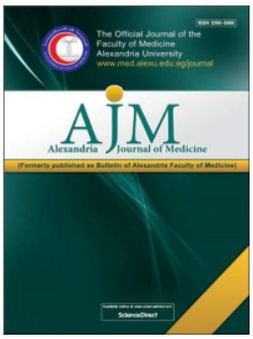

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Validity of procalcitonin and C-reactive protein as biomarkers in diagnosis of neonatal sepsis in a referral hospital, Kenya

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ABSTRACT

Background: Neonatal sepsis (NS) is a significant health concern causing high morbidity and mortality among neonates. The clinical symptoms of NS can overlap with other common neonatal conditions. The gold standard diagnostic method, the blood culture test, has numerous limitations including lengthy turnaround time, which delays appropriate management of NS. Acute phase protein; procalcitonin (PCT) and C-reactive protein (CRP) tests have emerged as potential alternatives due to short turnaround times, high sensitivity, and specificity in detecting NS. Nevertheless, there is limited data on their usability in Kenyan public hospitals. This study, therefore, was conducted to validate the performance of PCT and CRP tests in diagnosis of NS locally.

Methodology: Blood samples were collected from 196 neonates with suspected sepsis admitted at Moi Teaching and Referral Hospital (MTRH). Blood culture was performed using BacT/ALERT blood culture system. Bacteria growths were identified and antibiotic susceptibility for the isolates determined using Vitek II. Serum PCT levels were determined using the chemiluminescence immunoassay method. Serum CRP levels were measured using Immunoturbidimetry method.

Results: Growth of organisms occurred in 45.4% of the sepsis suspected neonates. The sensitivity, specificity, positive predictive value, negative predictive value and area under the curve for PCT were 93.3%, 98.1%, 97.6%, 94.6% and 0.959, whereas for CRP they were 100%, 72.8%, 74.3%, 100%, and 0.953, respectively.

Conclusion and Recommendation: The CRP test exhibited superior sensitivity, negative predictive value, but lower specificity, making it a more valuable tool for ruling out NS. Overall, however, PCT emerged as a more robust biomarker, offering a reliable balance between sensitivity and specificity, indicating its ability to identify cases with NS correctly. The area under the ROC curve confirms that CRP and PCT have high accuracy in detecting NS. The study recommends adoption of PCT and CRP biomarkers in the diagnostic protocols for NS.

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KEYWORDS
Neonatal sepsis; procalcitonin; C-reactive protein; diagnosis

1. Background information

Neonatal sepsis (NS) is a condition featured by nonspecific clinical manifestation in newborn infants less than 28 days old. It is characterized by a dysregulated response of the host's immune system to an infection. It encompasses a wide spectrum of manifestations, ranging from subtle or subclinical infections to severe and systemic presentations. These infections can be caused by various pathogens among them viruses, fungi and bacteria. Early-onset neonatal sepsis occurs within the first 72 hours of life, whereas the late-onset is manifested 72 hours after birth [1] Early-onset sepsis is often due to perinatal risk factors, whereas late-onset sepsis is associated with nosocomial and secondary infections [2].

Despite advances in neonatal medicine, NS remains a public health concern majorly in developing countries. Estimates show that the mortality rates caused by neonatal sepsis are two times higher in low- and middle-income countries compared to high-income countries [3] Besides, survivors of NS and even neonates whose blood culture are negative but treated with antibiotics are susceptible to adverse neurodevelopmental outcomes including visual impairment, cerebral palsy, cognitive delays and hearing loss [4].

Early diagnosis of neonatal sepsis remains a challenge owing to its nonspecific clinical presentation and difficulty in differentiating from noninfectious conditions [4]. Currently, blood culture is the mainstay conventional technique in NS detection. Nevertheless, the technique is not devoid of diagnostic challenges, including the presence of low or irregular bacteremia, maternal intrapartum antimicrobial exposure and inadequate blood volumes obtained from the

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neonates. Moreover, blood culture is considered time-consuming [5]. Previous studies have also reported that blood culture can give false positives resulting in indiscriminate use of antibiotics which can cause unintended harm such as necrotizing enterocolities, bronchopulmonary dysplasia, fungal infections and death. Besides, increased use of antibiotics increases the risk of development of antimicrobial resistance [5,6].

Consequently, diagnosis of neonatal sepsis tends to rest on new molecular approaches and non-culture -based methods including use of adjunct hematological indices, acute-phase proteins and pro-inflammatory cytokines. Nevertheless, the former has been demonstrated to have limited values and pose difficulty in interpreting due changes of normal ranges during neonatal period [5]. Recent studies have included acute-phase reactants such as procalcitonin (PCT) and C-reactive protein (CRP) to improve the detection of neonatal sepsis. Procalcitonin is a precursor of calcitonin produced by the thyroid gland, though in undetectable amounts. The biomarker is also secreted by other cells including monocytes and macrophages in condition of sepsis and severe bacterial infection. On the other hand, CRP is synthesized in the liver with its levels rising in response to inflammation, for example due to infection or various autoimmune disorders among other conditions [7].

Numerous studies conducted in different jurisdictions have reported PCT and CRP as reliable markers in detecting neonatal sepsis [8–10]. Nonetheless, it is well documented that as an acute protein produced in response to infectious stimuli and inflammation by the liver, CPR can be elevated by prenatal conditions such as maternal fever, stress delivery and fetal distress thereby, limiting its specificity. Besides, CRP takes 10–12 hours to respond to an infection and therefore is an unreliable marker for early-onset neonatal sepsis but a good predictor for late onset neonatal sepsis. In contrast, the levels of PCT are elevated within 2–4 hrs and last up to 30 hours [7]. Further, PCT concentrations and response are not affected by gestational age; therefore, it is a reliable marker for early-onset neonatal sepsis. The combination of these two biomarkers offers a better diagnostic efficacy [4].

The CRP and PCT test have been proposed as appropriate diagnostic markers for neonatal sepsis world-over. Nonetheless, there have been limitations in establishing universal reference ranges, cutoff levels and appropriate diagnostic values for CRP and PCT test in diagnosis of neonatal sepsis in clinical set-up [11]. Some authors have noted findings indicating PCT as more effective than CRP in diagnosis of neonatal sepsis [12,13] but reduced PCT specificity [14,15]. Besides, only a handful of studies have been carried out to address the utility of CRP and PCT test for neonatal diagnosis in low and middle-income countries [16].

The present study compared diagnostic performance of PCT and test referencing to the gold standard, the blood culture method. The CRP and PCT test are barely used for routine diagnosis of neonatal sepsis in Kenyan hospital, particularly the Western region. This study provides clinical validation for utility of CRP and PCT test for diagnosis of neonatal sepsis in a clinical setting in Western Kenya. The findings of this study are likely to accelerate adoption of CRP and PCT tests to enhance diagnosis and management of neonatal sepsis locally.

2. Material and methods

2.1. Study design

This was a prospective study conducted from January to May 2020. In this study, blood samples were collected systematically from neonates after obtaining written informed consent from their parents/guardians.

2.2. Study site

The study was conducted at the Newborn Unit (NBU) of the Riley Mother and Baby Hospital (RMBH), a component of Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya. the MTRH is one of the largest referral facilities in Kenya serving the entire western Kenya region and offers both clinical, training and research services. The hospital offers maternity and neonatal care to patients of diverse ethnic background in Rift Valley, Kenya. It has a fully functional NBU with a capacity of approximately 100 neonates at a time.

2.3. Study population

The study population comprised of neonates (0–28 days) suspected of both early and late onset sepsis admitted at RMBH NBU. The diagnosis of neonatal sepsis was done by a pediatrician. Neonatal sepsis was diagnosed based on the presence of the suggestive clinical features of sepsis including at least three of the following: convulsion, vomiting, lethargy, poor feeding, jaundices, hypoglycemia, bulging fontanels, hypothermia (≤36.5°C) and fever (≥38.0°C). Neonates who had received antibiotics, born with congenital anomalies or had undergone surgical procedure were excluded from this study. Samples were collected from the participant who presented these symptoms. After blood culture the cases that did not show bacteria growth on culture were classified as probable whereas the cases that show bacteria growth were classified as definite cases. A similar approach for

classification of results for neonatal sepsis diagnosis is provided by Kumar et al. [17].

2.4. Collection of clinical data

Clinical data (obstetric, gynecological, prenatal and neonatal data) was collected from mothers' obstetric records using data abstraction forms.

2.4.1. Sample processing and testing procedures

Samples were collected by a pediatrician. About 1.5 ml single drowned whole blood sample was collected aseptically from each subject by venous puncture. An aliquot of 1 ml of the blood was used for blood culture while the remaining sample was placed into a plain vacutainer and allowed to clot following which it was centrifuged at 10,000 rpm for 10 minutes to obtain serum for procalcitonin and C-reactive protein assays. Samples that were not analyzed immediately were stored at −20°C. Frozen serum samples were thawed prior to processing.

2.4.2. Blood culture

Blood culture was done using the BacT/ALERT blood culture system. Isolates from positive blood cultures were inoculated onto respective culture media plates and incubated at 37°C for 24 hours. The antibiotic susceptibility of the isolates was tested using Vitek II Compact which uses Clinical Laboratory Standards Institute (CLSI) guidelines for organism identification and interpretation of susceptibility. Negative blood cultures remained incubated for further 7 days before they were declared negative.

2.4.3. Procalcitonin (PCT) estimation

An aliquot of 100 µl of serum was taken and used for PCT estimation using Electro chemiluminescence immunoassay. The assay was carried out in an automated Elecsys e 411 (Roche Diagnostics, Rotkreuz, Switzerland).

2.4.4. C- reactive proteins (CRP) estimation

About 100 µl of serum was assayed for CRP using a turbidimetric method based on latex particles coated with monoclonal antibodies against CRP using the fully automated Roche Cobas Integra 400 plus analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

2.5. Statistical analysis

Data analysis was carried using SPSS software version 26. Mean and standard deviation were calculated. Cross tabulation was used to compare CRP and PCT results against the blood culture findings. Diagnostic efficiency was defined by the plot sensitivity against false positive rate (specificity) for the tests (CRP and PCT) against the gold standard (blood culture). Bayes' theorem was used to estimate the specificity and sensitivity of the two tests. Receiver operating characteristics (ROC) curve was used for analysis statistical difference of specificity and sensitivity of the assay and the differences were considered significant at 95% confidence level using a simple t-test ($p \leq 0.05$).

2.6. Ethical clearance

The study was approved by the Institutional Research and Ethics Committee (IREC) of MTRH and Moi University (Approval number; 0003286) prior to commencement. A written informed consent was sought from all mothers/guardians prior to commencement of the study. Confidentiality was maintained throughout the study where access to data was limited only to the principal investigator. Privacy of the data was assured by anonymization.

3. Results

3.1. Characteristics of study participants and culture results

The present study enrolled 196 neonates with suspected clinical sepsis. Their median gestational age was 38.35 ± 1.61. A majority (85.7%) were born at term with the remaining, 14.3% being born prematurely (Table 1). As shown in Table 1, females newborns comprised a slightly larger proportion at 55.6% whereas males were at 44.4%. Positive cultures were obtained in 45.4% of the samples whereas the rest returned a negative test result. A much higher incidence of neonatal sepsis (96.4%) was reported among the preterm neonates compared to the full-term (36.9%) neonates (Table 1). In addition, on gender-wise distribution of neonatal sepsis, it was revealed that a higher proportion of males (37.9%) returned a positive blood culture test verse their female counterparts (32.9%).

Table 1. Participants' sociodemographic and clinical characteristics.

Clinical data	Studied Group
Neonatal Gestational Age (in weeks) (Mean ± SD)	38.35 ± 1.61
Gestational Age	
Preterm	28 (14.3%)
Full term	168 (85.7%)
Neonatal Sex	
Males	87
Female	109
Blood Culture	
Positive	89(45.5%)
Negative	107(54.6%)
Gestational Age and Proven sepsis	
Preterm	27 (96.4%)
Full term	62 (36.9%)
Neonatal Sex and Proven Sepsis	
Male	33 (37.9%)
Female	46 (32.9%)

3.2. Microbial isolates from blood culture studies

As summarized in Figure 1, microorganism isolated from the positive blood cultures included Coagulase-Negative *Staphylococci* (CoNS) (20.4%), *Klebsiella pneumoniae* (4.2%), *Staphylococcus aureus* (4.1%), *Enterococcus spp* (3.6%), *Klebsiella spp* (3.6%), *Acinetobacter spp* (2.5%), *Escherichia coli* (2.5%), *Serratia marcescens* (1.5%), yeast (1.5%) and others (1.5%).

The neonates were divided into two groups as follows: Group 1: proven sepsis $n = 89$ which consisted of neonates whose blood sample yielded positive results in blood culture and Group 2: probable/suspected sepsis $n = 107$ which included neonates with suspected sepsis but yielded negative blood culture results (Table 2). The CRP and PCT values were compared in these groups at the standard cutoff of 0.5 mg/L and 1.0 ng/ml, respectively.

As shown in Table 2, all proven sepsis cases exhibited elevated levels of CRP (>0.5 mg/L) compared to the group with probable sepsis where only 27.8% displayed elevated levels of CRP. In regard to PCT, 93% of proven sepsis cases had elevated levels of the biomarkers (>1 ng/ml), whereas among the suspected sepsis cases less than 2% displayed elevated levels (>1.0 ng/ml) of PCT) (Table 2).

3.3. Diagnostic performance of CRP and PCT as NS biomarkers

The diagnostic performance of the biomarkers was quantified in terms of sensitivity and specificity. The sensitivity and specificity of CRP in diagnosis of neonatal sepsis were 100.0% and 72.2%, whereas for PCT were 93.3% and 98.1%, respectively. Further, the positive and negative predictive values were determined whereby the C-reactive protein test depicted a positive predictive value (PPV) of 74.8%, and negative predictive value (NPV) of 100.0%. Procalcitonin test had a PPV of 97.6%, and an NPV of 94.6% (Table 3).

Moreover, both biomarkers demonstrated high levels of diagnostic accuracy. Area under curve values (AUC) for serum PCT was 0.959 (95% CI: 0.182, 0.977) whereas the CRP had an AUC of 0.953 (95% CI: 0.754, 0.878) (Table 5).

Table 2. CRP and PCT levels versus blood culture outcomes.

Test	Categories	Blood Culture Groups; n (%)	
		Proved Sepsis (n = 89)	Probable Sepsis (n = 107)
CRP	Elevated (>5mg/L)	89 (100.0)	30 (27.8)
	Normal (0–5.0mg/L)	0	78 (72.2)
PCT	Elevated (>1ng/ml)	83 (93.3)	2 (1.9)
	Normal (0-1ng/ml)	6 (6.7)	105 (98.1)

Figure 1. Micro-organisms isolated in infants with neonatal sepsis.

Table 3. Sensitivity, specificity, PPV and NPV of PCT and CRP levels.

Tests	Sensitivity	Specificity	PPV	NPV
CRP	100.0%	72.2%	74.8%	100.0%
PCT	93.3%	98.1%	97.6%	94.6%

Table 4. Area under the curve and the performance of PCT and CRP.

Test	Result	Blood culture groups; n (%)		AUC (95% CI :)
		Proven Sepsis (89)	Probable sepsis (107)	
CRP	Elevated (>5mg/L)	89 (100.0)	30 (27.8)	0.953(0.754, 0.878)
	Normal (0–5.0mg/L)	0	78 (72.2)	
PCT	Elevated (>1ng/ml)	83 (93.3)	2 (1.9)	0.959(0.182, 0.977)
	Normal (0-1ng/ml)	6 (6.7)	105 (98.1)	

Table 5. Paired-sample area difference under the ROC curves for PCT and CRP.

	Asymptotic				Asymptotic 95% Confidence Interval	
Test Result Pair(s)	z	Sig. (2-tail)[a]	AUC Difference	Std. Error Difference[b]	Lower Bound	Upper Bound
Procalcitonin – CRP	.289	.772	.006	.180	−.037	.049

a. Null hypothesis: true area difference = 0
b. Under the nonparametric assumption

As shown in Table 4 below, the diagnostic performance of procalcitonin (PCT) and C-reactive protein (CRP) were statistically similar ($p > 0.05$). This was further confirmed by the asymptotic standard error difference; 0.006 (95% CI: −0.037, 0.049) for the difference in the area under the ROC curves between PCT and CRP and the confidence interval for the difference in their area under the ROC curves includes 0.

4. Discussion

Neonatal sepsis remains a global public health concern. Owing to its nonspecific clinical manifestation, diagnosis of neonatal sepsis remains a challenge. Blood culture has been recognized as the main diagnostic approach despite exhibiting intrinsic problems. Nonetheless, acute-phase proteins have received attention as remarkable rapid diagnostic biomarkers of neonatal sepsis. In the current study, C-reactive protein (CRP) and procalcitonin (PCT) were investigated for potential application as biomarkers for NS at neonatal hospitals in Kenya.

A total of 196 neonates with clinically suspected sepsis were recruited into the study with findings revealing that neonatal sepsis was more prevalent in males as compared to the female neonates. This may be attributed to the X-linked immunoregulatory gene factor that leads to an increased susceptibility to infections among males [18]. Moreover, the study revealed that preterm neonates, when compared to those born at term, were more prone to infection, an indication of potentially defective, immature immune system and/or reduced transfer of maternal antibodies [19,20]. The findings of this study are in tandem with previous studies [7,18].

Approximately 45% of the neonates yielded a positive blood culture test with *Klebsiella pneumoniae* being the most isolated gram-negative bacteria, whereas Coagulase-negative *Staphylococcus* (CoNS) was the most prevalent gram-positive isolate. Surprisingly, group B *streptococci* (GBS), which are commonly associated with early onset neonatal sepsis, were not detected in the present study. A number of factors, including maternal or postnatal administration of antibiotics, effectively curtailing the colonization or infection by this specific antigen as noted in previous studies [18,21] could have contributed to this finding. Despite excluding CoNS from their analysis of bacterial pathogens, Okomo et al. [22] acknowledged its presence as a potential contaminant or non-clinically relevant bacteria.

For validation of PCT and CRP, we first divided the neonates into two groups as described in section 3.2 with the first consisting of neonates with positive blood culture (proven sepsis) and the other group, neonates suspected with sepsis with negative blood culture. The latter group could not be ignored since lethal infection has been reported in the presence of negative blood cultures [23]. Indeed, this in part provides the justification for the need to include other sepsis biomarkers to aid in accurate diagnosis. Our findings revealed that there was a remarkably higher proportion of neonates with elevated PCT and CRP levels in the proven sepsis group than the probable NS suspected group. However, among the suspected neonates, some cases reported a PCT and CRP value above the cutoff value. Although the reason for the high values was not investigated, it could be explained by, among other reasons, the physiological increase of the biomarkers in healthy infants with peak values 1–2 days postnatal [24].

Further, the sensitivity, specificity, PPV and NPV of PCT and CRP test were assessed by comparing their results with the findings obtained from blood culture. The PCT test demonstrated a sensitivity of 93.3%, specificity of 98.1%, PPV of 97.6% and NPV of 94.6%. On the other hand, CRP showed a sensitivity of 100%, specificity of 72.2%, PPV of 74.8%, and NPV of 100%. The PCT emerged as a robust biomarker, offering a reliable balance between sensitivity and specificity, indicating its ability to correctly identify cases with and without sepsis. On the other hand, CRP had an excellent sensitivity but a lower specificity,

suggesting it may have a higher likelihood of producing false-positive results. Therefore, based on these findings, PCT emerged as a more reliable biomarker for neonatal sepsis diagnosis. Conversely, CRP may be more useful as a rule-out test, aiding in the exclusion of sepsis when negative results ensue, rather than confirming the presence of sepsis on its own [4,7].

Similar findings have been observed in previous studies, for example, Morad et al. [11] demonstrated that PCT showed sensitivity, specificity, PPV and NPV of 97.6%, 89%, 97% and 88.9%, respectively, whereas CRP showed a sensitivity (89.5%), specificity (66.7%), PPV (92.5%) and NPV (60.0%). Similarly, Kumar et al. [16] found the sensitivity, specificity, PPV and NPV of PCT were, 86.7%, 93.3%, 92.86% and 87.50%, respectively. Ranjan et al [25], Gilfillan and Bhandari [26] reported PCT sensitivity ranging from 83% to 100% and specificity ranging from 70% to 100%.

Nevertheless, the findings of the current study on C-reactive protein conflict with some other studies including Chawdhary et al. [27] which reported a sensitivity of 36.4%, specificity of 84.1%, PPV of 52.2%, and NPV of 73.4%. Also, Jeyaganguli et al. [28] found the sensitivity, specificity, PPV and NPV of CRP were 53.84%, 72.97%, 41.18% and 81.82%, respectively. The variations observed may be explained by the differences in the study population, timing of sample collection, variations in the cutoff values, the specific laboratory assays employed to measure CRP, the presence of non-bacterial infections or other sources of inflammation that may influence CRP levels and contribute to its variable performance as a diagnostic marker for sepsis [29–31].

In order to determine the accuracy of PCT and CRP testing, we determined the area under the curve (AUC) where a higher AUC indicates a better performance [29,31,32]. The findings of this study showed high areas under the ROC curves (AUC) for both PCT 0.959 (95% CI: 0.182, 0.977) and CRP 0.953 (95% CI: 0.754, 0.878), an indication that both biomarkers were of good diagnostic performance thereby, confirming their efficacy as biomarkers for diagnosing sepsis in neonates in our setting.

5. Conclusion

Both CRP and PCT are highly sensitive and specific biomarkers for diagnosing neonatal sepsis. The CRP test demonstrated superior sensitivity and negative predictive value, making it valuable for ruling out sepsis, while PCT shows higher specificity and positive predictive value, making it useful for confirming sepsis. The AUC analysis confirms both CRP and PCT have high accuracy in detecting neonatal sepsis, with no significant difference in diagnostic performance. They provide reliable means of diagnosis for sepsis in newborn units locally.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authors' contributions

Florence Chepyegon Tum conceived the study, designed the experiments and collected the data. Florence Chepyegon Tum, Joseph J.N. Ngeranwa, Geoffrey K. Maiyoh, Frank G. Onyambu participated in data analysis, writing and reviewing the manuscript.

Data availability statement

The author will provide data support this study upon request.

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