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Copyright AJCEM 2022: <https://dx.doi.org/10.4314/ajcem.v23i2.3>**Original Article****Open Access****Evaluation of procalcitonin as a biomarker of bacterial sepsis in adult population in a tertiary healthcare facility in Lagos, Nigeria**

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Abstract:

Background: Prompt antibiotic treatment of sepsis improves the outcome, but dependence on clinical diagnosis for empiric therapy leads to overuse of antibiotics which in turn promotes the emergence of antibiotic resistance. Blood culture takes time and molecular diagnosis may not be available or affordable. The use of procalcitonin (PCT) as a biomarker to guide antibiotic therapy in adults is less established compared to children. This study was therefore designed to evaluate the usefulness of PCT as a biomarker to aid early commencement of antibiotics among adult patients with sepsis in a tertiary healthcare facility in Lagos, Nigeria.

Methodology: Three hundred patients with clinical diagnosis of sepsis made by the managing physicians were recruited for the study. Criteria used for clinical diagnosis of sepsis include tachycardia, tachypnea, fever or hypothermia and presence of leukocytosis, bandemia or leucopenia. The patients were selected using systematic consecutive sampling methods. A sepsis work-up including quick sequential organ failure assessment (qSOFA), white blood cell count (WCC), aerobic blood culture and estimation of serum PCT levels were done for all the participants. Data were analysed using the Statistical Package for Social Sciences (SPSS) for windows version 25.0. Sensitivity, specificity, positive, and negative predictive values, accuracy and likelihood ratio of PCT against blood culture, WCC and qSOFA score were determined. Association between variables was measured using Fisher exact test (with Odds ratio and 95% confidence interval). P-value <0.05 was considered statistically significant.

Results: There were 127 (42.3%) males and 173 (53.7%) females with the mean age of 44.9±14.5 years. Majority (96.2%, n=75/78) of the patients who were culture positive for bacterial pathogens had PCT level ≥10ng/ml, which showed statistically significant association of bacteraemia with PCT level (OR=1362.5, 95% CI=297.9-6230.5, p<0.0001). At PCT cut-off value of 0.5ng/ml, the negative predictive value of 100% almost confirms absence of systemic bacterial infection. The high sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio of 94.9%, 98.6%, 96.2%, 98.2%, 97.7%, and 69.9 respectively recorded at PCT level of 10ng/ml indicates that this cut-off level is strongly diagnostic of systemic bacterial infection.

Conclusion: In this study, we observed that PCT levels were significantly higher in patients with positive culture (bacteraemia) and PCT was able to differentiate bacterial sepsis from non-bacterial infections. The findings of this study support the usefulness of PCT as a biomarker for early diagnosis of systemic bacterial infections in adult patients.

Keywords: procalcitonin; biomarker; sepsis; sequential organ failure assessment; adults; evaluation

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Évaluation de la procalcitonine en tant que biomarqueur de la septicémie bactérienne chez la population adulte dans un établissement de soins de santé tertiaires à Lagos, au Nigeria

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Abstrait:

Contexte: Un traitement antibiotique rapide de la septicémie améliore les résultats, mais la dépendance au diagnostic clinique pour le traitement empirique conduit à une surutilisation des antibiotiques qui à son tour favorise l'émergence de la résistance aux antibiotiques. L'hémoculture prend du temps et le diagnostic moléculaire peut ne pas être disponible ou abordable. L'utilisation de la procalcitonine (PCT) comme biomarqueur pour guider l'antibiothérapie chez l'adulte est moins établie que chez l'enfant. Cette étude a donc été conçue pour évaluer l'utilité de la PCT en tant que biomarqueur pour faciliter le début précoce des antibiotiques chez les patients adultes atteints de septicémie dans un établissement de soins de santé tertiaire à Lagos, au Nigeria.

Méthodologie: Trois cents patients avec un diagnostic clinique de septicémie posé par les médecins traitants ont été recrutés pour l'étude. Les critères utilisés pour le diagnostic clinique du sepsis comprennent la tachycardie, la tachypnée, la fièvre ou l'hypothermie et la présence d'une leucocytose, d'une bandémie ou d'une leucopénie. Les patients ont été sélectionnés à l'aide de méthodes d'échantillonnage consécutifs systématiques. Un bilan de septicémie comprenant une évaluation séquentielle rapide des défaillances d'organes (qSOFA), une numération des globules blancs (WCC), une hémoculture aérobie et une estimation des taux sériques de PCT a été effectué pour tous les participants. Les données ont été analysées à l'aide du package statistique pour les sciences sociales (SPSS) pour Windows version 25.0. La sensibilité, la spécificité, les valeurs prédictives positives et négatives, la précision et le rapport de vraisemblance de la PCT par rapport à l'hémoculture, le WCC et le score qSOFA ont été déterminés. L'association entre les variables a été mesurée à l'aide du test exact de Fisher (avec rapport de cotes et intervalle de confiance à 95 %). La valeur $P < 0,05$ a été considérée comme statistiquement significative.

Résultats: Il y avait 127 (42,3%) hommes et 173 (53,7%) femmes avec un âge moyen de $44,9 \pm 14,5$ ans. La majorité (96,2%, $n=75/78$) des patients dont la culture était positive pour les agents pathogènes bactériens avaient un taux de PCT ≥ 10 ng/ml, ce qui a montré une association statistiquement significative de la bactériémie avec le taux de PCT (OR=1 362,5, IC à 95%=297,9-6230.5, $p < 0.0001$). À la valeur seuil PCT de 0,5ng/ml, la valeur prédictive négative de 100% confirme presque l'absence d'infection bactérienne systémique. La sensibilité élevée, la spécificité, la valeur prédictive positive, la valeur prédictive négative, l'exactitude et le rapport de vraisemblance de 94,9%, 98,6%, 96,2%, 98,2%, 97,7% et 69,9 respectivement enregistrés au niveau PCT de 10 ng/ml indiquent que cette réduction- hors niveau est fortement le diagnostic d'une infection bactérienne systémique.

Conclusion: Dans cette étude, nous avons observé que les taux de PCT étaient significativement plus élevés chez les patients ayant une culture positive (bactériémie) et que la PCT était capable de différencier la septicémie bactérienne des infections non bactériennes. Les résultats de cette étude confirment l'utilité de la PCT en tant que biomarqueur pour le diagnostic précoce des infections bactériennes systémiques chez les patients adultes.

Mots clés: procalcitonine; biomarqueur; état septique; qSOFA; adultes; évaluation

Introduction:

Sepsis is an important cause of mortality worldwide resulting in 210,000 deaths annually in the United States of America (1). An audit revealed a high prevalence of sepsis, with 53% mortality in Nigeria especially in people with co-morbidities such as diabetes mellitus, chronic kidney disease, and acquired immune deficiency syndrome (AIDS) (2). Prompt and appropriate antibiotic administration enhances good clinical outcome. The consensus guidelines recommend antibiotic therapy within one hour of making a diagnosis of "suspected sepsis" and the choice of empiric antibiotic therapy is usually based on the focus of infection, history of recent antibiotic use, rise in inflammatory biomarkers such as C-reactive protein

(CRP) or procalcitonin (PCT), and local resistance pattern (3,4).

Isolation of the pathogen from culture is regarded as the "gold standard" for diagnosis of severe bacterial infections and sepsis (5). There are however, limitations to early diagnosis of severe bacterial infection which include diagnostic delays and low sensitivity in blood culture methods. It has also been shown that a delay in antibiotic therapy is associated with increase in morbidity and mortality especially in patients with septic shock (6). Nonetheless, over-prescription and inappropriate use of empiric antibiotics contributes to the emergence of antibiotic resistance (7). In USA, South Africa and Nigeria, reports showed that doctors over-prescribe antibiotics in up to 41%, 54%, and 75.5% of the time, respectively, leading to the

development of resistance (2,8). The study of antibiotic overuse in patients with suspected sepsis revealed that 29% of the patients received antibiotics for minimum of seven days despite the absence of bacterial disease from laboratory investigations (9). In another study (2), it was reported that all the patients with diagnosis of suspected sepsis received empiric antibiotics and further evaluation revealed that 24.5% were inappropriate while only 12.5% had culture results to guide definitive antibiotic therapy.

In this diagnostic dilemma, PCT has given much hope as a more specific biomarker for bacterial infection. Procalcitonin is a pre-hormone of calcitonin secreted by the C-cell of the thyroid in response to hypercalcaemia and negligible serum PCT concentrations are seen under healthy condition (10). There is however a significant rise in the level of procalcitonin in bacterial infections with systemic inflammation. Procalcitonin increases within two to four hours of bacterial infection, peaks at four to twenty hours, and falls when the infection is controlled. In viral infections, PCT concentration is normal whereas CRP takes 24 hours to rise, and is also elevated in viraemia. Procalcitonin level remains high as long as the bacterial infection persists which makes it suitable for diagnosis, monitoring prognosis, and offering guidance for appropriate antibiotic use in the treatment of bacterial infections (11,12).

In Nigeria, PCT has been reported to be useful in diagnosis of neonatal sepsis (13). Other studies have also shown that serum PCT helps clinicians to differentiate between typical bacterial and non-bacterial causes of lower respiratory tract infections (14). Elevated serum PCT concentration is both sensitive and specific in distinguishing bacterial from non-bacterial causes of sepsis, and also useful in monitoring the severity of bacterial infections. The level of PCT can be readily measured in the blood requiring little expertise and can be done in the absence of power supply. Procalcitonin guided management of severe bacterial infections reduces not only total antibiotic use but also emergence of antibiotic resistance (15, 16).

A national survey of antimicrobial prescribing in Nigeria reported very low utilization of biomarkers, with only about 0.5% across the four tertiary hospitals studied (17). This survey subsequently highlighted the need to use PCT as a guide for empiric antimicrobial therapy (17). This study was therefore designed to evaluate diagnostic use of PCT as a tool for differentiating bacterial from non-bacterial causes

of sepsis among adult patients in a tertiary healthcare facility in Lagos, Nigeria.

Materials and method:

Study area and design

This was a cross sectional study of 300 adult patients with clinical sepsis at the medical emergency unit and wards of Lagos University Teaching Hospital (LUTH), Lagos, Nigeria between May 2019 and April 2020.

Ethical approval

Ethical clearance was obtained from the LUTH Health Research Ethics Committee and a written consent was also obtained from all the participants.

Study population and selected participants

Patients with clinical diagnosis of sepsis made by the managing physicians were recruited for the study using systematic consecutive sampling method. A case of sepsis was defined as life threatening organ dysfunction caused by a dysregulated host response to infection (18). The clinical screening of all the patients recruited for the study was based on quick sequential organ failure assessment (qSOFA) score, which include criteria of; alteration in mental status, systolic blood pressure ≤ 100 mmHg and respiratory rate ≥ 22 /min in a patient with suspected infection. The score of 2 or more was considered as suspected sepsis with high risk of mortality (18,19).

Patients with other medical conditions that can interfere with the result of PCT were exempted from the study for example patients with ischemic bowel disease, medullary thyroid cancer, burns, post-operative complications and cardiogenic shock.

Diagnostic assessment of selected participants

A diagnostic sepsis workup which comprised white cell count (WCC), blood culture, and measurement of serum procalcitonin level were done for all selected patients. In patients with identifiable focus of infection, appropriate specimens such as sputum, pus and urine were also collected for microscopy, culture and sensitivity testing (result of this has been presented in another manuscript yet to be published).

Sample processing

Blood PCT concentration was determined using immuno-chromatographic test (ICT) kit (Liming Bio) according to the manufacturer's guidelines for the test procedure and interpretations (13,19,20).

Blood samples were cultured in BACTEC 9050 automated blood culture system. The incubation temperature was 35-37°C and when the culture bottles were flagged for growth or after five days of incubation, the bottles were removed from the system. Samples were taken from positive bottles and sub-cultured on MacConkey and 5% sheep blood agar plates. Blood agar plate was incubated in 5% CO₂ condition and MacConkey agar plate was incubated in ambient air for 16 to 24 hours.

Isolates were identified using standard laboratory procedures including colony morphology, Gram stain reaction, motility, and Microbact identification kit. Other specimens were analyzed using conventional standard laboratory protocols and the Clinical and Laboratory Standard Institute (CLSI) guideline (21).

Data analysis

The data collected were entered into Excel sheet and analysed using the International Business Machine Statistical Package for the Social Sciences (IBM SPSS) for windows version 25.0 (IBM Corp., Armonk, New York, USA). The data were presented in frequency tables and summary statistics. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratio of PCT against blood culture, WCC and qSOFA score were determined. Association between variables was measured using Fisher exact test (with Odds ratio and 95% confidence interval) and *p*-value < 0.05 was considered statistically significant.

Results:

Demographic and baseline characteristics of the study participants

The selected participants comprise 127 males (42.3%) and 173 females (53.7%) with age range from 20 to 82 years and mean age of 44.9±14.5 years. Among the underlying disease conditions identified from the selected participants, diabetes (24.3%) and HIV/AIDS (14.3%) were the most common co-morbidities (Table 1).

Bacterial culture positivity among participants

Of the 300 participants, 79 (26.3%) were culture positive while 221 (73.7%) were

culture negative. *Staphylococcus aureus* (29.1%, n=23) was the most frequent pathogen isolated from culture, followed by *Klebsiella pneumoniae* (19.0%, n=15) and *Escherichia coli* (16.5%, n=13) (Table 2).

Table 1: Demographic and baseline characteristics of the study participants

Characteristics	Frequency (%)
Gender	
Male	127 (42.3)
Female	173 (57.7)
Age group (years)	
20-29	48 (16.0)
30-39	75 (25.0)
40-49	60 (20.0)
50-59	68 (22.7)
60-69	32 (10.7)
≥70	17 (5.7)
Mean±SD	44.93±14.5
Co-morbidities	
Diabetes mellitus	73 (24.3)
HIV/AIDS	43 (14.3)
Heart failure	26(8.7)
Chronic renal failure	19 (6.3)
Malignancy	15 (5.0)
Others	22 (7.3)

qSOFA= quick sequential organ failure assessment; HIV/AIDS =human immunodeficiency virus/ acquired immune deficiency syndrome

Association of serum PCT levels with culture positivity

All the patients with PCT below 0.5 ng/ml (100%, n=121) and those with PCT level ≥0.5 to <2ng/ml (100%, n=47) were culture negative for bacterial pathogens, while only 7.4% (n=4) of the 54 patients with PCT level ≥ 2ng/ml to <10 ng/ml had bacterial growth. Majority (96.2%, n=75) of the patients with serum PCT level ≥10 ng/ml (n=78) were bacterial culture positive.

The different categories of PCT values were significantly associated with blood culture positivity or negativity (*p*<0.001) (Table 3). However, 9 (3.0%) of the 300 participants had contaminants isolated from their blood cultures and their PCT values were less than 0.5 ng/ml. All the positive culture samples had the same bacteria species isolated from two blood culture bottles.

Table 2: Bacterial pathogens isolated from the clinical specimens of selected patients

Isolate	Blood culture (%)	Urine (%)	Sputum (%)	Wound specimen (%)	Pus aspirate (%)	Ascitic fluid (%)	Total (%)
Gram-positive cocci							
<i>Staphylococcus aureus</i>	23 (29.1)	1 (4.5)	4 (14.8)	11 (32.4)	2 (40.0)	1 (100.0)	42 (25.0)
Coagulate negative staphylococci (CoNS)	7 (8.8)	6 (27.3)	0	3 (8.8)	1 (20.0)	0	17 (10.1)
<i>Enterococcus faecalis</i>	1(1.3)	0	0	0	0	0	1 (0.6)
<i>Streptococcus pneumoniae</i>	0	0	1 (3.7)	0	0	0	1 (0.6)
<i>Enterococcus faecium</i>	0	1 (4.5)	0	0	0	0	1 (0.6)
Sub-total	31 (39.2)	8 (36.4)	5 (18.5)	14 (41.2)	3 (60.0)	1 (100.0)	62 (36.9)
Gram-negative bacilli							
<i>Escherichia coli</i>	13 (16.5)	7 (31.8)	6 (22.2)	3 (8.8)	1 (20.0)	0	30 (17.9)
<i>Klebsiella pneumoniae</i>	15 (19.0)	1 (4.5)	9 (33.3)	3 (8.8)	0	0	28 (16.7)
<i>Pseudomonas aeruginosa</i>	2 (2.5)	1 (4.5)	0	6 (17.6)	0	0	9 (5.4)
<i>Klebsiella oxytoca</i>	3 (3.8)	0	3 (11.1)	2 (5.9)	0	0	8 (4.8)
<i>Acinetobacter baumannii</i>	3 (3.8)	2 (9.0)	0	2 (5.9)	0	0	7 (4.2)
<i>Enterobacter aerogenes</i>	2 (2.5)	1 (4.5)	2 (7.4)	0	0	0	5 (3.0)
<i>Proteus mirabilis</i>	2 (2.5)	0	0	1 (2.9)	1 (20.0)	0	4 (2.4)
<i>Citrobacter koseri</i>	0	0	2 (7.4)	1 (2.9)	0	0	3 (1.8)
<i>Serratia marcescens</i>	2 (2.5)	1 (4.5)	0	0	0	0	3 (1.8)
<i>Acinetobacter lwoffii</i>	2 (2.5)	1 (4.5)	0	0	0	0	3 (1.8)
<i>Providencia rettgeri</i>	2 (2.5)	0	0	0	0	0	2 (1.2)
<i>Citrobacter freundii</i>	1 (1.3)	0	0	1 (2.9)	0	0	2 (1.2)
<i>Enterobacter agglomerans</i>	1 (1.3)	0	0	0	0	0	1 (0.6)
<i>Pseudomonas fluorescens</i>	0	0	0	1 (2.9)	0	0	1 (0.6)
Sub-total	48 (60.8)	14 (63.6)	22 (81.5)	20 (58.8)	2 (40.0)	0	106 (63.1)
Grand total	79 (47.0)	22 (13.1)	27 (16.1)	34 (20.2)	5 (2.9)	1 (0.6)	168 (100)

Table 3: Univariate analysis of association of categories of serum PCT levels with blood culture positivity

PCT values (ng/ml)	Culture positive (%) (n=79)	Culture negative (%) (n=221)	Total (%)	OR (95% CI)	p-value
< 0.5ng	0	121 (100.0)	121 (100.0)	0.005 (0.003 - 0.085)	<0.0001*
≥ 0.5 - <2	0	47 (100.0)	47 (100.0)	0.023 (0.001 - 0.379)	<0.0001*
≥ 2.0 - <10	4 (7.4)	50 (92.6)	54 (100.0)	0.182 (0.063 - 0.523)	0.0003*
≥ 10	75 (96.2)	3 (3.8)	78 (100.0)	1362.5 (297.9 - 6230.5)	<0.0001*

PCT= Procalcitonin; OR = Odds Ratio; CI = Confidence Interval; * = statistically significant

Diagnostic parameters of PCT at different cut-off values

The cut-off values of PCT were set at 0.5ng/ml, 2ng/ml and 10ng/ml in relation to positive blood culture result. At cut-off value of 0.5ng/ml, the sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio are 100%, 54.7%, 44.1%, 100.0%, 66.7% and 2.2 respectively,

which implies that this cut off is not discriminatory for systemic bacterial infection due to high false positivity, low accuracy and low likelihood ratio. At cut-off value of 2ng/ml, the sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio are 100.0%, 76.0%, 59.8%, 100%, 82.3%, and 4.2 respectively, which ind-

icates that this cut off is slightly more discriminatory for systemic bacterial infection due to lower false positivity, higher accuracy, and higher likelihood ratio. At a cut-off value of 10 ng/ml, the sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio are 94.9%, 98.6%, 96.2%, 98.2%, 97.7% and 69.9 respectively, which indicate that this cut-off value is highly discriminatory for systemic bacterial infection due to very low false positivity (although few false negativity), very high accuracy and very high likelihood ratio (Table 4).

Association of PCT levels with blood cell count

Univariate analysis of association of PCT levels with WCC showed that the odd of an abnormal white blood cell count (leukopenia or leukocytosis) is lower with PCT value < 0.5 ng/ml (OR=0.047, 95% CI=0.025-0.087, $p < 0.0001$) but at PCT value of $\geq 0.5 - < 2$ ng/ml, abnormal WCC was not significantly associated with PCT value (OR=0.7451, 95% CI=0.3991-

1.391, $p=0.4622$), while the odd of abnormal WCC is higher with PCT value $\geq 2 - < 10$ ng/ml (OR=5.012, 95% CI=2.413-10.412, $p < 0.0001$) and PCT value > 10 ng/ml (OR=41.07, 95% CI =12.548 - 134.43, $p < 0.0001$) (Table 5). This implies that the probability of abnormal WCC is higher when there is elevated serum PCT level.

Association of PCT levels with qSOFA score

Univariate analysis of the association of serum PCT level with qSOFA cut off score of 2 showed that at PCT < 0.5ng/ml, the OR was 0.162 (95% CI=0.020-1.302, $p=0.087$), at PCT $\geq 0.5 - < 2$ ng/ml, the OR was 0.0515 (95% CI= 0.184 -1.638, $p=0.283$), at PCT $\geq 2 - < 10$ ng/ml, the OR was 0.603 (95% CI=0.203-1.791, $p= 0.362$) and at PCT ≥ 10 ng/ml, OR was 6.188 (95% CI=0.768-49.841, $p=0.086$) (Table 6). This analysis showed that there is no statistically significant association between PCT level and qSOFA cut off score of 2.

Table 4: Diagnostic parameters of PCT at different cut-off values compared with blood culture as "gold standard"

PCT levels (ng/ml)	Positive		Negative		Total (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%)	LR
	TP (%)	FP (%)	TN (%)	FN (%)							
0.5	79 (26.3)	100 (33.3)	121 (40.3)	0	300 (100)	100 (95.4 - 100)	54.8 (47.9 - 61.5)	44.1 (36.7-51.7)	100 (97.0-100)	66.7	2.2
2.0	79 (26.3)	53 (17.7)	168 (56.0)	0	300 (100)	100 (99.4 - 100)	76.0 (69.8 - 81.5)	59.8 (50.9-68.3)	100.0 (97.8-100)	82.3	4.2
10.0	75 (25.3)	3 (1.0)	218 (72.7)	4 (1.3)	300 (100)	94.9 (87.5 - 98.6)	98.6 (96.1 - 99.7)	96.2 (89.2-99.2)	98.2 (95.5-99.5)	97.7	69.9

PCT = Procalcitonin; TP=True Positive; FP=False Positive; TN=True Negative; FN=False Negative; PPV = Positive Predictive Value; NPV=Negative Predictive Value; LR = Likelihood Ratio; CI = Confidence Interval

Table 5: Univariate analysis of association of categories of serum PCT levels with abnormal white cell count

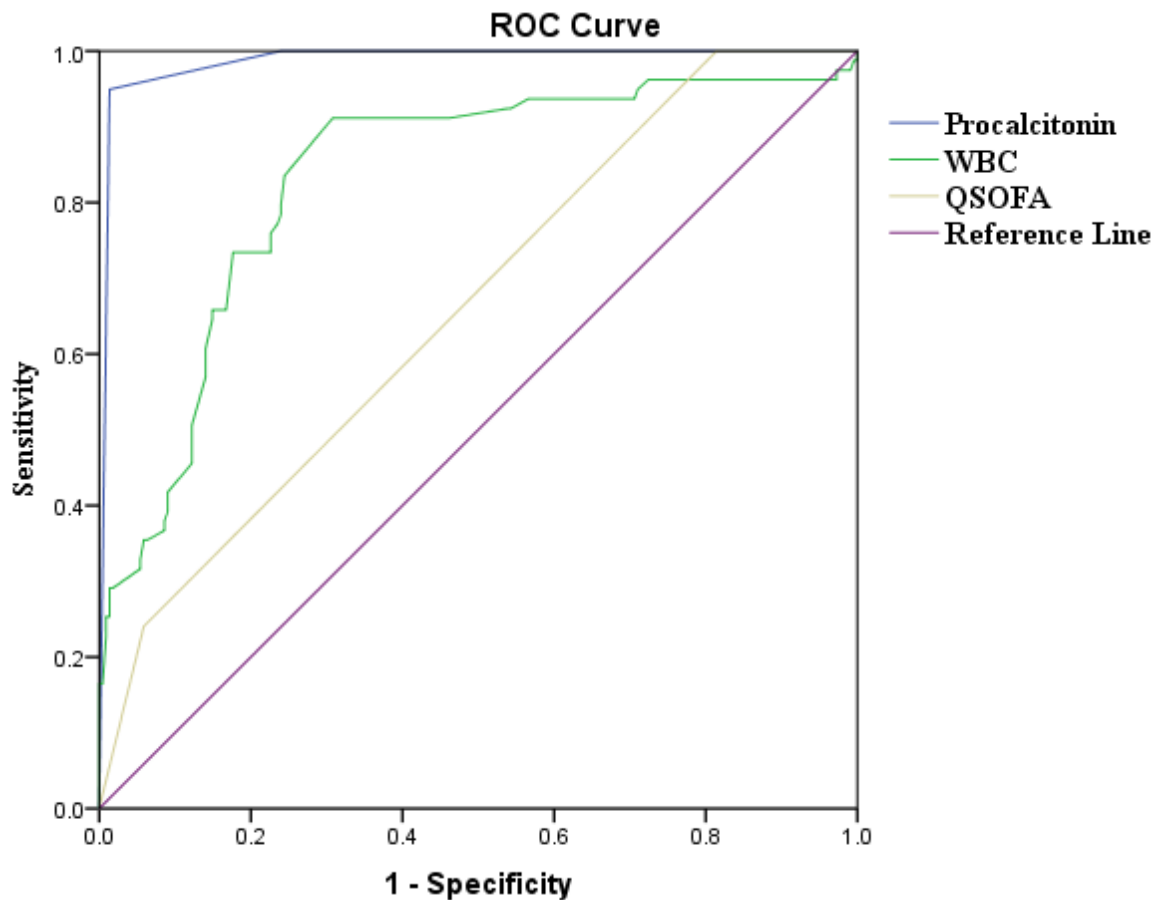
PCT values (ng/ml)	Abnormal WBC (%) (leucocytosis or leucopenia)	Normal WBC (%)	Total (%)	OR (95% CI)	p value
<0.5	18 (14.8)	103 (85.2)	121 (100)	0.047 (0.025 - 0.087)	<0.0001*
$\geq 0.5 - < 2$	22 (46.8)	25 (53.2)	47 (100)	0.7451 (0.3991 - 1.391)	0.4622
$\geq 2 - < 10$	44 (81.5)	10 (18.5)	54 (100)	5.012 (2.413 - 10.412)	<0.0001*
≥ 10	75 (96.2)	3(3.8)	78 (100)	41.07 (12.548 - 134.43)	<0.0001*
Total	159 (53.0)	141 (47.0)	300 (100)		

PCT= Procalcitonin, WBC= White blood cell, OR= Odd ratio, and CI= Confidence interval; * = statistically significant

Table 6: Univariate analysis of association of categories of PCT levels with qSOFA score

PCT value (ng/ml)	qSOFA score ≥2 (%)	qSOFA score <2 (%)	Total (%)	OR (95% CI)	p-value
<0.5	112 (92.6)	9 (7.4)	121 (100)	0.162 (0.020 - 1.302)	0.087
≥0.5 - <2	41 (87.2)	6 (12.8)	47 (100)	0.515 (0.184 - 1.638)	0.283
≥2 - <10	45 (83.3)	9 (16.7)	54 (100)	0.603 (0.203 - 1.791)	0.362
≥ 10	77 (98.7)	1 (1.3)	78 (100)	6.188 (0.768-49.841)	0.086
Total	275 (91.7)	25 (8.3)	300 (100)		

PCT= Procalcitonin, qSOFA quick Sequential Organ Failure Assessment, WBC= White blood cell, OR= Odd ratio, and CI= Confidence interval



Parameters	AUC	95% CI	p-value
Procalcitonin	0.987	0.976-0.999	<0.001*
WBC	0.832	0.777-0.887	0.003*
qSOFA	0.661	0.594- 0.729	0.154

AUC=area under the curve; CI=confidence interval; *=statistically significant; qSOFA = quick sequential organ failure assessment; WBC=white blood cell; ROC=receiver operating characteristics

Fig 1: Comparison of diagnostic usefulness of PCT, WCC and qSOFA in sepsis using receiver operating characteristics curve analysis

Comparison of diagnostic values of PCT, WCC and qSOFA score in adult sepsis

The receiver operating characteristics (ROC) curve analysis was performed to determine the diagnostic usefulness of PCT compared to white cell count (WCC) and qSOFA

score in the selected patients with systemic bacterial infections. PCT had higher area under the curve (AUC) of 0.987 (95% CI=0.976-0.999, $p<0.0001$) than that of WCC with AUC of 0.832 (95% CI=0.777-0.887, $p=0.003$) and qSOFA with AUC of 0.66 (95% CI = 0.594 -

0.729, $p=0.154$). Overall, PCT levels showed a higher diagnostic usefulness in patients with sepsis ($p<0.001$) and is a better tool to guide antibiotic therapy in patients with suspected sepsis when compared to WCC and qSOFA (Fig 1).

While PCT is a better tool, WCC (from statistical analysis) is equally useful as shown by AUC of 0.832 and $p=0.003$ (which is statistically significant). However, qSOFA appear not to be so useful in this study by low AUC of 0.666 and $p=0.154$ (which is not statistically significant). The ROC curve findings agree with the statistical analysis in the tables above.

Discussion:

High levels of serum PCT among adult patients with culture proven sepsis in this study have been reported in previous studies in Nigeria (13) and elsewhere (19,22). These studies reported serum PCT level as a sensitive and specific marker for detection of systemic bacterial infections. At PCT cut-off values of 0.5ng/ml, 2ng/ml and 10ng/ml, sensitivity, specificity, PPV, NPV, accuracy and likelihood ratio were reported relative to positive blood culture. At PCT cut off value of 0.5 ng/ml, the sensitivity and NPV are high (100%) but the specificity is reduced (54.8%) and PPV is much reduced (44.1%). This cut off value is therefore not discriminatory for systemic bacterial infection because of the high false positives and low positive likelihood ratio (PLR) of 2.2, but may confirm absence of systemic bacterial infection because the predictive value of a negative test (at $PCT < 0.5\text{ng/ml}$) is high. This is in agreement with the study of Liaudat et al., (23) who reported PCT as an early marker of sepsis in hospitalized patients and found a high NPV (95%) at PCT cut-off of 0.5ng/ml. Similarly, Bossink and colleagues (24) reported a 90% NPV at the same PCT cut-off value. Our finding is also consistent with previous reports on neonatal sepsis in Nigeria and South Africa (13, 25).

At PCT cut off value of 2 ng/ml, the sensitivity and NPV are high (100%) but the specificity, PPV and positive likelihood ratio (PLR) are a little higher (76.0%, 59.8%, and 4.2 respectively) than values reported at PCT cut off of 0.5 ng/ml. These values indicate that this cut off is slightly more discriminatory for systemic bacterial infections due to lower false positivity. At PCT cut off of 10ng/ml, the sensitivity, specificity, PPV, NPV, and accuracy are high (94.6%, 98.6%, 96.2%, 98.2% and 97.7% respectively), and the positive likelihood ratio is higher (69.9), which implies that this

cut off value is highly discriminatory for systemic bacterial infections due to the very low false positivity, very high accuracy and very high positive likelihood ratio. Therefore, patients with PCT level of $\geq 10\text{ng/ml}$ have very high probability of having systemic bacterial infections and physicians can objectively commence empirical antibiotic therapy while awaiting culture result. This finding agrees with the report of Arowosegbe et al., (13) in paediatrics population in Nigeria.

Univariate analysis of the association of PCT with abnormal WCC (leukocytosis or leukopenia) showed that the odd ratio of obtaining abnormal WCC progressively increased with increasing PCT levels, and at PCT level of $\geq 10\text{ng/ml}$, there was statistically significant association between elevated PCT level and abnormal WCC. This implies that patients with systemic bacterial infections who have elevated serum PCT level will most likely have abnormal WCC. This finding is consistent with the previous report of Magrini et al., (26). The receiver operating characteristics (ROC) curve analysis for PCT in predicting systemic bacterial infections showed area under the curve (AUC) of 0.987 (95% CI=0.976–0.999), which implies that PCT is a useful diagnostic tool for early diagnosis of systemic bacterial infection. This is in agreement with the study of Boraey and colleagues (27) in Egypt who reported AUC of 0.92 on ROC curve analysis. Ballot and colleagues (25) also reported a similar AUC of 0.778 in South Africa but previously, a lower AUC was reported in Nigeria (13).

From the comparison of the diagnostic values of PCT in detecting systemic bacterial infection with other screening parameters such as WCC and qSOFA using ROC curve analysis, the AUC was higher for PCT (0.987) than for WCC (0.832) and qSOFA (0.661), which is comparable to the reports of Magrini et al., (26), Park and colleagues (28), and Mueller et al., (5). Therefore, analysis of the results from this study revealed that PCT is a better tool, but WCC may equally be useful as shown by the AUC of 0.832 and $p=0.003$ (which is statistically significant), implying that WCC can serve as a useful alternative if PCT is not available, especially in low resource settings. However, qSOFA score appear not to be useful in this study as shown by the low AUC of 0.66 and $p=0.154$ (which is not statistically significant).

Blood culture is considered the "gold standard" for the laboratory evaluation of a patient with suspected systemic bacterial infections such as sepsis. In this study, 26.3% (79/300) of the blood cultures yielded positive

results for bacterial pathogens. The commonest bacterial isolate was *Staphylococcus aureus* (29.1%, 23/79), followed by *Klebsiella pneumoniae* (19.0%, 15/79) and *Escherichia coli* (16.5%, 13/79). This microbial pattern will enable physicians in making appropriate choice of antibiotics to be used in empirical therapy during initial management of patients with sepsis. The blood culture positivity rate and microbial pattern in this study are in keeping with the report of Kingsley and colleagues (29) in south-south Nigeria who reported 23.4% culture positivity although lower than 31.4% reported in southwest Nigeria (30).

We also noted that 3% of the blood cultures yielded skin contaminants, which may be attributed to the process of blood collection. Interestingly, serum PCT level in all the patients with contaminants was less than 0.5 ng/ml. This further supports the use of PCT levels as a tool to exclude contamination (when PCT level will be <0.5ng/ml) in addition to confirming severe bacterial infections (when PCT levels will be ≥ 10 ng/ml), especially in low resource settings where a single blood culture is often used. This observation also corroborated a previous report that PCT levels can be used to differentiate true positive from false positive blood cultures (22).

Conclusion:

Most studies on diagnostic evaluation of PCT in this part of the world had focused on paediatric populations. Our findings support the usefulness of PCT as a biomarker for early diagnosis of sepsis in adult patients. This will also bring about timely intervention and appropriate antimicrobial use in managing critically ill adult patients, and because of its low turn-around time (<30mins), PCT estimation will help physicians more to rationally decide on antibiotic therapy, and a low PCT level may be used to rule out bacterial sepsis.

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