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Serum Pentraxin-3 Versus C-Reactive Protein in Differentiating Bacterial From Viral Febrile Illness in Children: A Prospective Case-Control Study

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Abstract

Background: Distinguishing bacterial from viral causes of fever in young children remains a central diagnostic problem in paediatric emergency care, and C-reactive protein (CRP), the most widely used marker, has limited sensitivity in the early hours of illness and limited specificity in several viral infections. Pentraxin-3 (PTX3) is a long pentraxin released rapidly at the site of infection by neutrophils, macrophages and endothelial cells, independent of hepatic synthesis. We compared serum PTX3 with CRP for differentiating bacterial from viral febrile illness in children.
Methods: This prospective case-control study was conducted at the Central Teaching Hospital of Pediatrics, Baghdad, between 1 December 2024 and 1 February 2025. We enrolled 60 children with confirmed bacterial infection, 55 with confirmed viral infection and 30 healthy controls. Serum PTX3 was measured by enzyme-linked immunosorbent assay and CRP by immunoturbidimetry at presentation. Diagnostic performance was assessed by receiver operating characteristic (ROC) analysis with Youden-derived cut-offs, and areas under the curve (AUC) were compared by the DeLong test. A logistic model combining both markers was also evaluated.
Results: Median PTX3 was 10.55 ng/mL (IQR 7.41–14.59) in bacterial, 4.46 ng/mL (2.97–6.26) in viral and 2.07 ng/mL (1.28–2.87) in healthy children ($p < 0.001$ for all pairwise comparisons). CRP followed the same gradient (77.42, 16.54 and 1.66 mg/L, respectively; $p < 0.001$). PTX3 and CRP correlated moderately (Spearman $\rho = 0.54$, $p < 0.001$). For bacterial versus viral infection, PTX3 ≥ 6.76 ng/mL gave an AUC of 0.881 (95% CI 0.818–0.943), sensitivity 83.3% and specificity 81.8%, whereas CRP ≥ 50.8 mg/L gave an AUC of 0.825 (0.746–0.905), sensitivity 70.0% and specificity 89.1% (AUC difference $p = 0.222$). At the conventional CRP threshold of 20 mg/L specificity fell to 60.0%. Combining the two markers raised the AUC to 0.908 (0.852–0.963), sensitivity to 93.3% and negative predictive value to 91.7%, significantly better than CRP alone ($p = 0.014$).
Conclusion: Serum PTX3 discriminates bacterial from viral febrile illness in children at least as well as CRP, with a more favourable sensitivity profile, and the two markers are complementary. PTX3 deserves evaluation as an adjunct to CRP in paediatric fever pathways aimed at reducing unnecessary antibiotic use.

Keywords: pentraxin-3; C-reactive protein; febrile children; bacterial infection; viral infection; biomarker; diagnostic accuracy; Iraq

1. Introduction

Fever is one of the most frequent reasons for children to attend emergency and outpatient services, and although most febrile episodes are self-limiting viral illnesses, a minority represent serious bacterial infections that demand prompt antimicrobial therapy [1,2]. The clinician's difficulty is that the two cannot be separated reliably on history and examination alone, and this diagnostic uncertainty is itself an independent driver of antibiotic overuse: in a recent multicentre analysis of febrile children with respiratory tract infection or fever without source, physician-rated uncertainty doubled the odds that a child with a virus-adjudicated diagnosis received antibiotics [3]. Each unnecessary course adds to the selective pressure that sustains antimicrobial resistance, so better early discrimination between bacterial and viral aetiologies is a priority for paediatric stewardship [2,4].

C-reactive protein (CRP) and procalcitonin remain the first blood tests requested in this setting [4]. CRP is a short pentraxin synthesised almost exclusively by hepatocytes under the transcriptional control of interleukin-6, and its plasma concentration rises several hundred-fold during acute inflammation [5,6]. That hepatic, cytokine-dependent route, however, imposes a lag of many hours between the onset of infection and a measurable rise, and the magnitude of the response is similar in several viral infections, notably adenovirus and influenza, that generate strong systemic inflammation [6,7]. The consequence is a trade-off that is well documented in children: in a meta-analysis of 37 studies of fever without source in infants up to 36 months, a CRP cut-off of 10–20 mg/L gave the highest pooled sensitivity (0.75) but a cut-off above 40 mg/L was needed for a specificity above 0.90 [7], and in a European cohort of more than 17,000 febrile children a threshold of 20 mg/L detected 87% of serious bacterial infections at the cost of a specificity of only 59% [8]. White blood cell and neutrophil counts add little to CRP [8]. There is therefore a clear need for a marker whose kinetics and cellular source are different from those of CRP.

Pentraxin-3 (PTX3) is the prototypic long pentraxin and a fluid-phase pattern-recognition molecule of humoral innate immunity. Unlike CRP, it is produced locally at the site of infection by macrophages, myeloid dendritic cells, endothelial cells and fibroblasts in response to Toll-like receptor engagement, tumour necrosis factor-α and interleukin-1β, and it binds conserved microbial moieties, activates complement and promotes phagocytosis [9]. Importantly, neutrophils store preformed PTX3 in specific granules and release it within minutes of microbial recognition, so that circulating concentrations rise far faster than those of hepatically synthesised acute-phase proteins [9,10]. In adults, plasma PTX3 is elevated in critically ill patients with a gradient from systemic inflammatory response syndrome to septic shock [11], peaks within the first day of sepsis and persists in those who die [12], tracks organ dysfunction in the largest sepsis cohort studied to date [13], and discriminates bacterial infection with and without sepsis in emergency-department patients with suspected infection [14]. Paediatric evidence is accumulating. A meta-analysis confirmed higher PTX3 in septic than in healthy neonates [15], PTX3 added to procalcitonin and CRP in neonatal sepsis [16], and in a prospective study of 40 children with suspected sepsis PTX3 achieved an AUC of 0.872 and varied with clinical severity whereas CRP and procalcitonin did not [17]. In children with lower respiratory tract infection PTX3 correlated with peak temperature, disease severity and blood culture positivity [18,19], and in cerebrospinal fluid it separated bacterial from aseptic meningitis in children [20] and adults [21].

What is missing from this literature is a direct, head-to-head comparison of serum PTX3 and CRP in a general population of febrile children with microbiologically or clinically confirmed bacterial or viral infection across the common foci encountered in practice (respiratory, urinary, gastrointestinal, bloodstream, central nervous system and skin). Most paediatric PTX3 studies have addressed a single organ system, used CSF rather than serum, or compared infected children with healthy controls rather than with children carrying a viral infection, which is the comparison that matters at the bedside. No data are available from Iraq or the wider region, where antibiotic use in children is high and rapid multiplex viral testing is not routinely available. The present study therefore measured serum PTX3 and CRP in febrile children attending a tertiary paediatric hospital in Baghdad and compared their ability, individually and in combination, to differentiate bacterial from viral febrile illness.

2. Materials and Methods

2.1 Study Design and Setting

This prospective case-control study was conducted in the emergency department and paediatric wards of the Central Teaching Hospital of Pediatrics, Baghdad, Iraq, between 1 December 2024 and 1 February 2025. The protocol was approved by the hospital's institutional ethics committee on 1 November 2024 (no reference number is assigned by this committee), and written informed consent was obtained from a parent or legal guardian of every child before enrolment. The study was conducted in accordance with the Declaration of Helsinki, with safeguards for voluntary participation and confidentiality.

2.2 Participants

Children presenting with fever, defined as an axillary temperature of 38.0 °C or higher measured at triage or reported by the caregiver within the preceding 24 hours, were screened consecutively. Children were eligible if the final diagnosis after full evaluation was an acute bacterial or an acute viral infection. Exclusion criteria were antibiotic treatment in the 72 hours before sampling, chronic illness (congenital heart disease, chronic renal or hepatic disease,

malignancy, primary or secondary immunodeficiency), corticosteroid or immunosuppressive therapy, recent surgery or trauma, known autoimmune or autoinflammatory disease, and mixed or undetermined aetiology. A group of healthy children of similar age and sex, attending the outpatient clinic for routine follow-up or elective minor procedures with no febrile illness in the preceding four weeks, was enrolled as a reference group.

The final diagnosis in each febrile child was assigned by two paediatricians who reviewed the clinical course, imaging, haematology and microbiology results and who were blinded to the PTX3 result. Bacterial infection required a positive culture of blood, urine or cerebrospinal fluid, a positive rapid antigen test for group A streptococcus with compatible pharyngotonsillitis, or a characteristic clinical and radiological picture (lobar or segmental consolidation, pyelonephritis with pyuria and positive urine culture, osteoarticular infection with imaging and culture or aspirate support, or bacterial meningitis defined by cerebrospinal fluid findings and culture or Gram stain). Viral infection required a positive virological test (influenza A/B antigen or PCR, SARS-CoV-2 PCR, rotavirus/adenovirus/norovirus stool antigen, respiratory viral panel where available) or a clinically unequivocal viral syndrome (bronchiolitis in infancy, roseola or other viral exanthem, aseptic meningitis with lymphocytic cerebrospinal fluid and negative bacterial culture) with negative bacterial cultures and spontaneous resolution without antibiotics. In total 60 children with bacterial infection, 55 with viral infection and 30 healthy controls were enrolled (n = 145).

2.3 Sample Collection and Laboratory Methods

Venous blood (3 mL) was drawn at presentation, before any antibiotic was given, into plain tubes, allowed to clot and centrifuged at 3,000 rpm for 10 minutes. One serum aliquot was analysed immediately for CRP; the remainder was stored at −80 °C for batched PTX3 assay. Serum PTX3 was measured in duplicate with a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (manufactured in China) according to the manufacturer's instructions and expressed in ng/mL. CRP was measured by particle-enhanced immunoturbidimetry on an automated biochemistry analyser (mg/L), and complete blood counts were obtained on an automated haematology analyser. Laboratory staff were blinded to the clinical classification.

2.4 Sample Size

With an expected AUC of 0.85 for PTX3 against a null AUC of 0.70, a two-sided α of 0.05 and power of 0.90, a minimum of 48 children per infection group was required; the enrolled sample of 60 bacterial and 55 viral cases exceeded this target and allowed a comparison of correlated ROC curves.

2.5 Statistical Analysis

Analyses were performed with IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro–Wilk test; because PTX3, CRP and leucocyte counts were non-normally distributed, they are reported as median and interquartile range (IQR). The three groups were compared with the Kruskal–Wallis test, followed by pairwise Mann–Whitney U tests with Bonferroni correction (significance threshold $p < 0.017$); categorical variables were compared with the chi-square test. The association between PTX3 and CRP in febrile children was assessed with Spearman's rank correlation.

Diagnostic performance for bacterial versus viral infection was evaluated by receiver operating characteristic (ROC) analysis. The area under the curve (AUC) with 95% confidence interval was calculated, the optimal cut-off was identified by the Youden index, and sensitivity, specificity, positive and negative predictive values, likelihood ratios and overall accuracy were derived at that cut-off; CRP was additionally assessed at the conventional threshold of 20 mg/L. The combined performance of the two markers was examined by binary logistic regression, with the predicted probability of bacterial infection used as a composite index. Correlated ROC curves were compared with the DeLong test. All tests were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Characteristics of the study groups

The three groups were comparable in age and sex (Table 1). Peak temperature was higher in the bacterial than in the viral group (median 39.3 versus 38.9 °C, $p < 0.001$), but the interval between fever onset and sampling was similar

(2.0 versus 2.2 days, p = 0.479), so the two infection groups were sampled at an equivalent stage of illness. Total leucocyte and absolute neutrophil counts were markedly higher in bacterial infection than in viral infection or health (p < 0.001).

Table 1: Baseline characteristics of the study groups

Variable	Bacterial (n = 60)	Viral (n = 55)	Healthy (n = 30)	p value
Age, months	33 (17–46)	25 (18–44)	30 (16–45)	0.615
Male, n (%)	31 (51.7)	27 (49.1)	15 (50.0)	0.962
Peak temperature, °C	39.3 (39.0–39.6)	38.9 (38.5–39.2)	36.7 (36.6–37.0)	< 0.001 [a]
Fever duration before sampling, days	2.0 (1.5–2.5)	2.2 (1.7–2.7)	—	0.479 [b]
White blood cells, ×10⁹/L	15.4 (13.1–20.0)	8.9 (7.5–10.5)	7.7 (6.6–9.0)	< 0.001
Absolute neutrophil count, ×10⁹/L	11.3 (9.5–14.4)	4.7 (3.7–5.5)	3.3 (3.0–3.9)	< 0.001

Data are median (interquartile range) unless stated. p values from Kruskal–Wallis or chi-square test. [a] Bacterial versus viral p < 0.001. [b] Mann–Whitney U test, bacterial versus viral.

3.2 Final Diagnoses

Community-acquired pneumonia and urinary tract infection together accounted for more than half of the bacterial group, while viral lower respiratory tract infection, influenza and viral gastroenteritis accounted for almost three-quarters of the viral group (Table 2). Eight children (13.3%) had culture-proven bacteraemia or sepsis and four had bacterial meningitis.

Table 2: Final diagnoses in the febrile children

Bacterial infection (n = 60)	n (%)	Viral infection (n = 55)	n (%)
Community-acquired pneumonia (lobar/segmental)	18 (30.0)	Viral lower respiratory tract infection / bronchiolitis	18 (32.7)
Urinary tract infection / pyelonephritis	16 (26.7)	Influenza A or B	12 (21.8)
Bacteraemia / sepsis (culture-positive)	8 (13.3)	Viral gastroenteritis (rotavirus, norovirus, adenovirus)	10 (18.2)
Group A streptococcal pharyngotonsillitis	8 (13.3)	SARS-CoV-2 infection	6 (10.9)
Bone and joint infection	6 (10.0)	Roseola / viral exanthem	5 (9.1)
Bacterial meningitis	4 (6.7)	Aseptic (viral) meningitis	4 (7.3)

3.3 Serum PTX3 and CRP concentrations

Both markers showed a stepwise gradient from healthy children through viral to bacterial infection (Table 3). Median PTX3 was about five-fold higher in bacterial infection than in health and 2.4-fold higher than in viral infection, and every pairwise difference was significant after Bonferroni correction (p < 0.001). CRP showed a steeper gradient in absolute terms, with a median of 77.42 mg/L in bacterial infection against 16.54 mg/L in viral infection, but the viral group also differed clearly from healthy children (p < 0.001), reflecting the appreciable CRP response in several viral illnesses. The interquartile ranges of PTX3 in the bacterial (7.41–14.59 ng/mL) and viral (2.97–6.26 ng/mL) groups did not overlap, whereas those of CRP (35.18–129.37 versus 8.12–29.85 mg/L) were also separated but with a wider spread in the bacterial group. Among febrile children PTX3 and CRP were moderately correlated (Spearman ρ = 0.54, p < 0.001), indicating related but not redundant information (Figure 2).

Table 3: Serum PTX3 and CRP concentrations by group

Marker	Bacterial (n = 60)	Viral (n = 55)	Healthy (n = 30)	p (overall)	p (bacterial vs viral)	p (viral vs healthy)
PTX3, ng/mL	10.55 (7.41–14.59)	4.46 (2.97–6.26)	2.07 (1.28–2.87)	< 0.001	< 0.001	< 0.001
CRP, mg/L	77.42 (35.18–129.37)	16.54 (8.12–29.85)	1.66 (1.12–2.29)	< 0.001	< 0.001	< 0.001

Data are median (interquartile range). Overall p from Kruskal–Wallis; pairwise comparisons by Mann–Whitney U with a Bonferroni threshold of 0.017. Bacterial versus healthy $p < 0.001$ for both markers. Spearman correlation between PTX3 and CRP in febrile children $\rho = 0.54$ ($p < 0.001$).

3.4 Diagnostic Performance for Bacterial Versus Viral Infection

PTX3 yielded an AUC of 0.881 (95% CI 0.818–0.943) and CRP an AUC of 0.825 (0.746–0.905); the difference did not reach statistical significance (DeLong p = 0.222) (Table 4, Figure 1). At the Youden-optimal cut-off of 6.76 ng/mL, PTX3 identified 50 of 60 bacterial infections (sensitivity 83.3%) and correctly classified 45 of 55 viral infections (specificity 81.8%), with balanced predictive values of 83.3% and 81.8% and a negative likelihood ratio of 0.20. CRP at its optimal cut-off of 50.8 mg/L was more specific (89.1%) but detected only 42 of 60 bacterial infections (sensitivity 70.0%; negative likelihood ratio 0.34). When CRP was applied at the conventional threshold of 20 mg/L, sensitivity rose to 85.0% but 22 of 55 viral infections (40.0%) were misclassified as bacterial, so that the positive predictive value fell to 69.9% and the overall accuracy to 73.0%.

The logistic model combining both markers (predicted probability ≥ 0.42) achieved the best overall performance: AUC 0.908 (0.852–0.963), sensitivity 93.3% (56/60), specificity 80.0% (44/55), negative predictive value 91.7%, negative likelihood ratio 0.08 and accuracy 87.0%. The combined AUC was significantly larger than that of CRP alone (p = 0.014) and numerically, though not significantly, larger than that of PTX3 alone (p = 0.101). Only four bacterial infections were missed by the combined model, compared with ten by PTX3 and eighteen by CRP at their optimal cut-offs.

Table 4: Diagnostic performance of PTX3, CRP and their combination for discriminating bacterial from viral infection

Marker	AUC (95% CI)	Cut-off	Sensitivity, % (TP/n)	Specificity, % (TN/n)	PPV, %	NPV, %	LR+	LR−	Accuracy, %
PTX3	0.881 (0.818–0.943)	≥ 6.76 ng/mL	83.3 (50/60)	81.8 (45/55)	83.3	81.8	4.58	0.20	82.6
CRP	0.825 (0.746–0.905)	≥ 50.8 mg/L	70.0 (42/60)	89.1 (49/55)	87.5	73.1	6.42	0.34	79.1
CRP (conventional threshold)	—	≥ 20 mg/L	85.0 (51/60)	60.0 (33/55)	69.9	78.6	2.12	0.25	73.0
PTX3 + CRP (logistic model)	0.908 (0.852–0.963)	probability ≥ 0.42	93.3 (56/60)	80.0 (44/55)	83.6	91.7	4.67	0.08	87.0

AUC comparisons (DeLong): PTX3 versus CRP p = 0.222; combination versus CRP p = 0.014; combination versus PTX3 p = 0.101. TP, true positive; TN, true negative; PPV/NPV, positive/negative predictive value; LR, likelihood ratio. Cut-offs were derived from the study sample by the Youden index.

4. Discussion

In this prospective study of 115 febrile children with adjudicated bacterial or viral infection and 30 healthy controls, serum PTX3 discriminated bacterial from viral illness with an AUC of 0.881, numerically higher than that of CRP (0.825) and with a more balanced sensitivity–specificity profile at its optimal cut-off. The two markers were only moderately correlated, and combining them produced a model with an AUC of 0.908, a sensitivity of 93.3% and a negative predictive value of 91.7%, significantly better than CRP alone. To our knowledge this is the first head-to-head comparison of serum PTX3 and CRP across the full spectrum of bacterial and viral foci seen in a general paediatric emergency population, and the first from Iraq.

4.1 Comparison with Previous Studies

Our PTX3 concentrations are consistent with the paediatric literature. The median of 10.55 ng/mL in bacterial infection and the cut-off of 6.76 ng/mL sit close to the 8.84 ng/mL threshold that separated children with lower respiratory tract infection from controls in an Egyptian cohort (sensitivity 93.3%, specificity 70%, AUC 0.907) [18] and to the 7.94 ng/mL threshold that identified community-acquired pneumonia in a second Egyptian study, in which PTX3 outperformed both CRP and procalcitonin [22]. The healthy-control median of 2.07 ng/mL is in line with the 2.6 ng/mL reported in adult emergency patients without bacterial infection or systemic inflammation [14]. In a paediatric intensive care cohort in China, the AUC of PTX3 for sepsis exceeded those of CRP, procalcitonin and leucocyte indices [23], and in Turkish children with sepsis or septic shock PTX3 was significantly elevated at admission [24]; more recently, PTX3 achieved an AUC of 0.872 for sepsis and tracked clinical severity whereas CRP

did not [17]. These sepsis studies compared infected with uninfected children; our data extend the finding to the clinically more demanding bacterial-versus-viral contrast, where PTX3 retained an AUC close to 0.9.

The behaviour of PTX3 in viral infection deserves comment. We observed an intermediate elevation in the viral group (median 4.46 ng/mL) that was significantly above healthy values, so PTX3 is not a bacterial-specific marker in the strict sense. This agrees with reports that PTX3 rises in children with viral lower respiratory tract infection in proportion to severity [19,25], that it is part of a plasma-marker rule predicting severe viral bronchiolitis [25], and that it is associated with disease severity in adults with hantavirus haemorrhagic fever [26]. Conversely, in 103 Turkish children with PCR-confirmed SARS-CoV-2 infection, most of them mild, PTX3 did not differ significantly from controls even though CRP did [27], which illustrates that the PTX3 response to uncomplicated viral illness is modest. The clinically useful property is therefore quantitative: the magnitude of the rise in invasive bacterial disease is substantially larger than in viral disease, and the interquartile ranges of the two groups in our cohort did not overlap.
The CRP results reproduce a well-known limitation. At the conventional threshold of 20 mg/L CRP was sensitive (85%) but misclassified 40% of viral infections, almost exactly the 87% sensitivity and 59% specificity found in more than 17,000 European febrile children [8], and consistent with pooled estimates for fever without source [7]. Raising the cut-off to 50.8 mg/L restored specificity to 89% but sacrificed sensitivity (70%). Influenza, adenovirus and SARS-CoV-2 are recognised causes of high CRP in children; in adenoviral pharyngitis, for example, mean CRP exceeded 70 mg/L and peaked on the third day of fever [28]. In our viral group, which included influenza, adenovirus gastroenteritis and SARS-CoV-2, the CRP interquartile range extended to almost 30 mg/L. The comparatively modest AUCs of CRP and leucocyte count for bacterial respiratory infection in a large Chinese cohort (0.55 and 0.58) make the same point [29].

4.2 Mechanistic Interpretation

The complementary behaviour of the two pentraxins follows from their different biology. CRP is a hepatocyte product whose synthesis depends on interleukin-6 reaching the liver; its concentration begins to rise 6–12 hours after the inflammatory stimulus and peaks after about 48 hours [5,6]. Its magnitude is a function of the systemic cytokine load rather than of the pathogen, which explains both its delayed sensitivity in children sampled early and its elevation in cytokine-rich viral infections. PTX3, in contrast, is synthesised at the site of infection by macrophages, dendritic cells, endothelial cells and fibroblasts in response to Toll-like receptor agonists, interleukin-1β and tumour necrosis factor-α, but not to interleukin-6 [9]. It is also stored preformed in the specific granules of mature neutrophils and released within minutes of microbial recognition, partly localising to neutrophil extracellular traps [10]. Bacterial infections provoke intense neutrophil recruitment and degranulation, and in our bacterial group the absolute neutrophil count was more than twice that of the viral group (Table 1); the neutrophil reservoir of PTX3 therefore offers a direct mechanistic link between the bacterial pattern of inflammation and the larger PTX3 response. PTX3 binds conserved microbial structures on bacteria and fungi, activates and regulates the complement cascade and acts as an opsonin, so its release is functionally coupled to the clearance of bacterial pathogens [9]. These properties are the basis of the early kinetics described in adults, in whom PTX3 peaks within the first 24 hours of sepsis while CRP is still rising [11,12], and they explain why in newborns with infection PTX3 was already different between infected and healthy infants at a time when CRP at 12 hours of life was not [30]. In our cohort the two infection groups were sampled at the same median interval from fever onset (about two days), which removes timing as an explanation for the difference between the markers and suggests that PTX3 carries pathogen-related information rather than simply earlier information.

The moderate correlation between PTX3 and CRP ($\rho = 0.54$) and the gain in AUC on combining them indicate that each captures a partly independent dimension of the host response, a local, neutrophil- and endothelium-driven component for PTX3 and a systemic hepatic component for CRP. A similar logic underlies the host-protein signatures now in clinical evaluation, which combine a bacterially induced protein (CRP) with virally induced proteins (TRAIL, IP-10) and achieve AUCs of 0.9 or higher in febrile children [31,32], although such multi-analyte panels have not consistently met predefined targets in the youngest infants [33,34] and their performance is reduced in children already on antibiotics [35]. A two-marker combination of PTX3 and CRP, both measurable on widely available immunoassay platforms, may offer a pragmatic alternative in settings where proprietary host-response assays are not accessible.

4.3 Clinical Implications

The most useful operating characteristic of the combined model is its negative likelihood ratio of 0.08: a child with a low combined probability has a post-test probability of bacterial infection well below 10% even in a population with

a 50% pre-test probability. In a real emergency population, where bacterial infection accounts for roughly 10–25% of febrile presentations [8,32], the negative predictive value would be correspondingly higher. Such a rule-out property is exactly what is needed to withhold or stop antibiotics safely, the decision in which diagnostic uncertainty most strongly drives overuse [3]. PTX3 alone, with a negative likelihood ratio of 0.20, is already more reassuring than CRP at its optimal cut-off (0.34), and unlike the 20 mg/L CRP threshold it reaches that sensitivity without halving specificity. These properties argue for prospective evaluation of a PTX3-plus-CRP pathway against clinical outcomes, including antibiotic prescription rates, in paediatric emergency care.

4.4 Strengths and Limitations

Strengths of the study include its prospective design, the use of pre-antibiotic samples, adjudication of the final diagnosis by two paediatricians blinded to PTX3, confirmation of bacterial infection by culture or rapid antigen testing in the majority of cases, a viral comparator group rather than only healthy controls, a wide range of infection foci reflecting routine practice, and comparable fever duration in the two infection groups. Several limitations must be acknowledged. First, this was a single-centre study in a tertiary hospital, and the case-control design with a 1:1 bacterial-to-viral ratio does not reproduce the lower bacterial prevalence of an unselected febrile population; positive predictive values in particular will be lower in practice, although sensitivity, specificity and likelihood ratios are transferable. Second, the cut-offs for PTX3, CRP and the combined model were derived from the same sample by the Youden index and were not validated in an independent cohort, so the reported accuracy is likely optimistic, and the combined model in particular requires external validation. Third, children with mixed or undetermined aetiology, who form a substantial proportion of real-world presentations, were excluded; performance in this group is unknown. Fourth, procalcitonin was not measured, so we cannot position PTX3 relative to the other marker in common use. Fifth, PTX3 is not specific to infection: it rises in acute appendicitis [36], after myocardial injury and in other non-infectious inflammatory states [37], and serial measurements, which might add information on treatment response as shown in adult pneumonia [38], were not obtained. Sixth, the viral group was heterogeneous and the number of children with any single virus was small, which precludes virus-specific conclusions. Finally, PTX3 was measured by ELISA on stored samples; a rapid point-of-care assay would be required before the marker could influence decisions in real time.

5. Conclusion

In febrile children attending a tertiary paediatric hospital in Baghdad, serum PTX3 separated bacterial from viral infection with an AUC of 0.88, equalling or exceeding CRP and offering a better balance of sensitivity and specificity at a single cut-off of 6.76 ng/mL. Because PTX3 is released locally and rapidly by neutrophils and tissue cells whereas CRP depends on delayed hepatic synthesis, the two markers reflect partly independent components of the host response, and their combination achieved an AUC of 0.91 with a negative likelihood ratio of 0.08. PTX3, alone or alongside CRP, is a promising adjunct for the early identification of children who can safely be managed without antibiotics; external validation in an unselected febrile population and development of a rapid assay are the necessary next steps.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Conflicts of interest: The author declares no conflict of interest.
Ethical approval: The study was approved by the institutional ethics committee of the Central Teaching Hospital of Pediatrics, Baghdad, on 1 November 2024, and written informed consent was obtained from the parents or legal guardians of all participants.

Figure legends

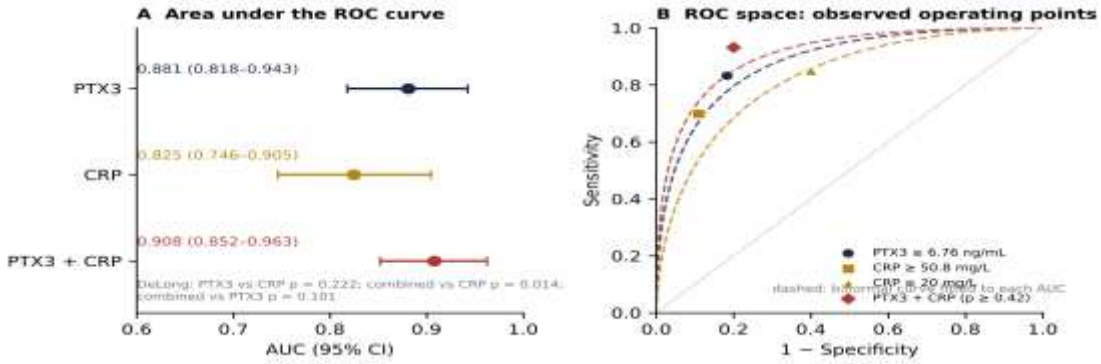


Figure 1. *Diagnostic performance of serum PTX3, CRP and their logistic combination for discriminating bacterial from viral infection in febrile children (n = 115). (A) Area under the ROC curve with 95% confidence interval for each marker; p values are from the DeLong test for correlated ROC curves. (B) Observed operating points at the Youden-optimal cut-offs (PTX3 ≥ 6.76 ng/mL, CRP ≥ 50.8 mg/L, combined probability ≥ 0.42) and at the conventional CRP threshold of 20 mg/L, plotted in ROC space; dashed lines are binormal ROC curves fitted to each reported AUC and are shown for orientation only.*

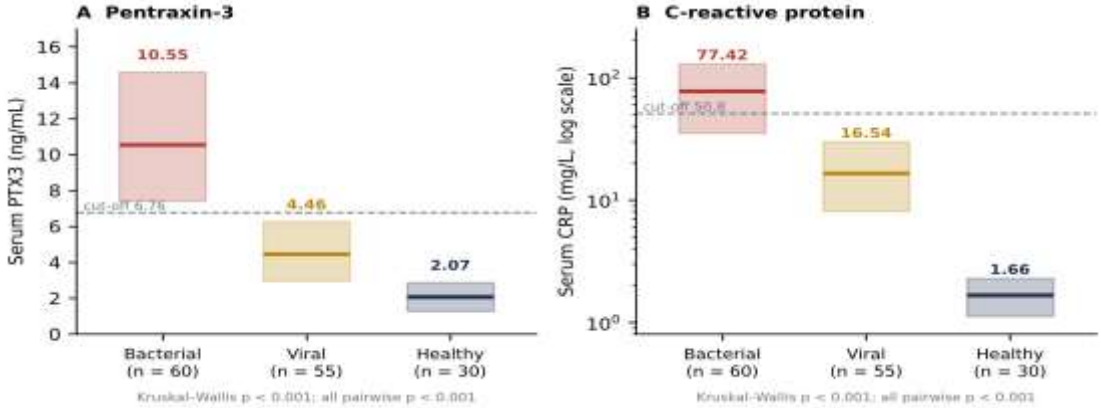


Figure 2. *Serum concentrations of (A) pentraxin-3 and (B) C-reactive protein (logarithmic scale) in children with bacterial infection (n = 60), viral infection (n = 55) and healthy controls (n = 30). Boxes show the interquartile range and the heavy line the median; the dashed line marks the Youden-optimal cut-off for bacterial versus viral infection. Kruskal–Wallis p < 0.001 for both markers; all pairwise Mann–Whitney comparisons p < 0.001 (Bonferroni threshold 0.017).*

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