 %), *E.coli* (16%) and *Klebsiella* (14 %) as the most frequent causal pathogens in their cohort study. In general, Staphylococci (i.e.,*Staphylococcus aureus*) and Gram-negative rods from the Enterobacteriacea family are the most common causative agents of bacteraemia.

Our study showed a higher mean PCT level of 27.8 (ng/ml) in the bacteraemia group (group 1) than in the non bacteraemia group (group 2) with PCT level of 11.7 (ng/ml). This may be explained by the fact that interferon-gamma (IFN-γ) inhibits IL-1 beta-induced calcitonin mRNA expression and PCT secretion, so serum PCT levels increase less in viral infections as compared with bacterial infections [39]. This observation is consistent with the findings of Siyu Wang *et al*,.2018[31] and Junyan Qu *et al*,.2015 [32] who also had a higher PCT mean values with respect to the bacteraemia group.

CRP was also found to be of value in detecting bacterial infection in febrile patients but WBC was not. Other studies have also used CRP levels to identify bacterial infections in febrile patients [33, 34] however from our study; PCT was superior to CRP and WBC in identifying bacterial infection. This was further confirmed by calculating the area under the ROC curves, PCT (AUC= 0, 71) and CRP (AUC= 0, 66) performed equally well in differentiating bacterial infections from non-bacterial infections in febrile patients than WBC (AUC=0.45). Moreover, their Youden's index and their cut-off values showed the best combination of sensitivity and specificity in confirming that PCT was the best biomarker in differentiating bacterial infections from non-bacterial infections in febrile patients than CRP and WBC. From our study, the Youden's index of PCT (53%) was higher than that of CRP (47%) and WBC (9%) to rapidly confirm the presence of a bacterial infection in febrile patients. It may be attributed to the fact, proven by previous studies, that PCT does not appear to be pivotally influenced by viral infections, autoimmune or allergic disorders, immunosuppressive, or steroids.[40---42] Nonetheless, CRP and WBC are biomarkers of inflammation rather than a of infection. Its level rises in most pathological cases associated with inflammation, such as bacterial/viral infections, trauma, systemic disease flare and post-surgical period. [43]

These results corroborates with those of Junyan Qu *et al.,* 2015 who also had a higher Youden's index of 48.5% and 34% for PCT and CRP respectively. A cut–off value of 1.45 ng/mL for PCT had a 100% sensitivity and a 52.5% specificity to detect the presence of bacterial infection than CRP with a cut–off value of 117 ng/ml which had only 72.7 % sensitivity and 74.6% specificity and WBC with a cut-off value of 17.7 ng/mL had a 27.3% sensitivity and 81.4% specificity to confirm the presence of a bacterial infection. Furthermore, PCT had a higher NPV (100%) to rule out the presence of bacterial infections in blood stream infections (BSI) than CRP with a NPV of (93%) and WBC with a NPV of (85%). The finding of a significantly higher PCT level than CRP and WBC in BSI is consistent with reports of Siyu Wang *et al.,* 2019 [31], who found a cut-off of 1.50, a sensitivity of 100%, a specificity of 42.3%, NPV of 94.5%, PPV of 100% and AUC of 0.896 for PCT versus a cut-off of 46.8, sensitivity of 91.7%, specificity of 53%, NPV of 96.6%, PPV of 31.4% and AUC of 0.7 for CRP. M. Limper *et al.,*2011[35] had a cut-off of 0.21,sensitivity of 90%,specificity of 71% and AUC of 0.84 for PCT versus cut-off of 8.5, sensitivity of 89%, specificity of 4.3% and AUC of 0.65 for CRP and Simon *et al.,*2004 [ 36] ,reported a sensitivity 92% , specificity of 73% for PCT versus 86% and 70% respectively for CRP .

In conclusion, PCT with a greater sensitivity, predictive value and AUC proved to be a valuable marker for the rapid and early diagnosis of bacterial infection in febrile patients with pending or no hemoculture results, than CRP and WBC markers of infection in a malaria endemic region of Cameroon. Therefore by implementing PCT as a routine marker in the work-up of febrile patients, the diagnostic power will be improved. This may eventually lead to a reduction in antibiotic prescriptions, costs and adverse events in patients.

**Limitation**

**Acknowledgment**

The authors thank; the Director General of the Institute of medical Research and medicinal plant studies for granting the permission needed for this work to be carried out, the clinicians, nurses and laboratory technicians of the Douala General Hospital and the Yaoundé University Teaching Hospital, Cameroon for their clinical assistance.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Abbreviations**

CRP - C-reactive protein
ESR - Erythrocyte sedimentation rate
PCT - Procalcitonin
TNF - Tumor necrosis factor
IL-6 - Interleukine 6
IL-2 - Interleukine 2
WBC - White blood count
AUC - Area under the curve
ROC - Receiver operating characteristic curve
NPV - Negative predictive value
PPV - Positive predictive value
BSI – Blood stream infections
FP - False positive
FN - False negative

**REFERENCES**

I. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.

II. Hart C, Kariuki S. Antimicrobial resistance in developing countries. BMJ.1998;317(7159):647.

III. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, *et al.* Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis. 2005;5(8):481–93.

IV. Lubell Y, Dondorp A, Guerin PJ, Drake T, Meek S, Ashley E, *et al.* Artemisinin resistance–modelling the potential human and economic costs. Malar J. 2014;13:452.

V. Circiumaru B, Baldock G, Cohen J (1999) A prospective study of fever in the intensive care unit. Intensive Care Med 25:668–673

VI. Kokturk N, Demir N, Oguzulgen IK, Demirel K, Ekim N (2005) Fever in pulmonary embolism. Blood Coagul Fibrinolysis 16:341–347

VII. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, 1. receptors and role in inflammation. *Clin Immunol* 2005; *117* : 104-11.

VIII. Meisner M. Biomarkers of sepsis: clinically useful? 2. *Curr Opin Crit Care* 2005; *11* : 473-80.

IX. Mitaka C. Clinical laboratory differentiation of infectious 3. versus non-infectious systemic inflammatory response syndrome. *Clin Chim Acta* 2005; *351* : 17-29.

X. Reimer LG, Wilson ML, Weinstein MP. Update on detection 4. of bacteremia and fungemia. *Clin Microbiol Rev* 1997; *10* : 444-65.

XI. Kristoffersen KB, Sogaard OS, Wejse C, Black FT *et al.* (2009) Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission-a randomized trial. Clin Microbiol Infect 15:481-487.

XII. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K (2008) The role of procalcitonin in febrile neutropenic patients: Review of the literature. Infection 36:396-406.

XIII. Bouadma L, Luyt CE, Tubach F *et al.* (2010) Use of procalcitonin to educe patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 375:463-474.

XIV. Whicher, J., Bienvenu, J. and Monneret, G. (2001) Procalcitonin as an Acute Phase Marker. *Annals of Clinical Biochemistry*, **38**, 483-493.

XV. 15. Schuetz P, Mueller B, Trampuz A (2007) Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. Infection 35:352-355.

XVI. Jeong, S., Park, Y., Cho, Y. and Kim, H.S. (2012) Diagnostic Utility of Procalcitonin and C-Reactive Protein for the Prediction of Bacteremia Determined to by Blood Culture. *Clinica Chimica Acta*, **413**, 1731-1736.

XVII. van Rossum AMC, Wulkan RW, Murphy AMO (2004) Procalcitonin as an early marker of infection in neonates and children. Lancet Inf Dis 4:620-630.

XVIII. Meisner M (2000) Procalcitonin: A new, innovative infection parameter. Biochemical and clinical aspects. Georg Thieme Verlag, Stutgard Newyork.

XIX. Christ –CRAIN M. *et al.*, Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections : cluster-randomised single blinded intervention trial, Lancet 2004 363( 9409) 600-607.

XX. Tillet, W.S., and Francis, T.,Serological Reactions in Pneumonia with a non-Protein Somatic fraction of Pneumococcus. J.Exp. Med. 52:561 ( 1930)

XXI. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; *44* : 837-45.

XXII. Ying GS, Maguire M, Quinn G, Kulp MT, Cyert L; Vision in Preschoolers (VIP) Study Group. ROC analysis of the accuracy of Noncycloplegic retinoscopy, Retinomax Autorefractor, and SureSight Vision Screener for preschool vision screening. *Invest Ophthalmol Vis Sci* 2011; *52* : 9658-64.

XXIII. Kumar R, Indrayan A. Receiver operating characteristic (ROC) curve for medical researchers. *Indian Pediatr* 2011; *48* : 277-87.

XXIV. Heper Y, Akalin EH, Mistik R, *et al.* Evaluation of C-reactive protein, procalcitonin, tumor necrosis factor alpha, and interleukin-10 levels as diagnostic and prognostic parameters in patients with community-acquired sepsis, severe sepsis, and septic shock. Eur J Clin Microbiol Infect Dis. 2006;25:481-491.

XXV. Riedel S, Bourbeau P, Schwartz B, *et al.* Timing of specimen collection for blood cultures from febrile patients with bacteremia. J Clin Microbiol. 2008;46:1381-1385.

XXVI. Lee CC, Chen SY, Tsai CL, *et al.* Prognostic value of mortality in emergency department sepsis score,procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. Shock. 2008;29:322-327

XXVII. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med* 2000; *26* (Suppl 2):S148-52.

XXVIII. Endo S, Aikawa N, Fujishima S, Sekine I, Kogawa K, Yamamoto Y, *et al*. Usefulness of procalcitonin serum level for the discrimination of severe sepsis from sepsis: a multicenter prospective study. *J Infect Chemother* 2008;*14*:244-9.

XXIX. Muller B, Becker KL, Schachinger h, Rickenbacher PR, Huber PR, Zimmerli W, *et al*. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 2000; *28*:977-83.

XXX. Helena Brodska´• Karin Malı´cˇkova´• Va´clava Ada´mkova• Hana Bena´kova´ • Marke´ta Markova´ Sˇtˇastna´• Toma´sˇ ZimaSignificantly higher procalcitonin levels could differentiate Gramnegative sepsis from Gram-positive and fungal sepsis Clin Exp Med-012-0191-8 2012.

XXXI. Wang S, Xie Z, Shen Z. Serum procalcitonin and C-reactive protein in the evaluation of bacterial infection in generalized pustular psoriasis. An Bras Dermatol. 2019;94:542---8.

XXXII. 33. Lee CC, hong MY, Lee NY, Chen PL, Chang CM, Ko WC. Pitfalls in using serum C-reactive protein to predict bacteremia in febrile adults in the ED. *Am J Emerg Med* 2012; *30* : 562-9. 34. Nahum E, Livni G, Schiller O, Bitan S, Ashkenazi S, Dagan O. Role of C-reactive protein velocity in the diagnosis of early bacterial infections in children after cardiac surgery. *J Intensive Care Med* 2012; *27* : 191-6.

XXXIII. 35. Limper M, de Kruif MD, Ajubi NE, van Zanten AP, Brandjes DP, Duits AJ, *et al*. Procalcitonin as a potent marker of bacterial infection in febrile Afro-Caribbean patients at the emergency department. *Eur J Clin Microbiol Infect Dis* 2011; *30* : 831-6.

XXXIV. 36. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; *39* : 206-17.

XXXV. 39. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, *et al*. *In vitro* and *in vivo* calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. *Endocrinology* 2003; *144* : 5578-84.

XXXVI. 40. Oshita H, Sakurai J, Kamitsuna M. Semi-quantitative procalcitonin test for the diagnosis of bacterial infection: clinical use and experience in Japan. J Microbiol Immunol Infect. 2010;43:222---7.

XXXVII. 41. Lanoix JP, Bourgeois AM, Schmidt J, Desblache J, Salle V, Smail A, et al. Serum procalcitonin does not differentiate between infection and disease flare in patients with systemic lupus erythematosus. Lupus. 2011;20:125---30.

XXXVIII. 42. Eberhard OK, Langefeld I, Kuse ER, Brunkhorst FM, Kliem V, Schlitt HJ, et al. Procalcitonin in the early phase after renal transplantation --- will it add to diagnostic accuracy? Clin Transplant. 1998;12:206---11.

XXXIX. 43. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med. 1999;17:1019---25.