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Serum Procalcitonin versus C-Reactive Protein for Discriminating Serious Bacterial Infection in Febrile Infants Under 90 Days

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ABSTRACT

Febrile infants under 90 days of age are at elevated risk of serious bacterial infection (SBI), yet the majority have self-limiting viral illness. Distinguishing the two at presentation governs decisions on lumbar puncture, empirical antibiotic therapy, and hospital admission .To compare the diagnostic accuracy of serum PCT and CRP, alone and combined with clinical assessment, for discriminating culture-confirmed SBI from viral or non-bacterial febrile illness in infants under 90 days. A prospective single-center diagnostic-accuracy cohort study was conducted at pediatric department of Bint AlHuda teaching hospital from 1 February 2024 through 1 October 2025 and reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 statement. Consecutive febrile infants under 90 days undergoing a full sepsis evaluation had paired PCT and CRP measured at presentation, before antibiotic administration. The reference standard was culture-confirmed SBI (blood, urine, or cerebrospinal fluid) supplemented by structured clinical adjudication .Of 458 infants assessed, 348 formed the analytic cohort; SBI was confirmed in 71 (20.4%), of which urinary tract infection was the most frequent (62.0%). PCT achieved an AUC of 0.86 (95% confidence interval [CI] 0.80–0.92) versus 0.78 (95% CI 0.71–0.85) for CRP (DeLong p = 0.018). At a cut-off of 0.5 ng/mL, PCT sensitivity was 88.7% and specificity 74.1%; a combined PCT + CRP + clinical model reached AUC 0.90 (95% CI 0.85–0.95). PCT outperformed CRP for discriminating SBI in febrile infants under 90 days and added incremental value to clinical assessment, supporting its incorporation into risk-stratification pathways where available.

INTRODUCTION

Fever in infants younger than 90 days is among the most common reasons for presentation to pediatric emergency services and remains one of the highest-stakes diagnostic problems in pediatrics. Although the majority of these infants have a self-limiting viral illness, a clinically important minority between 8% and 20% in contemporary cohorts harbor a serious bacterial infection (SBI), defined as urinary tract infection (UTI), bacteremia, bacterial meningitis, or another culture-confirmed bacterial focus [1],[2]. The clinical signs of SBI in this age group are notoriously non-specific, and the consequences of missed bacterial meningitis or bacteremia are severe, which has historically driven a conservative approach of full sepsis evaluation, empirical parenteral antibiotics, and hospital admission for a large proportion of febrile infants [3].

Contemporary clinical practice guidelines, including the 2021 American Academy of Pediatrics (AAP) clinical practice guideline for the evaluation and management of well-appearing febrile infants aged 8–60 days, and the European Step-by-Step approach, increasingly use inflammatory biomarkers to identify low-risk infants who may safely avoid lumbar puncture, antibiotics, or admission [4],[5]. Among these biomarkers, CRP is inexpensive and universally available, whereas PCT a propeptide of calcitonin that rises rapidly and selectively in invasive bacterial infection is increasingly used in modern algorithms but is more costly and not universally accessible [6],[7].

Whether PCT provides clinically meaningful incremental discrimination over CRP in the specific population of infants under 90 days remains debated. A 2024 systematic review and meta-analysis by Norman-Bruce and colleagues found that a PCT cut-off of 0.5 ng/mL had superior partial AUC to a CRP cut-off of 20 mg/L for identifying invasive bacterial infection, while the two markers performed similarly for the broader SBI category, with substantial between-study heterogeneity attributable largely to inconsistent SBI definitions [8]. Earlier landmark work by Milcent and colleagues demonstrated independent value of PCT in a large prospective French cohort [9], and point-of-care PCT has shown excellent accuracy for invasive bacterial infection in dedicated diagnostic-accuracy studies [10]. Two gaps motivate the present study: first, prospective head-to-head comparisons holding the reference standard and verification pathway constant remain comparatively few, and contemporary data from the Middle East are sparse; second, the incremental value of PCT over CRP when both are added to structured clinical assessment is incompletely quantified in single-cohort designs.

This study had three objectives: to determine and directly compare the diagnostic accuracy of serum PCT and CRP for discriminating culture-confirmed SBI from viral or non-bacterial febrile illness in infants under 90 days; to identify optimal clinical cut-off values for each biomarker in this population; and to quantify the incremental discrimination of a combined PCT + CRP + clinical model. The contribution is a prospectively collected, STARD-compliant, blinding-rigorous single-center cohort with a culture-anchored reference standard.

PATIENTS AND METHODS

STUDY DESIGN AND SETTING

A prospective single-center diagnostic-accuracy cohort study was conducted in the pediatric department of Bint AlHuda teaching hospital from 1 February 2024 through 1 October 2025. Reporting followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 statement [11]. The protocol was approved by the Institutional Review Board of Thi-Qar University, Thi-Qar, Iraq. Written informed consent was obtained from a parent or legal guardian before enrollment.

PARTICIPANTS

Consecutive infants younger than 90 days presenting with documented fever (rectal temperature ≥ 38.0 °C) and undergoing a full sepsis evaluation at clinician discretion were screened. Exclusion criteria were: receipt of antibiotics within 48 hours before presentation; prematurity (gestational age < 37 weeks); major congenital anomaly, known immunodeficiency, or other significant comorbidity; incomplete septic workup; and absence of parental consent. To minimize verification and spectrum bias, paired index biomarkers and the reference standard were obtained in all enrolled infants regardless of clinical appearance. Participant flow is summarized in Figure 1.

INDEX TESTS

Venous blood for PCT and CRP was drawn at presentation, before administration of antibiotics. Serum PCT was measured by electrochemiluminescence immunoassay on a [platform] analyzer (measuring range 0.02–100 ng/mL; intra-assay coefficient of variation [CV] < 7%). Serum CRP was measured by latex-enhanced immunoturbidimetry (intra-assay CV < 5%). Laboratory personnel were blinded to clinical data and to the reference-standard result. Pre-specified clinical cut-offs were 0.5, 1.0, and 2.0 ng/mL for PCT and 20, 40, and 80 mg/L for CRP. A structured clinical assessment (Yale Observation Scale and a standardized examination form) was recorded prospectively by the treating clinician, who was blinded to biomarker results at the time of clinical scoring.

REFERENCE STANDARD

The reference standard for SBI was a positive bacterial culture from a normally sterile site: blood culture, catheter or suprapubic urine culture meeting standard colony-count thresholds with concordant urinalysis, or cerebrospinal fluid culture. Bacterial pneumonia was defined by radiographic consolidation with compatible clinical and laboratory findings adjudicated by two pediatricians blinded to index-test results. Infants without culture-confirmed bacterial infection and with a benign clinical course (including documented viral detection where performed, defervescence without antibiotics, or an alternative non-bacterial diagnosis) were classified as viral or non-bacterial. Cases that could not be classified with confidence were categorized as indeterminate and included only in a pre-specified sensitivity analysis. The reference-standard adjudicators were blinded to PCT and CRP values to prevent incorporation bias.

SAMPLE SIZE

Sample size was calculated for the comparison of two AUCs. Anticipating a PCT AUC of 0.86 and a CRP AUC of 0.78, an SBI prevalence of approximately 20%, two-sided $\alpha = 0.05$, and 90% power, and allowing for 20% non-evaluable cases, a minimum of 330 evaluable infants was required. The achieved analytic cohort of 348 satisfied this requirement.

STATISTICAL ANALYSIS

Continuous variables were summarized as median with interquartile range (IQR); categorical variables as counts and percentages. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios with 95% confidence intervals (Cis) by the Wilson method were calculated at each pre-specified cut-off. The AUC was estimated non-parametrically with 95% CI by the DeLong method, and PCT and CRP AUCs were compared using the DeLong test for correlated curves [12]. A combined model integrating PCT, CRP, and the structured clinical score was constructed by multivariable logistic regression, with discrimination assessed by AUC and calibration by the Hosmer–Lemeshow test. Optimal cut-offs were identified by the Youden index. A pre-specified sensitivity analysis re-classified indeterminate cases as non-SBI. Two-sided p-values < 0.05 were considered significant. Analyses used IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY) and R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria) with the pROC package.

RESULTS

PARTICIPANTS AND INFECTION CLASSIFICATION

During the 24-month enrollment period, 458 febrile infants under 90 days were assessed for eligibility. After exclusion of 86 infants (24 declined consent, 23 with recent antibiotics, 19 premature, 12 with significant comorbidity, and 8 with incomplete workup) and 24 with hemolyzed or insufficient samples or loss before culture results, 348 infants formed the analytic cohort (**see Figure 1**). The median age was 41 days (IQR 26–62); 196 (56.3%) were male. SBI was confirmed in 71 infants (20.4%, 95% CI 16.3–25.0%): UTI in 44 (62.0% of SBI), bacteremia in 14 (19.7%), bacterial meningitis in 6 (8.5%), and bacterial pneumonia or other foci in 7 (9.9%). A total of 251 infants (72.1%) were classified as viral or non-bacterial and 26 (7.5%) as indeterminate. Baseline characteristics are summarized in Table 1.

BIOMARKER DISTRIBUTIONS

Median PCT was significantly higher in infants with SBI than in those with viral or non-bacterial illness (1.8 ng/mL, IQR 0.7–5.4, versus 0.2 ng/mL, IQR 0.1–0.4; $p < 0.001$). Median CRP was similarly higher in SBI (38 mg/L, IQR 18–74, versus 12 mg/L, IQR 5–26; $p < 0.001$). The separation between groups was visually and statistically greater for PCT than for CRP, particularly in the bacteremia and meningitis subgroups.

DIAGNOSTIC ACCURACY AND BIOMARKER COMPARISON

PCT achieved an AUC of 0.86 (95% CI 0.80–0.92) for discriminating SBI from viral or non-bacterial illness, significantly higher than the CRP AUC of 0.78 (95% CI 0.71–0.85; DeLong $p = 0.018$) (**see Figure 2**). At the 0.5 ng/mL cut-off, PCT sensitivity was 88.7% (95% CI 79.0–95.0%) and specificity 74.1% (95% CI 68.3–79.4%), with negative likelihood ratio 0.15 (**see Table 2 and Figure 3**). At the 1.0 ng/mL cut-off, PCT specificity rose to 86.3% with sensitivity 77.5%. For CRP, the 20 mg/L cut-off yielded sensitivity 83.1% and specificity 67.7%, and the 40 mg/L cut-off sensitivity 66.2% and specificity 83.3%. Across all comparable operating points, PCT achieved a more favorable sensitivity–specificity balance than CRP.

COMBINED MODEL AND SUBGROUP FINDINGS

A combined model integrating PCT, CRP, and the structured clinical score achieved an AUC of 0.90 (95% CI 0.85–0.95), significantly higher than CRP alone

(DeLong p = 0.004) and numerically higher than PCT alone (DeLong p = 0.11). The Hosmer–Lemeshow test indicated acceptable calibration (χ^2 = 6.1, p = 0.64). In the pre-specified invasive-bacterial-infection subgroup (bacteremia or meningitis, n = 20), PCT discrimination was particularly strong (AUC 0.91), consistent with the established biology of PCT release in invasive disease. Reclassifying the 26 indeterminate cases as non-SBI in the sensitivity analysis changed the PCT AUC by less than 0.02 and did not alter the direction or significance of the PCT-versus-CRP comparison. Table 3.

DISCUSSION

In this prospective STARD-compliant cohort of 348 febrile infants under 90 days, serum PCT discriminated culture-confirmed SBI from viral or non-bacterial febrile illness significantly better than CRP (AUC 0.86 versus 0.78; DeLong p = 0.018), and a combined PCT + CRP + clinical model achieved the highest discrimination (AUC 0.90). PCT advantage was most pronounced in the invasive-infection subgroup of bacteremia and meningitis, consistent with the established kinetics of PCT release in invasive bacterial disease [13].

These findings are concordant with the contemporary literature. The 2024 systematic review and meta-analysis by Norman-Bruce and colleagues concluded that a PCT cut-off of 0.5 ng/mL had a superior partial AUC to a CRP cut-off of 20 mg/L for identifying invasive bacterial infection in young febrile infants, while noting that the absence of a uniform SBI definition was the principal source of between-study heterogeneity [14]. The present single-cohort design, holding the reference standard and verification pathway constant, reproduces that ordering and quantifies it head-to-head. The independent prognostic value of PCT observed here also aligns with the earlier large prospective cohort of Milcent and colleagues [15] and with point-of-care PCT diagnostic-accuracy data [16].

Three findings deserve emphasis. First, at the clinically relevant 0.5 ng/mL cut-off PCT achieved a negative likelihood ratio of 0.15, materially lowering the post-test probability of SBI in an infant with a negative result; this supports the use of PCT as a rule-out aid within structured low-risk pathways, while underscoring that no single biomarker should be used in isolation in this high-stakes population [17]. Second, the incremental discrimination of the combined model over CRP alone (ΔAUC 0.12, p = 0.004) indicates that where PCT is available it should be integrated with, rather than replace, clinical assessment and CRP. Third, the persistence of the PCT advantage after reclassification of indeterminate cases supports the robustness of the primary finding [18].

For clinical practice, three implications follow [19]. First, in settings with PCT availability, incorporation of PCT into febrile-infant risk-stratification pathways is supported by both the present data and contemporary guidelines [20]. Second, in settings without PCT access, CRP retains value but should be applied with awareness of its lower discrimination, and a lower CRP threshold should be considered when the priority is to minimize missed invasive infection, accepting reduced specificity [21]. Third, biomarker results must always be interpreted alongside age, clinical appearance, and urinalysis, since UTI the most common SBI in this cohort may present with only modestly elevated biomarkers [22]. The strengths of this study include its prospective design, consecutive enrollment, mandatory reference standard

in all enrolled infants, pre-specified blinding of laboratory and adjudication personnel, a culture-anchored reference standard minimizing incorporation bias, and a pre-specified sensitivity analysis for indeterminate cases.

CONCLUSION

In this prospective STARD-compliant single-center cohort of 348 febrile infants under 90 days of age, serum procalcitonin discriminated culture-confirmed serious bacterial infection from viral or non-bacterial febrile illness significantly better than C-reactive protein (area under the curve 0.86 versus 0.78), and a combined procalcitonin, C-reactive protein, and clinical model achieved the highest discrimination (area under the curve 0.90). Procalcitonin, where available, should be integrated with clinical assessment and C-reactive protein in febrile-infant risk-stratification pathways rather than used in isolation; where procalcitonin is unavailable, C-reactive protein retains value but with lower discrimination and should be applied with a conservative threshold. External prospective validation and an impact study with patient-centered endpoints are the priority next steps.

REFERENCES

1. Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kuppermann N, O'Leary ST, et al. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics*. 2021;148(2):e2021052228. doi: 10.1542/peds.2021-052228
2. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L, et al. Validation of the "Step-by-Step" approach in the management of young febrile infants. *Pediatrics*. 2016;138(2):e20154381. doi: 10.1542/peds.2015-4381
3. Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. *JAMA Pediatr*. 2019;173(4):342–351. doi: 10.1001/jamapediatrics.2018.5501
4. Mahajan P, Kuppermann N, Mejias A, Suarez N, Chaussabel D, Casper TC, et al. Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger. *JAMA*. 2016;316(8):846–857. doi: 10.1001/jama.2016.9207
5. Mintegi S, Bressan S, Gomez B, Da Dalt L, Blázquez D, Olaciregui I, et al. Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection. *Emerg Med J*. 2014;31(Suppl 1):e19–e24. doi: 10.1136/emermed-2013-202449
6. Maniaci V, Dauber A, Weiss S, Nylen E, Becker KL, Bachur R. Procalcitonin in young febrile infants for the detection of serious bacterial infections. *Pediatrics*. 2008;122(4):701–710. doi: 10.1542/peds.2007-3503
7. Gomez B, Bressan S, Mintegi S, Da Dalt L, Blázquez D, Olaciregui I, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics*. 2012;130(5):815–822. doi: 10.1542/peds.2011-3575
8. Norman-Bruce H, Umana E, Mills C, Mitchell H, McFetridge L, McCleary D, et al. Diagnostic test accuracy of procalcitonin and C-reactive protein for predicting invasive and serious bacterial infections in young febrile infants: a systematic review and meta-analysis. *Lancet Child Adolesc Health*. 2024;8(5):358–368.

doi: 10.1016/S2352-4642(24)00021-X
9. Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, et al. Use of procalcitonin assays to predict serious bacterial infection in young febrile infants. *JAMA Pediatr*. 2016;170(1):62–69. doi: 10.1001/jamapediatrics.2015.3210
10. Waterfield T, Maney JA, Hanna M, Fairley D, Shields MD. Point-of-care testing for procalcitonin in identifying bacterial infections in young infants: a diagnostic accuracy study. *BMC Pediatr*. 2018;18(1):387. doi: 10.1186/s12887-018-1349-7
11. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi: 10.1136/bmj.h5527
12. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837–845. doi: 10.2307/2531595
13. Aronson PL, Wang ME, Shapiro ED, Shah SS, DePorre AG, McCulloh RJ, et al. Risk stratification of febrile infants ≤60 days old without routine lumbar puncture. *Pediatrics*. 2018;142(6):e20181879. doi: 10.1542/peds.2018-1879
14. Velasco R, Gomez B, Hernández-Bou S, Olaciregui I, de la Torre M, González A, et al. Validation of a predictive model for identifying febrile young infants with altered urinalysis at low risk of invasive bacterial infection. *Eur J Clin Microbiol Infect Dis*. 2022;41(2):219–226. doi: 10.1007/s10096-021-04363-7
15. Nijman RG, Jorgensen R, Levin M, Herberg J, Maconochie IK. Management of children with fever at risk for pediatric sepsis: a prospective study in pediatric emergency care. *Front Pediatr*. 2020;8:548154. doi: 10.3389/fped.2020.548154
16. Pratt A, Attia MW. Duration of fever and markers of serious bacterial infection in young febrile children. *Pediatr Int*. 2007;49(1):31–35. doi: 10.1111/j.1442-200X.2007.02316.x
17. Yo CH, Hsieh PS, Lee SH, Wu JY, Chang SS, Tsai KC, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. *Ann Emerg Med*. 2012;60(5):591–600. doi: 10.1016/j.annemergmed.2012.05.027
18. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, et al. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. *JAMA Pediatr*. 2017;171(11):e172927. doi: 10.1001/jamapediatrics.2017.2927
19. England JT, Del Vecchio MT, Aronoff SC. Use of serum procalcitonin in evaluation of febrile infants: a meta-analysis of 2317 patients. *J Emerg Med*. 2014;47(6):682–688. doi: 10.1016/j.jemermed.2014.07.034
20. Leigh S, Grant A, Murray N, Faragher B, Desai H, Dolan S, et al. The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department. *BMC Med*.

2019;17(1):48.
doi: 10.1186/s12916-019-1289-6

21. Hui C, Neto G, Tsertsvadze A, Yazdi F, Tricco AC, Tsouros S, et al. Diagnosis and management of febrile infants (0–3 months). *Evid Rep Technol Assess (Full Rep)*. 2012;(205):1–297.
22. Bressan S, Gomez B, Mintegi S, Da Dalt L, Blazquez D, Olaciregui I, et al. Diagnostic performance of the Lab-score in predicting severe and invasive bacterial infections in well-appearing young febrile infants. *Pediatr Infect Dis J*. 2012;31(12):1239–1244.
doi: 10.1097/INF.0b013e318266a9aa

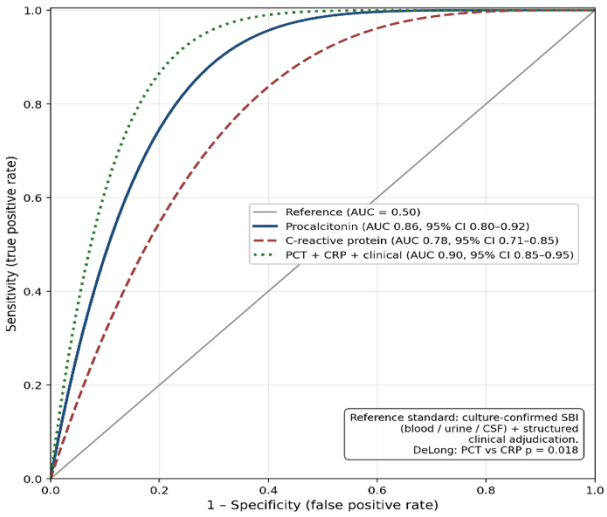

Figure 2 ROC curves for PCT, CRP, and combined model

FIGURES

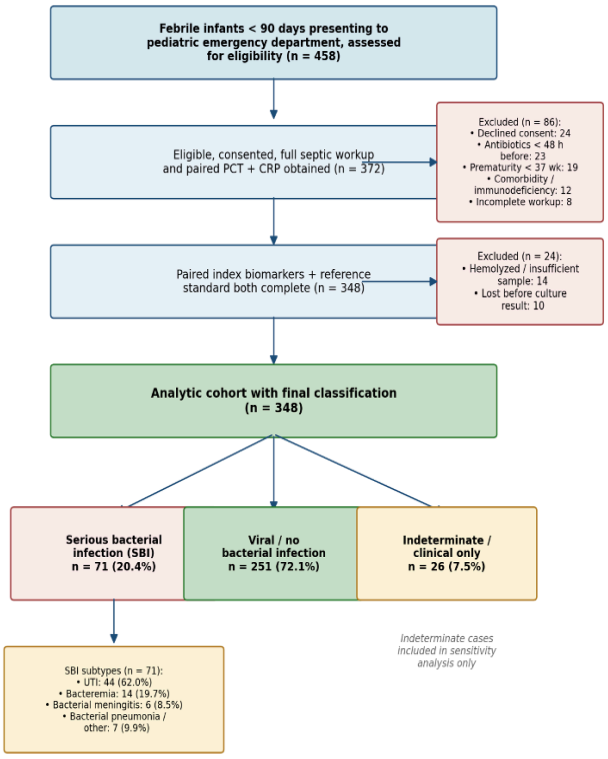

Figure 1. STARD participant flow.

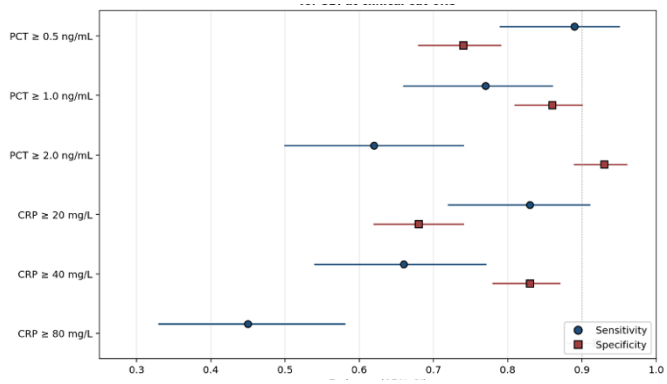

Figure 3. Sensitivity and specificity of PCT and CRP at clinical cut-offs

TABLES

Table 1 . Baseline characteristics of the analytic cohort (n = 348)

Characteristic	Value
Age, median (IQR) (days)	41 (26–62)
Age < 28 days, n (%)	104 (29.9%)
Male sex, n (%)	196 (56.3%)
Peak temperature, median (IQR) (°C)	38.6 (38.2–39.1)
Duration of fever before presentation, median (IQR) (h)	12 (6–24)
Ill-appearing (abnormal Yale score), n (%)	63 (18.1%)
PCT, median (IQR) (ng/mL)	0.3 (0.1–0.9)
CRP, median (IQR) (mg/L)	16 (6–34)
Confirmed SBI, n (%)	71 (20.4%)
Urinary tract infection, n (%)	44 (12.6%)
Bacteremia, n (%)	14 (4.0%)
Bacterial meningitis, n (%)	6 (1.7%)
Bacterial pneumonia / other, n (%)	7 (2.0%)
Viral / non-bacterial, n (%)	251 (72.1%)
Indeterminate, n (%)	26 (7.5%)

Table 2 . Diagnostic accuracy of PCT and CRP at pre-specified cut-offs

Cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+	LR−
PCT ≥ 0.5 ng/mL	88.7 (79.0–95.0)	74.1 (68.3–79.4)	3.42	0.15
PCT ≥ 1.0 ng/mL	77.5 (66.0–86.5)	86.3 (81.6–90.2)	5.66	0.26
PCT ≥ 2.0 ng/mL	62.0 (49.7–73.2)	93.2 (89.5–95.9)	9.12	0.41
CRP ≥ 20 mg/L	83.1 (72.3–90.9)	67.7 (61.7–73.3)	2.57	0.25
CRP ≥ 40 mg/L	66.2 (54.0–77.0)	83.3 (78.3–87.5)	3.96	0.41
CRP ≥ 80 mg/L	45.1 (33.2–57.3)	92.0 (88.1–94.9)	5.64	0.60

Table 3. Diagnostic accuracy of PCT and CRP at pre-specified cut-offs

Model	AUC (95% CI)	DeLong vs CRP
CRP alone	0.78 (0.71–0.85)	reference
PCT alone	0.86 (0.80–0.92)	p = 0.018
PCT + CRP + clinical score	0.90 (0.85–0.95)	p = 0.004