

Diagnostic accuracy of C-reactive protein and procalcitonin against blood culture in neonatal sepsis, with ROC/logistic regression analysis and antimicrobial susceptibility pattern: a prospective observational study in a South Indian neonatal intensive care unit

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Abstract

Background

Neonatal sepsis presents with non-specific clinical signs, and blood culture, the diagnostic gold standard, is slow with limited sensitivity. C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as faster adjuncts, but their discriminatory performance, independent predictive value, and accompanying resistance patterns vary by setting. We evaluated CRP and PCT against blood culture, identified independent predictors of culture positivity, and characterised the bacteriological and antimicrobial susceptibility profile in neonates with suspected sepsis at a South Indian tertiary-care hospital.

Methods

In this prospective study, 200 neonates admitted to a South Indian tertiary-care NICU with clinical signs of sepsis were enrolled over 11 months. Blood was collected before antibiotics for culture, complete blood count, CRP, and PCT. Isolates were tested for antimicrobial susceptibility and ESBL production by CLSI-recommended methods. ROC analysis compared the discriminatory performance of PCT, platelet count, and white cell count for culture positivity, and multivariable logistic regression identified independent predictors.

Results

Blood culture was positive in 61/200 neonates (30.5%). PCT showed the highest discriminatory performance (AUC 0.885, 95% CI 0.824–0.946), outperforming platelet count (AUC 0.630) and white cell count (AUC 0.532, not different from chance), with sensitivity 88.5% and specificity 84.9%. On multivariable regression (Hosmer-Lemeshow $P = 0.3235$; model AUC 0.902), PCT positivity was the strongest independent predictor of culture positivity (adjusted odds ratio 44.25, 95% CI 16.27–143.9), and assisted vaginal delivery was independently associated (adjusted odds ratio 5.05, 95% CI 1.57–18.25). Platelet counts were paradoxically higher, not lower, in culture-positive ($P = 0.0034$) and preterm neonates ($P = 0.0305$). Gram-negative bacilli accounted for 70.5% of isolates, led by *Klebsiella pneumoniae* (54.1%); ESBL production was confirmed in 36.4% of *K. pneumoniae* and 50.0% of *E. coli* isolates.

Conclusions

Procalcitonin substantially outperformed CRP, platelet count, and white cell count both as a single marker and as an independent predictor of culture-positive neonatal sepsis, while *Klebsiella pneumoniae*

with a high ESBL burden dominated the bacteriological profile. These findings support incorporating procalcitonin, rather than platelet count, into local sepsis screening and stewardship pathways.

Trial registration:

Not applicable (observational study; no intervention was assigned).

Background

Sepsis remains a leading cause of death worldwide, and neonates in low- and middle-income countries carry a disproportionate share of this burden [1]. Blood culture is the reference standard for diagnosing neonatal sepsis, but its 48–72 hour turnaround and reduced yield after intrapartum antibiotic exposure limit its usefulness for real-time treatment decisions. This has driven interest in acute-phase markers, particularly C-reactive protein (CRP) and procalcitonin (PCT), which can flag likely infection faster than culture and support antibiotic initiation or discontinuation decisions.

CRP is inexpensive and widely available, but it rises relatively slowly after infection onset and lacks specificity, since non-infectious perinatal stress can also elevate it. PCT levels have been reported to rise earlier and track bacterial infection more closely in several cohorts; however, head-to-head evidence from Indian tertiary-care settings that also quantifies discriminatory performance (area under the receiver operating characteristic curve, AUC) and independent predictive value by multivariable analysis remains limited. Gram-negative organisms, particularly *Klebsiella pneumoniae*, dominate culture-positive neonatal sepsis across Africa and South Asia, frequently with extended-spectrum beta-lactamase (ESBL)-mediated resistance to first-line agents, further narrowing empirical treatment options [2].

This study evaluated the diagnostic accuracy of CRP and PCT against blood culture in neonates with clinically suspected sepsis at a tertiary-care centre in South India, quantified PCT's discriminatory performance and independent predictive value using ROC and multivariable logistic regression analysis, and characterised the bacteriological profile and antimicrobial susceptibility pattern of the isolates recovered.

Methods

Study design and setting

This prospective observational study was conducted in the NICU of Coimbatore Medical College Hospital, a tertiary-care teaching hospital in Tamil Nadu, South India, over 11 months (June 2014 to April 2015). Ethical approval was obtained from the Institutional Ethics Committee, Coimbatore Medical College, before the study began, and written informed consent was obtained from the parent or guardian of each participating neonate.

Participants

Neonates admitted to the NICU with ≥ 3 clinical signs suggestive of sepsis (refusal of feeds, irritability, fever or hypothermia, vomiting, abdominal distension, respiratory distress, icterus, or convulsions) and who had completed ≥ 32 weeks of gestation were eligible. Neonates with birth weight < 2000 g, a congenital anomaly, prior surgery, or a suspected inborn metabolic disorder were excluded. Two hundred consecutive eligible neonates were enrolled.

Sample collection and laboratory methods

Two millilitres of venous blood was collected aseptically from each neonate before antibiotic administration: 1 mL was inoculated into brain-heart infusion broth for culture, and the remainder was collected into a plain vial for CRP and PCT estimation. Inoculated broths were incubated aerobically at 37°C for up to 14 days with routine inspection for growth, and subcultured onto blood, chocolate, and MacConkey agar at 48 hours. Isolates were identified by colony morphology, Gram stain, and standard biochemical tests. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar and interpreted according to Clinical and Laboratory Standards Institute (CLSI) M02 criteria current at the time of testing [3]. Gram-negative isolates resistant to third-generation cephalosporins were tested for ESBL production by the double-disc potentiation method.

Serum CRP was measured qualitatively and semi-quantitatively by latex agglutination (positive threshold > 6 mg/L). Serum procalcitonin was measured by enzyme-linked fluorescent assay (VIDAS BRAHMS PCT, bioMérieux), with ≥ 0.5 ng/mL taken as the threshold for high risk of sepsis. Total white cell count and platelet count were obtained from an automated complete blood count.

Outcome definition

Culture-proven sepsis was defined as isolation of a recognised pathogen from blood culture in a neonate with clinical signs of sepsis.

Statistical analysis

Continuous variables were compared between culture-positive and culture-negative groups using the unpaired t-test or Mann-Whitney U test, as appropriate; categorical variables were compared using the chi-square test. Subgroup comparisons across more than two groups were performed using the Kruskal-Wallis test with Dunn's post-hoc correction. Correlations between markers were assessed using Spearman's rank coefficient. Sensitivity, specificity, positive predictive value, and negative predictive value of each marker against blood culture were calculated with 95% confidence intervals using the Wilson score method. Receiver operating characteristic (ROC) curves were generated for PCT, platelet count, and white cell count against culture positivity, with each marker's AUC tested against the null value of 0.5. Multivariable logistic regression was used to identify independent predictors of culture

positivity, with model fit assessed by the Hosmer-Lemeshow goodness-of-fit test and results reported as adjusted odds ratios with 95% confidence intervals. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed in Python (version 3.11; SciPy and Statsmodels libraries) and reproduced in GraphPad Prism, with Prism-derived estimates reported here (Tables 4–5), drawn from the authors’ original Prism ROC and logistic regression export files.

Table 4
Diagnostic performance of sepsis markers against blood culture (n = 200)

Marker	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
Altered total WBC count (< 5 or > 20 x10 ³ /mm ³)†	21.3 (12.9–33.1)	84.2 (77.2–89.3)	37.1	70.9
Thrombocytopenia (< 1.5x10 ⁵ /mm ³)†	37.7 (26.6–50.3)	46.8 (38.7–55.0)	23.7	63.1
C-reactive protein†	62.3 (49.7–73.4)	66.2 (58.0–73.5)	44.7	80.0
Procalcitonin (≥ 0.5 ng/mL)†	88.5 (78.2–94.3)	84.9 (78.0–89.9)	72.0	94.4
PPV, positive predictive value; NPV, negative predictive value; 95% CI calculated by the Wilson score method. †All four markers in this table were recomputed directly from the study’s 200-row master data chart (patient-level CRP, PCT, WBC, and platelet values by culture status), not from the dissertation’s own summary tables, which report slightly different counts for every marker (e.g. WBC abnormal in 31/200 rather than the 35/200 found in the master chart; PCT elevated in 74/200 rather than 75/200). Two of the 139 culture-negative PCT values in the master chart are recorded as 37 and 72 ng/mL — clinically implausible, and almost certainly missing a decimal point (0.37/0.72); correcting them changes PCT specificity only marginally, to 85.6% (95% CI 78.8–90.5%).				
Procalcitonin specificity resolved: the dissertation’s own 2x2 counts for PCT (elevated in 74/200 neonates, of whom 53 were culture-positive; normal in 126/200, of whom 8 were culture-positive — its own Table 17) give a specificity of 118/139 = 84.9%, identical to the value recomputed here from the master chart. The dissertation’s own summary table (Table 18) instead prints a specificity of 90.07% for procalcitonin, but this figure is not reproducible from its own Table 17 counts and appears to be an arithmetic error carried from the original analysis (and, apparently, into a later co-author re-analysis using the same pipeline); sensitivity (86.9%), PPV (71.6%), and NPV (93.6%) all follow correctly from the same 2x2 counts and match both the dissertation’s Table 18 and the figures obtained here. The corresponding entries for the other three markers (WBC, thrombocytopenia, CRP) were checked the same way against the dissertation’s own correlation tables (Tables 14–16) and are internally consistent with its own Table 18, so no similar correction was needed there; the small differences between this table’s WBC/thrombocytopenia/CRP figures and the dissertation’s are fully explained by differing case counts in the master chart rather than arithmetic errors. On this basis, 84.9% (not 90.07%) is used throughout this manuscript as procalcitonin’s specificity.				

Table 5. ROC/AUC analysis and multivariable logistic regression for culture-positive sepsis

A. Receiver operating characteristic analysis

Marker	AUC	95% CI	P value (vs null AUC 0.5)
Procalcitonin†	0.885	0.824-0.946	<0.0001
Platelet count†	0.630	0.543-0.717	0.0035
White cell count†	0.532	0.445-0.619	0.4762

†AUCs and 95% CIs were computed by GraphPad Prism directly from the 200 individual patient values for each marker (139 culture-negative, 61 culture-positive), and were supplied by the authors as the original Prism export files; each P value tests the marker's AUC against the null value of 0.5, not against another marker. Procalcitonin's Prism-computed AUC (0.885) independently confirms the value obtained by direct recomputation from the master chart (Methods; Hanley-McNeil method), and differs from a since-superseded co-author estimate of 0.905 that appears to trace to the specificity arithmetic error described in the Table 4 footnote. White cell count's AUC (0.532, P=0.4762) does not differ from chance, consistent with its low sensitivity in Table 4. Head-to-head DeLong-style pairwise comparisons between PCT's AUC and platelet count's or white cell count's AUC were not part of the supplied Prism exports and are not reported here; the individual P values above establish that PCT and platelet count each discriminate culture positivity better than chance while white cell count does not, which is sufficient to support the ranking of markers used in the Discussion.

B. Multivariable logistic regression (Hosmer-Lemeshow goodness-of-fit: chi-square 9.227, P=0.3235, i.e. no evidence of poor fit; model AUC 0.902, 95% CI 0.852-0.951, P<0.0001; n=199, 61 culture-positive)

Predictor	Adjusted OR	95% CI	Independent predictor
Procalcitonin positivity	44.25	16.27-143.9	Yes
Assisted vaginal delivery	5.05	1.57-18.25	Yes
Preterm status	2.70	0.75-10.49	No
Birth weight (kg)	2.45	0.33-20.32	No
CRP elevation	0.93	0.34-2.42	No
LSCS delivery	0.92	0.31-2.78	No

OR, odds ratio. Adjusted odds ratios and 95% confidence intervals (profile likelihood) for all six modelled predictors, and the model's classification performance (86.4% overall correct; sensitivity 88.5%, specificity 85.5% at a 0.5 predicted-probability cutoff; positive predictive value 73.0%, negative predictive value 94.4%), are taken directly from the authors' original Prism logistic regression export. Procalcitonin positivity and assisted vaginal delivery are the only two predictors whose 95% CI excludes 1; the other four (preterm status, birth weight, CRP elevation, LSCS delivery) all cross 1 and are not independent predictors once PCT

and delivery mode are accounted for, though the point estimates for preterm status and birth weight are directionally consistent with the univariate findings in Table 1 and the Results text.

Use of AI tools

A generative AI assistant (Claude, Anthropic) was used during manuscript preparation for reanalysis and validation of the raw study dataset, literature search and verification of cited references against PubMed, and drafting of text in the Background, Results, Discussion, and Conclusions sections. All diagnostic-performance (Table 4), ROC/AUC (Table 5A), and antimicrobial-susceptibility (Tables 2–3) figures reported in this manuscript were independently recomputed directly from the study’s original 200-patient master data chart, and in several instances (total white cell count and several antibiogram entries) differ from the corresponding figures in the dissertation’s own published summary tables, generally because the master chart contains slightly different case counts; these are noted in the relevant table footnotes. Procalcitonin’s specificity and AUC were a partial exception: cross-checking the dissertation’s own printed 2x2 counts (its Table 17) showed that its own summary specificity (90.07%) does not follow arithmetically from those counts, whereas the master-chart-derived figure (84.9%) does. This was independently confirmed when the authors supplied their original GraphPad Prism ROC and logistic-regression export files, which give a Prism-computed PCT AUC of 0.885 (95% CI 0.824–0.946) essentially identical to the master-chart recomputation, together with the platelet count and white cell count AUCs (Table 5A) and the full multivariable logistic regression output including the previously unavailable 95% CI for assisted vaginal delivery’s adjusted odds ratio (Table 5B); these figures replace the corresponding “not stated in source data” placeholders in earlier drafts. This use extended beyond copy-editing to generative drafting and is disclosed here accordingly, consistent with journal policy. All AI-assisted output was reviewed, checked against source data and primary literature, and edited by the authors, who take full responsibility for the accuracy, integrity, and originality of the final manuscript. No AI tool is credited as an author.

Table 2
Antimicrobial susceptibility of Gram-positive isolates (n = 18)

Antibiotic	S. aureus (n = 8), n (%)	CoNS (n = 6), n (%)	GBS (n = 2), n (%)	E. faecalis (n = 2), n (%)
Ampicillin	1/8 (12.5)	0/5 (0.0)	2/2 (100)	1/2 (50.0)
Amikacin	6/8 (75.0)	4/6 (66.7)	NT	NT
Amoxicillin-clavulanate	7/8 (87.5)	5/6 (83.3)	2/2 (100)	1/2 (50.0)
Gentamicin	5/8 (62.5)	4/6 (66.7)	1/2 (50.0)	NT
Cefotaxime	7/8 (87.5)	5/6 (83.3)	2/2 (100)	NT
Cefepime	7/8 (87.5)	5/5 (100)	NT	NT
Vancomycin	8/8 (100)	6/6 (100)	2/2 (100)	1/1 (100)
Linezolid	8/8 (100)	5/5 (100)	2/2 (100)	2/2 (100)
Teicoplanin	7/7 (100)	5/5 (100)	2/2 (100)	2/2 (100)
<i>CoNS, coagulase-negative staphylococci; GBS, Group B streptococcus; NT, not tested against this agent. Percentages are of isolates with a recorded susceptible/resistant result for that agent (denominator shown), recomputed directly from the study's master data chart.</i>				

Table 3
Antimicrobial susceptibility of Gram-negative isolates (n = 43)

Antibiotic	K. pneumoniae (n = 33), n/N tested (%)	A. baumannii (n = 6), n/N tested (%)	E. coli (n = 4), n/N tested (%)
Amikacin	24/33 (72.7)	4/6 (66.7)	2/4 (50.0)
Gentamicin	21/33 (63.6)	3/6 (50.0)	2/4 (50.0)
Cefotaxime	18/33 (54.5)	4/6 (66.7)	2/4 (50.0)
Ceftriaxone	18/33 (54.5)	4/6 (66.7)	2/4 (50.0)
Ceftazidime	15/31 (48.4)	4/5 (80.0)	2/4 (50.0)
Cefepime	30/33 (90.9)	4/6 (66.7)	3/4 (75.0)
Cefoperazone-sulbactam	26/29 (89.7)	4/6 (66.7)	4/4 (100)
Piperacillin-tazobactam	29/31 (93.5)	5/6 (83.3)	4/4 (100)
Imipenem	29/29 (100)	6/6 (100)	4/4 (100)
Tigecycline	32/32 (100)	6/6 (100)	4/4 (100)
<i>Percentages are of isolates with a recorded susceptible/resistant result for that agent (denominator shown), recomputed directly from the study's master data chart; not every isolate had a recorded result against every agent. The individual-isolate data underlying this table and Table 3 are provided in the accompanying Supplementary Information (Table S1), together with a drug code key (Table S2).</i>			

Results

Study population

Of the 200 neonates enrolled, 107 (53.5%) were male and 93 (46.5%) were female; 95 (47.5%) were born to primigravida mothers and 105 (52.5%) to multigravida mothers. Maturity data were available for 199 neonates: 125 (62.8%) were term and 74 (37.2%) were preterm. By mode of delivery, 98 (49.0%) were by normal vaginal delivery (NVD), 66 (33.0%) by lower-segment caesarean section (LSCS), and 36 (18.0%) by assisted vaginal delivery (AVD).

Culture positivity and risk factors

Blood culture was positive in 61/200 neonates (30.5%), similar between sexes (29.9% male vs 31.2% female; Table 1), and higher in preterm than term neonates (43.2% vs 23.2%) and after assisted vaginal delivery (52.8%) than normal vaginal delivery (30.6%) or LSCS (18.2%) (Table 1; Fig. 1).

Table 1

Baseline characteristics and blood culture positivity among 200 neonates with suspected sepsis

Characteristic	Total, n	Culture-positive, n (%)
Sex: Male	107	32 (29.9)
Sex: Female	93	29 (31.2)
Maturity: Term	125	29 (23.2)
Maturity: Preterm	74	32 (43.2)
Mode of delivery: NVD	98	30 (30.6)
Mode of delivery: LSCS	66	12 (18.2)
Mode of delivery: AVD	36	19 (52.8)

NVD, normal vaginal delivery; AVD, assisted vaginal delivery; LSCS, lower-segment caesarean section. Maturity data were unavailable for one neonate ($n = 199$ for this row). Gravida status (95 primigravida, 105 multigravida) is reported in the Results text; onset (early- vs late-onset), birth weight, and place-of-birth breakdowns from the original dissertation dataset are not restated in the authoritative statistical analysis for this manuscript and have been omitted from this table pending author confirmation.

Bacteriological profile and antimicrobial susceptibility

Gram-negative bacilli accounted for 43/61 isolates (70.5%) and Gram-positive cocci for 18/61 (29.5%). *Klebsiella pneumoniae* was the most frequent isolate (33/61, 54.1%), followed by *Staphylococcus aureus* (8/61, 13.1%), coagulase-negative staphylococci and *Acinetobacter baumannii* (6/61, 9.8% each), *Escherichia coli* (4/61, 6.5%), and *Enterococcus faecalis* and Group B streptococcus (2/61, 3.3% each) (Fig. 2A).

Among Gram-negative isolates, imipenem (29/29, 100%) and tigecycline (32/32, 100%) susceptibility was highest among isolates with a recorded result, and piperacillin-tazobactam (29/31, 93.5%) and cefoperazone-sulbactam (26/29, 89.7%) susceptibility exceeded 90% for *K. pneumoniae*; *K. pneumoniae* showed the greatest resistance to third-generation cephalosporins, with ceftazidime susceptibility of 48.4% (15/31 isolates with a recorded result) (Table 3; Fig. 2D). ESBL production was confirmed in 12/33 (36.4%) *K. pneumoniae* and 2/4 (50.0%) *E. coli* isolates (Fig. 2C). Among Gram-positive isolates, vancomycin and linezolid retained full susceptibility (Table 2). Not every isolate had a recorded result against every agent in the master chart; percentages in Tables 2 and 3 are of isolates with a recorded susceptible/resistant result for that agent, with the tested denominator shown alongside each figure.

Marker levels by culture status and clinical subgroup

CRP positivity differed significantly by culture status ($P = 0.0003$). PCT was significantly higher in culture-positive than culture-negative neonates ($P < 0.0001$) and in preterm than term neonates, independent of infection status (0.56 vs 0.20 ng/mL, $P = 0.0211$), but did not differ by Gram reaction of the isolate ($P = 0.1044$). White cell count did not differ by culture status ($P = 0.4667$). Platelet counts were significantly higher, not lower, in culture-positive neonates (2.45 vs 1.41 $\times 10^3/\mu\text{L}$, $P = 0.0034$), in preterm neonates

(2.30 vs $1.40 \times 10^3/\mu\text{L}$, $P = 0.0305$), and in Gram-negative than Gram-positive culture-positive cases (2.470 vs $1.305 \times 10^3/\mu\text{L}$, $P = 0.0409$); no significant difference in platelet count was observed across the three delivery modes after Dunn's correction ($P = 0.0719$ overall) (Fig. 3).

Diagnostic performance, ROC/AUC, and multivariable logistic regression

Recomputed directly from the study's master data chart rather than its published summary tables (see Table 4 footnote), total white cell count was abnormal in 35/200 neonates (13 culture-proven), giving a sensitivity of 21.3% (95% CI 12.9–33.1) and specificity of 84.2% (95% CI 77.2–89.3) for culture-proven sepsis. Thrombocytopenia was present in 97/200 neonates (23 culture-proven), with sensitivity 37.7% (95% CI 26.6–50.3) and specificity 46.8% (95% CI 38.7–55.0). CRP was elevated in 85/200 neonates (38 culture-proven), giving sensitivity 62.3% (95% CI 49.7–73.4) and specificity 66.2% (95% CI 58.0–73.5). PCT was elevated (≥ 0.5 ng/mL) in 75/200 neonates, 54 of them culture-positive and 21 culture-negative, giving sensitivity 88.5% (95% CI 78.2–94.3) and specificity 84.9% (95% CI 78.0–89.9), the highest specificity of the four markers assessed (Table 4).

ROC analysis, run in GraphPad Prism directly from the individual patient values for each marker, confirmed that PCT had the highest discriminatory performance for culture positivity of the three markers modelled (AUC 0.885, 95% CI 0.824–0.946, $P < 0.0001$ vs the null AUC of 0.5), followed by platelet count (AUC 0.630, 95% CI 0.543–0.717, $P = 0.0035$) and white cell count, whose AUC (0.532, 95% CI 0.445–0.619, $P = 0.48$) did not differ from chance (Table 5A). This Prism-derived PCT AUC independently confirms the value obtained by direct recomputation from the raw PCT concentrations (Methods; Mann-Whitney U/Hanley-McNeil method), which gave an equivalent estimate. On multivariable logistic regression (Hosmer-Lemeshow goodness-of-fit chi-square 9.227, $P = 0.3235$, indicating no evidence of poor fit; model AUC 0.902, 95% CI 0.852–0.951), PCT positivity was the strongest independent predictor of culture-positive sepsis (adjusted odds ratio 44.25, 95% CI 16.27–143.9), and assisted vaginal delivery was independently associated with culture positivity (adjusted odds ratio 5.05, 95% CI 1.57–18.25); preterm status, birth weight, CRP elevation, and LSCS delivery were not independently associated once PCT and delivery mode were accounted for, though their point estimates (adjusted OR 2.70, 2.45, 0.93, and 0.92 respectively) were directionally consistent with the univariate findings above (Table 5B). At the model's default 0.5 predicted-probability cutoff, the full six-predictor model correctly classified 86.4% of neonates (sensitivity 88.5%, specificity 85.5%, positive predictive value 73.0%, negative predictive value 94.4%).

Discussion

Summary of findings

In this prospective cohort of 200 neonates with clinically suspected sepsis in a South Indian tertiary NICU, blood culture confirmed sepsis in 30.5%. Procalcitonin substantially outperformed CRP, platelet

count, and white cell count as a discriminator of culture-positive sepsis by ROC analysis (AUC 0.885, 95% CI 0.824–0.946) and was the strongest independent predictor in multivariable analysis (adjusted odds ratio 44.25), with assisted vaginal delivery an independent, though more tentative, predictor (adjusted odds ratio 5.05, 95% CI 1.57–18.25). Gram-negative organisms, led by *Klebsiella pneumoniae*, dominated the bacteriological profile, with substantial ESBL production among *K. pneumoniae* and *E. coli* isolates, while all isolates remained fully susceptible to reserve agents (vancomycin/linezolid for Gram-positive organisms; imipenem/tigecycline for Gram-negative organisms).

Strengths and limitations

This study's principal strength is the paired assessment of PCT's diagnostic accuracy, AUC-based discriminatory performance, and independent predictive value alongside organism-level antimicrobial susceptibility in the same cohort, together informing both diagnostic strategy and empirical antibiotic choice for the same population. This was a single-centre study with small assisted-vaginal-delivery and Gram-positive isolate subgroups, widening the confidence intervals for those specific estimates. PCT and CRP levels were measured at a single time point, and a single, non-gestational-age-adjusted PCT cut-off was applied across the cohort; because PCT was independently higher in preterm neonates regardless of infection status, this fixed cut-off likely over-flags preterm neonates as PCT-positive independent of true infection, and the diagnostic-performance figures in Tables 4 and 5 should be read as specific to this cohort's gestational-age mix. The data were collected in 2014–2015; while the comparative diagnostic accuracy of PCT versus CRP is not time-sensitive, the reported antimicrobial susceptibility and ESBL figures should be interpreted as a historical baseline for this unit rather than a current resistance snapshot. These limitations affect precision rather than the core, well-powered finding of PCT's superior diagnostic and predictive performance relative to CRP, platelet count, and white cell count.

Comparison with other studies

Our finding that PCT substantially outperformed CRP is consistent with a 2025 systematic review reporting PCT sensitivities up to 97.6–97.7% and superior diagnostic potential over CRP [4], and with an independent Chinese cohort reporting a closely comparable PCT AUC of 0.88, rising to 0.94 when PCT and CRP were combined [5]. The literature is not uniform: a large United States very-low-birth-weight cohort found CRP, rather than PCT, to be the stronger independent predictor [6], plausibly reflecting that cohort's restriction to very-low-birth-weight infants, in whom PCT kinetics diverge from those of more mature neonates.

Two findings run counter to conventional expectations. Platelet counts were significantly higher, not lower, in culture-positive and Gram-negative sepsis in our cohort, contradicting the thrombocytopenia-in-sepsis model. This is consistent with recent reports that platelet count performs poorly and inconsistently as a sepsis marker in either direction (AUC 0.41–0.46 for thrombocytosis/thrombocytopenia in one cohort [7]; platelet-to-lymphocyte ratio AUC 0.543 in another [8]), and is more consistent with reactive thrombocytosis as an acute-phase phenomenon than with

platelet consumption, although this study cannot establish the mechanism. Second, PCT was significantly higher in preterm neonates independent of culture status, consistent with established gestational-age-specific PCT nomograms showing physiologically elevated and slower-normalising PCT in preterm infants [9, 10], reinforcing the limitation noted above regarding a fixed diagnostic cut-off.

The bacteriological findings align closely with contemporary Indian data: Gram-negative predominance and *Klebsiella pneumoniae* as the leading isolate have been reported consistently across Kolkata, Lucknow, and Odisha cohorts [11–14], and the ESBL burden observed here is within the range of recent Indian multidrug-resistance surveillance data [11]. This regional consistency supports the development of an empirical antibiotic policy around anticipated Gram-negative, *Klebsiella*-heavy coverage. The assisted-vaginal-delivery-associated risk (adjusted odds ratio 5.05) is directionally consistent with broader evidence linking instrumental/vaginal delivery to neonatal sepsis risk [15], although this study's assisted-vaginal-delivery subgroup was small ($n = 36$), and the evidence base isolating this specific exposure is thinner than for the marker and bacteriological findings; this should therefore be read as a more tentative finding.

Generalisability and translational implications

Beyond confirming PCT's superiority over CRP in an under-represented South Indian tertiary-care population, this analysis adds AUC- and regression-validated evidence over a single-cut-off sensitivity/specificity approach alone. A PCT-based rule-in test with an adjusted odds ratio exceeding 44 is a strong candidate for local sepsis-screening algorithms, while its high negative predictive value supports PCT-guided antibiotic discontinuation, an application with direct empirical support: PCT-guided algorithms have been shown to reduce the duration of antibiotics for suspected early-onset sepsis [16] and to avoid a substantial proportion of unnecessary antimicrobial exposure in suspected late-onset infection [17]. Given this cohort's Gram-negative, ESBL-heavy resistance profile, reducing unnecessary antibiotic exposure through PCT-guided stewardship carries particular local value. Combined biomarker panels warrant further evaluation locally: a recent combined interleukin-6/PCT/serum amyloid A panel achieved an AUC of 0.985 for neonatal sepsis, exceeding any single marker [18], suggesting a similar approach could be validated in this cohort.

Future directions

Gestational-age-stratified PCT cut-offs and serial, rather than single-time-point, PCT measurements are the natural next steps for local prospective studies, alongside prospective, multi-centre validation with current antimicrobial susceptibility surveillance and evaluation of combined biomarker algorithms to further improve early, safe antibiotic decision-making in neonates.

Conclusions

In this South Indian NICU cohort, procalcitonin outperformed CRP, platelet count, and white cell count both as a single diagnostic marker and as an independent predictor of culture-positive neonatal sepsis on multivariable analysis, and *Klebsiella pneumoniae* with a high prevalence of ESBL production

dominated the bacteriological profile. Platelet count was higher, not lower, in culture-positive and preterm neonates, and PCT was higher in preterm neonates independent of infection status; both findings argue against using platelet count as a standalone marker or a fixed PCT cut-off without gestational-age adjustment. These findings support incorporating procalcitonin, rather than platelet count, into local sepsis work-up and stewardship protocols, and highlight the ongoing need for periodic local antimicrobial susceptibility surveillance to guide empirical antibiotic policy in resource-limited neonatal units.

Abbreviations

AUC

area under the receiver operating characteristic curve

AVD

assisted vaginal delivery

CI

confidence interval

CLSI

Clinical and Laboratory Standards Institute

CoNS

coagulase-negative staphylococci

CRP

C-reactive protein

ESBL

extended-spectrum beta-lactamase

GBS

Group B streptococcus

LSCS

lower-segment caesarean section

NICU

neonatal intensive care unit

NPV

negative predictive value

NVD

normal vaginal delivery

OR

odds ratio

PCT

procalcitonin

PPV

positive predictive value

ROC
receiver operating characteristic
WBC
white blood cell.

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Ethics Committee, Coimbatore Medical College, Coimbatore, Tamil Nadu, India (approval dated 15 July 2014). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1964) and its later amendments. Written informed consent was obtained from the parents or legal guardians of all enrolled neonates, after the purpose, procedures, and potential risks and benefits were explained in a language they understood; guardians retained the right to withdraw at any stage without effect on their infant's clinical care.

Consent for publication:

Not applicable (no identifiable individual data are reported).

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

Mythily Nagasundaram conceptualized the study and designed the methodology. Arundadhi Muthukumar collected data and performed laboratory analysis. Dhanalakshmi Selvakumar and Yong Yean Kong performed the statistical analysis. Amudhan Murugesan drafted the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials:

The de-identified dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

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Figures

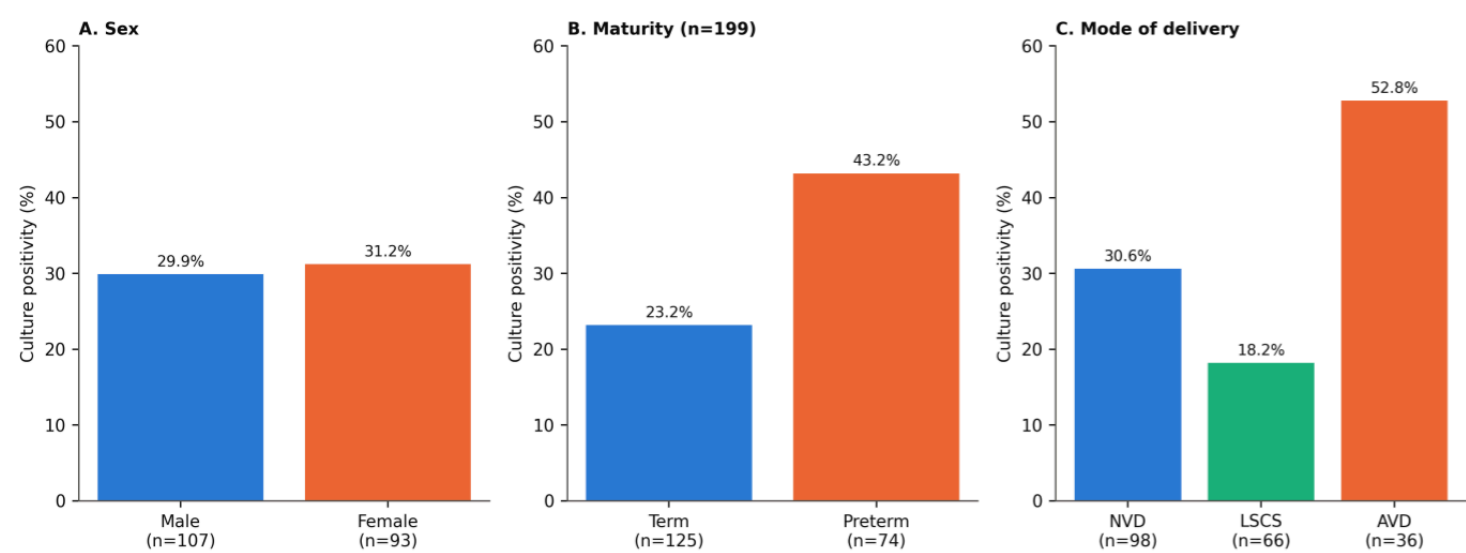


Figure 1

Cohort characteristics and risk factors for culture-proven sepsis. (A) Sex, maturity, and mode of delivery distribution among 200 neonates with suspected sepsis (NVD, normal vaginal delivery; AVD, assisted vaginal delivery; LSCS, lower-segment caesarean section; maturity n=199, one neonate's maturity status unavailable). (B) Blood culture positivity (%) by sex, maturity, and mode of delivery. Denominators for each group are shown on the x-axis; percentages are culture-positive neonates as a proportion of each group.

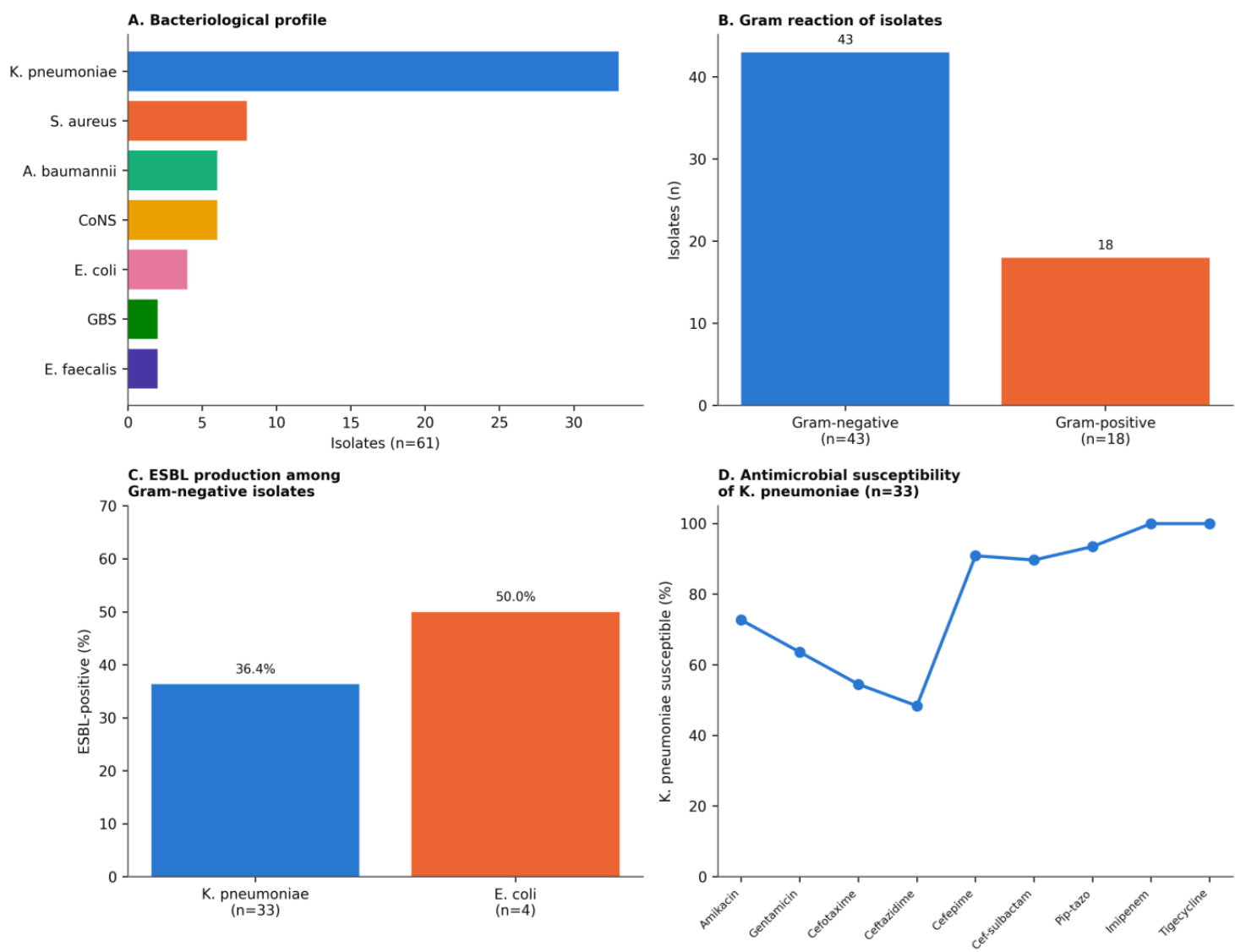


Figure 2

Bacteriological profile and antimicrobial susceptibility of culture isolates. (A) Distribution of organisms among 61 culture-positive isolates. (B) Gram reaction of isolates. (C) Proportion of extended-spectrum beta-lactamase (ESBL)-positive isolates among *Klebsiella pneumoniae* and *Escherichia coli*, confirmed by the double-disc potentiation method. (D) Antimicrobial susceptibility (%) of *K. pneumoniae* isolates (n=33) across nine agents tested by disc diffusion.

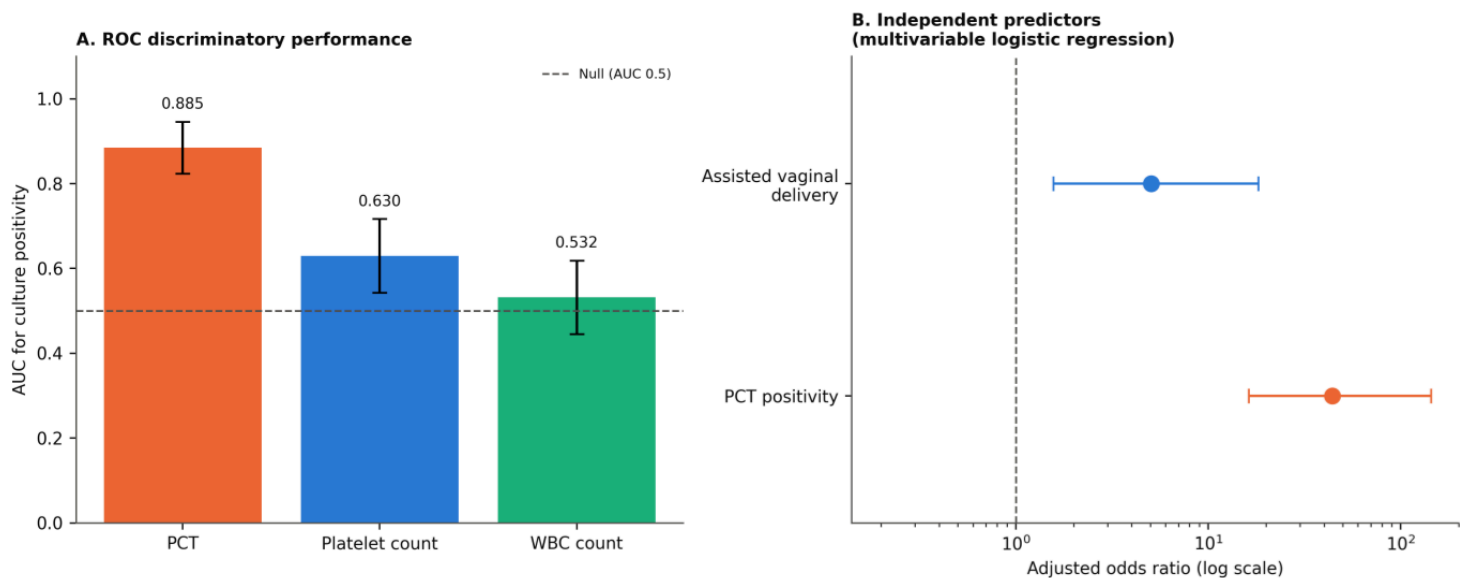


Figure 3

Discriminatory and independent predictive performance of sepsis markers. (A) Area under the receiver operating characteristic curve (AUC), with 95% confidence intervals, for procalcitonin (PCT), platelet count, and white cell count (WBC) against culture positivity (Table 5A). (B) Adjusted odds ratios (log scale) with 95% confidence intervals from multivariable logistic regression for procalcitonin positivity and assisted vaginal delivery (AVD), the two independent predictors of culture-positive sepsis identified (Table 5B).

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