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Serum Presepsin (Soluble Cd14-St) Levels in Patients with Systemic Inflammatory Response Syndrome and Sepsis: A Comparison with The Sepsis-3 Reclassification

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Abstract

Background: Pediatric sepsis and systemic inflammatory response syndrome are clinical entities associated with high morbidity and mortality, for which early diagnosis and risk stratification are difficult. This study aimed to investigate the diagnostic value of presepsin, procalcitonin, C-reactive protein and leukocyte count in pediatric systemic inflammatory response syndrome and sepsis.

Methods: This prospective study initially enrolled 21 systemic inflammatory response syndrome (SIRS) patients, 25 sepsis patients and 40 healthy controls aged 1 month–18 years in 2015, classified according to the 2001 International Sepsis Definitions Conference criteria. To address current methodological standards, all patient-group subjects were subsequently reclassified according to the Sepsis-3 consensus definitions; 34 patients met Sepsis-3 criteria and 40 healthy controls were retained. Systemic inflammatory response syndrome and sepsis were defined according to the criteria of the 2001 International Sepsis Definitions Conference.

Results: Leukocyte, C-reactive protein, procalcitonin and presepsin levels were significantly higher in both the systemic inflammatory response syndrome and sepsis groups than in controls (all $p<0.001$). Under the Sepsis-3 reclassification (sepsis, n=34 vs. controls, n=40), all four biomarkers remained significantly elevated in the sepsis group (all $p<0.001$), with presepsin and procalcitonin achieving the highest diagnostic performance (AUC 0.976 each). In distinguishing patient groups from controls, procalcitonin and presepsin showed high sensitivity and specificity with strong diagnostic performance. However, diagnostic power was more limited for differentiating systemic inflammatory response syndrome from sepsis under the 2001 criteria.

Conclusions: In pediatric systemic inflammatory response syndrome and sepsis, leukocyte count, C-reactive protein, procalcitonin and presepsin are sensitive indicators of systemic inflammatory response. Procalcitonin and presepsin are strong markers for distinguishing patient groups from healthy controls under both the 2001 SCCM criteria and the Sepsis-3 reclassification; however, because the performance of individual biomarkers in differentiating systemic inflammatory response syndrome from sepsis is limited, multimarker diagnostic algorithms are needed.

Keywords: C-reactive protein, Procalcitonin, Sepsis, SIRS, soluble CD14-ST.

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Sistemik İnflamatuvar Yanıt Sendromu ve Sepsisli Hastalarda Serum Presepsin (Soluble Cd14-St) Düzeyleri: Sepsis-3 Yeniden Sınıflandırması ile Karşılaştırma

Öz

Giriş: Pediatrik sepsis ve sistemik inflamatuar yanıt sendromu, yüksek morbidite ve mortalite ile ilişkili klinik tablolardır ve bu durumlarda erken tanı ve risk sınıflandırması zordur. Bu çalışmanın amacı, pediatrik sistemik inflamatuar yanıt sendromu ve sepsiste presepsin, prokalcitonin, C-reaktif protein ve lökosit sayısının tanısal değerini araştırmaktı.

Yöntemler: Bu prospektif çalışmaya, 2015 yılında, 2001 Uluslararası Sepsis Tanımları Konferansı kriterlerine göre sınıflandırılmış, 1 ay–18 yaş arası 21 sistemik inflamatuar yanıt sendromu (SIRS) hastası, 25 sepsis hastası ve 40 sağlıklı kontrol ilk olarak dahil edilmiştir. Mevcut metodolojik standartlara uymak amacıyla, tüm hasta grubu denekleri daha sonra Sepsis-3 konsensüs tanımlarına göre yeniden sınıflandırılmıştır; 34 hasta Sepsis-3 kriterlerini karşılamış ve 40 sağlıklı kontrol deneği çalışmada tutulmuştur. Sistemik inflamatuar yanıt sendromu ve sepsis, 2001 Uluslararası Sepsis Tanımları Konferansı kriterlerine göre tanımlanmıştır.

Bulgular: Lökosit, C-reaktif protein, prokalcitonin ve presepsin düzeyleri, hem sistemik inflamatuar yanıt sendromu hem de sepsis gruplarında kontrol grubuna göre anlamlı olarak daha yüksekti (tümü p<0,001). Sepsis-3 yeniden sınıflandırmasına göre (sepsis, n=34 vs. kontrol grubu, n=40), dört biyobelirteç de sepsis grubunda anlamlı olarak yüksek kaldı (tümü p<0,001); presepsin ve prokalcitonin en yüksek tanısal performansa ulaştı (her biri için AUC 0,976). Hasta gruplarını kontrol grubundan ayırt etmede, prokalcitonin ve presepsin, güçlü tanısal performansla yüksek duyarlılık ve özgüllük göstermiştir. Ancak, 2001 kriterleri altında sistemik inflamatuar yanıt sendromunu sepsisten ayırt etmede tanısal güç daha sınırlıydı.

Sonuç: Pediatrik sistemik inflamatuar yanıt sendromu ve sepsiste, lökosit sayısı, C-reaktif protein, prokalcitonin ve presepsin, sistemik inflamatuar yanıtın duyarlı göstergeleridir. Prokalsitonin ve presepsin, hem 2001 SCCM kriterleri hem de Sepsis-3 yeniden sınıflandırması kapsamında hasta gruplarını sağlıklı kontrol grubundan ayırt etmek için güçlü belirteçlerdir; ancak, sistemik inflamatuar yanıt sendromunu sepsisten ayırt etmede tek tek biyobelirteçlerin performansı sınırlı olduğundan, çoklu belirteçli tanısal algoritmalara ihtiyaç vardır.

Anahtar kelimeler: C-reaktif protein, Prokalsitonin, Sepsis, SIRS, soluble CD14-ST.

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) represents a stereotyped, non-specific host response that may be triggered by infectious stimuli as well as by noninfectious conditions including burns, pancreatitis, trauma, and certain rheumatologic disorders, and is identified through a characteristic cluster of clinical and laboratory abnormalities. When SIRS occurs in the context of documented or suspected infection, it is classified as sepsis—a life-threatening condition that carries a substantial burden of morbidity and death in children if not promptly identified and managed. A key clinical obstacle is that the signs and laboratory features of sepsis closely overlap with those of noninfectious SIRS, rendering the distinction between sepsis and noninfectious causes of SIRS genuinely challenging in everyday practice[1,2].

Standard inflammatory markers used in daily paediatric practice—fever, white blood cell count, erythrocyte sedimentation rate, and C reactive protein (CRP)—each carry notable limitations in specificity. CRP, in particular, is a non-specific acute-phase reactant that rises across a broad range of infectious and noninfectious conditions alike, including viral illness, autoimmune disease, and trauma[3]. Procalcitonin (PCT), a hormone precursor released in response to bacterial endotoxins, has been recognized as a more infection-specific parameter; circulating PCT concentrations rise substantially during bacterial sepsis and invasive infection, while typically remaining near-normal in viral illness and many noninfectious inflammatory conditions[4,5]. Despite these properties, substantial inter-study heterogeneity in optimal threshold values across varying age

groups and clinical contexts has undermined the consistent diagnostic utility of PCT; the relevant cut off values remain poorly standardised[3,6]. This gap has driven ongoing efforts to identify supplementary biomarkers that can facilitate earlier detection of SIRS and sepsis while ideally enabling their clinical differentiation.

Presepsin (soluble CD14-ST), a monocyte/macrophage derived fragment of the CD14 receptor released during phagocyte activation, has attracted growing attention as a candidate sepsis biomarker. Described initially in 2005, circulating presepsin concentrations have been shown to rise substantially in bacterial infections and sepsis, reflecting the magnitude of the innate immune response at the molecular level[1,7,8]. Adult studies indicate that presepsin may differentiate sepsis from healthy or noninfectious conditions with discriminatory capacity at least comparable to, or exceeding, that of CRP and PCT[7]. Investigations in neonatal and paediatric cohorts similarly points to presepsin as a potentially valuable early-sepsis indicator, with some series reporting greater sensitivity and diagnostic accuracy compared with CRP and PCT[9-11]. Nevertheless, variability across age groups, clinical contexts, and proposed threshold values means that cautious, context specific interpretation is required and that routine integration remains problematic[12,13].

Given the persistent diagnostic difficulties posed by sepsis and its associated burden of morbidity and death, current evidence increasingly favours multimarker panel approaches over dependence on any single "ideal" biomarker. Combined models incorporating presepsin, PCT, and CRP have yielded superior accuracy over individual markers in several studies[2,13].

The present study was designed to examine presepsin concentrations in paediatric patients presenting with SIRS or sepsis, with or without a definable infectious source, and to evaluate its diagnostic utility—relative to leukocyte count, CRP, and PCT—in this context. Three specific objectives were pursued: to compare the four biomarkers across children with SIRS, sepsis, and healthy controls; to determine how well each marker distinguishes patient groups from controls and from each other; and to explore whether presepsin has a practicable role in the clinical workup of childhood SIRS and sepsis.

METHODS

The study was carried out prospectively at the Department of Paediatrics, Kahramanmaraş University Faculty of Medicine, over the period from 1 January to 15 December 2015. Ethical approval was obtained from the the local ethics committee on 09 March 2015 (decision no: 2015/04-07). The study was additionally supported by the Kahramanmaraş University Scientific Research Projects Coordination Unit (project no: 2015/1 82D). Written informed consent was secured from parents or legal guardians prior to any study procedure; children without such consent were not enrolled.

The study enrolled children who presented to the paediatric outpatient clinic or were admitted to the ward and fulfilled the diagnostic criteria for SIRS and/or sepsis during the study period. Those managed in the emergency observation area without formal ward admission were also considered eligible if they completed all required study procedures. A total of 86 subjects were initially enrolled: 21 (24.4%) in the SIRS group, 25 (29.1%) in the sepsis group and 40 (46.5%) in the control group. Group assignment followed the 2001 International Sepsis Definitions Conference criteria[1]. Children who met SIRS criteria but had negative blood cultures with only clinically suspected infection were placed in the SIRS group, whereas those with SIRS plus a confirmed or clinically probable infectious focus—regardless of culture result—were

assigned to the sepsis group. All 46 patients were subsequently re-evaluated against the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[14]. Of these, 34 satisfied Sepsis-3 requirements and constituted the Sepsis-3 group; the remaining 12 were excluded owing to insufficient data or failure to reach the organ-dysfunction threshold. The control group (n=40) was unchanged in both analytical phases. Patient-group inclusion required: age between 1 month and 18 years, fulfilment of SIRS criteria, absence of alternative SIRS triggers (burns, trauma, rheumatologic disease), and no prior history of immunodeficiency, chronic illness, or antibiotic exposure. Control participants had to fall within the same age range, show no SIRS criteria, and be free of chronic disease.

Comprehensive demographic and clinical information were gathered for all participants through a standardized data collection form, capturing age, sex, anthropometric measurements, admission and discharge dates, medical history, physical examination findings, and clinical status at enrolment. At the time of diagnosis, peripheral venous blood was drawn from all participants for full blood count, CRP, PCT, and presepsin assays. Blood cultures were collected from SIRS and sepsis patients on admission; control subjects did not undergo culture sampling. Serum destined for presepsin measurement was separated by centrifugation at 3000 rpm for 10 minutes and kept at −45°C until analysis.

Laboratory measurements were carried out in conformity with international quality standards. Serum presepsin concentrations were determined quantitatively using a Human Presepsin ELISA Kit (Abbexa Ltd, UK) on a Chemwell 2910 EIA analyser (USA). CRP was assayed by nephelometry (Siemens BN II, Germany), PCT by chemiluminescence immunoassay (Advia Centaur CP, Siemens, Germany), and complete blood counts by laser-based optical flow-cell technology (Advia 2120/2120i, Siemens, Germany).

Statistical Analysis

Data were analyzed with SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as median (minimum–maximum) and categorical variables as frequency and percentage. Because continuous variables deviated from a normal distribution (Shapiro–Wilk test), between-group comparisons were conducted with the Kruskal–Wallis test, with post hoc pairwise testing by the Mann–Whitney U test. The chi-square (χ^2) test served for categorical comparisons, and Spearman rank correlation examined associations among continuous variables. Biomarker discriminatory performance (leukocyte count, CRP, PCT, presepsin) was quantified by receiver operating characteristic (ROC) analysis, including calculation of the area under the curve (AUC) and the optimal cut-off value; a two-tailed p value of less than 0.05 defined statistical significance.

RESULTS

The study enrolled 86 participants, of whom 46 were patients attending the paediatric outpatient clinic or admitted to the ward, and 40 were healthy volunteers satisfying the control inclusion criteria. Patient-group participants were divided into SIRS and sepsis subgroups; the majority of sepsis cases had localised bacterial infections, and disseminated findings were present in only four children. Three comparison groups were therefore constituted: SIRS, sepsis, and control.

Half of all participants (43/86; 50%) were male, and the overall median age was 69.5 (range 1–192) months. Sex distribution and age did not differ significantly across groups (p=0.202 and p=0.071, respectively; Table 1).

Blood cultures were negative in all SIRS patients (21/21). Among sepsis patients, 11 (44%) yielded positive cultures; the predominant organism was Escherichia coli (E. coli) (7/11, 63.6%), followed by Streptococcus pneumoniae (S. pneumoniae) (2/11, 18.2%), Klebsiella pneumoniae (K. pneumoniae) (1/11, 9.1%) and Staphylococcus aureus (S. aureus) (1/11, 9.1%) (Table 1).

Table I: Comparison of Demographic, Laboratory, and Culture Results Among SIRS, Sepsis, and Control Groups

Parameter	SIRS n (%), n=21	Sepsis n (%), n=25	Control n (%), n=40	SIRS vs Control p value	Sepsis vs Control p value	SIRS vs Sepsis p value	All groups p value
Age (months)£	69.1 (6-177)	49.7 (2-172)	82.1 (1-192)	0.459	0.459	0.176	0.071
Sex *Girls* *Boys*	8 (9.3) 13 (15.1)	16 (18.6) 9 (10.5)	19 (22.1) 21 (24.4)	0.482	0.194	0.080	0.202
Leukocyte count (K/uL) £	21260 (2220–34720)	20010 (5980–33250)	8630 (4700–14670)	**<0.001**	**<0.001**	0.894	**<0.001**
CRP (mg/L) £	39.50 (3–151)	109 (3–387)	3 (3–17)	**0.007**	**<0.001**	**0.002**	**<0.001**
PCT (ng/mL) £	0.33 (0.06–50.1)	4.92 (0.01–75)	0.01 (0.01–0.24)	**<0.001**	**<0.001**	**0.011**	**<0.001**
Presepsin (pg/mL) £	401.1 (143–730)	466 (146–935)	122.75 (1–495.5)	**<0.001**	**<0.001**	0.187	**<0.001**
Culture Results *Culture negative* *Culture positive*	21 (100) 0 (0)	14 (56.0) 11 (44.0)	NA	NA	NA	<0.001	NA
Microorganisms grown in culture *E. coli* *S. pneumoniae* *K. pneumoniae* *S. aureus*	NA	7 (28.0) 1 (4.0) 1 (4.0) 2 (8.0)	NA	NA	NA	NA	NA

CRP: C-reactive protein, NA: not applicable, PCT: procalcitonin, SIRS: systemic inflammatory response syndrome.

Post-hoc pairwise comparisons were performed using the Mann-Whitney U test.

Notes: £Numeric variables are presented as median (minimum–maximum). Bold p values indicate statistical significance (p<0.05).

White cell counts were comparable between SIRS and sepsis yet substantially exceeded control values (p<0.001). CRP was elevated in both patient groups and was highest in the sepsis group (p<0.001). PCT was significantly raised in both groups relative to controls (p<0.001 for each), reaching its peak in the sepsis group. Presepsin was similarly elevated in both patient groups compared with controls and tended to be highest in sepsis (p<0.001; Table 1). Collectively, these data show that all four biomarkers robustly discriminate patient groups from healthy controls.

All four biomarkers differed significantly between patient groups and controls (all p<0.05). In the head-to-head SIRS–sepsis comparison, only CRP and PCT were significantly higher in the sepsis group; differences in leukocyte count and presepsin did not reach significance (Table 1). As shown in Figure 1, values for every marker followed an ascending gradient from controls through SIRS to sepsis.

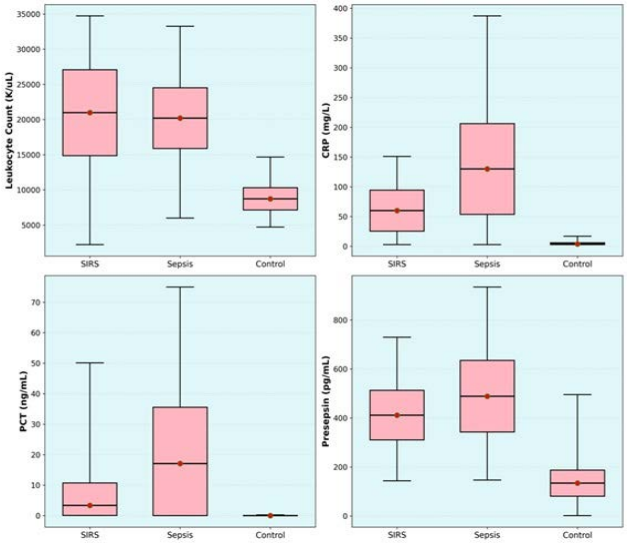

Figure 1. Group-wise Distributions of Leukocyte Count, CRP, PCT, and Presepsin

Pairwise Spearman correlations were computed to explore biomarker interrelationships. The most notable association was between presepsin and leukocyte count (R^2=0.251, p<0.001), with presepsin accounting for approximately one quarter of the variance in leukocyte count—a moderate relationship highlighting that each marker carries complementary rather than redundant information (Figure 2).

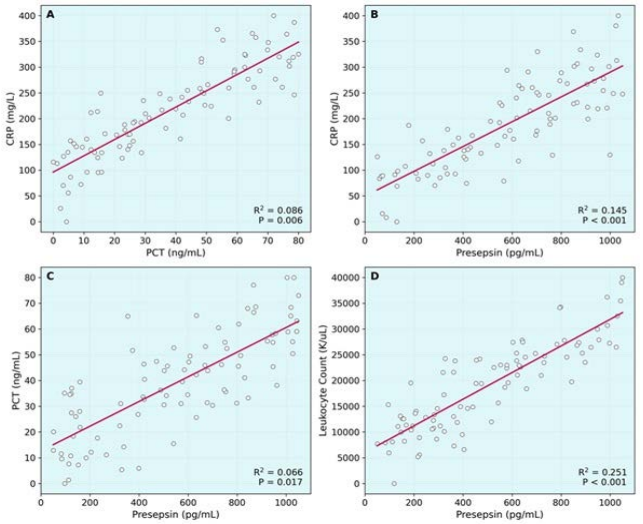

Figure 2. Scatter plots with linear regression showing pairwise correlations between inflammatory markers. Panels depict (A) PCT vs CRP, (B) Presepsin vs CRP, (C) Presepsin vs PCT, and (D) Presepsin vs Leukocyte count. R^2 statistics and corresponding P-values are indicated within each subplot.

The discriminatory metrics for each biomarker are detailed in Table 2. Overall AUC values were consistently elevated. PCT and presepsin demonstrated the greatest accuracy, combining high sensitivity and specificity with favourable likelihood ratios. Leukocyte count and CRP contributed meaningfully but achieved lower overall discriminatory capacity than PCT and presepsin.

Table II: Diagnostic performance of leukocyte count, CRP, PCT, and presepsin for identifying SIRS and sepsis

Parameter	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	+LR	−LR	p
SIRS							
Leukocyte count (K/uL)	>11980	0.898 (0.792–0.961)	90.00	97.50	36.00	0.100	<0.001
CRP (mg/L)	>4	0.956 (0.868–0.991)	95.00	90.00	9.50	0.056	<0.001
PCT (ng/mL)	>0.11	0.982 (0.908–0.997)	90.00	97.50	36.00	0.100	<0.001
Presepsin (pg/mL)	>230	0.964 (0.880–0.994)	95.00	95.00	19.00	0.053	<0.001
Sepsis							
Leukocyte count (K/uL)	>11980	0.963 (0.884–0.993)	96.00	97.50	38.40	0.041	<0.001
CRP (mg/L)	>6	0.925 (0.833–0.976)	88.00	92.50	11.73	0.130	<0.001
PCT (ng/mL)	>0.11	0.969 (0.893–0.995)	96.00	97.50	38.40	0.041	<0.001
Presepsin (pg/mL)	>195	0.970 (0.894–0.996)	96.00	90.00	9.60	0.044	<0.001

AUC: area under the receiver operating characteristic curve (95% confidence interval), CRP: C-reactive protein, PCT: procalcitonin, LR: likelihood ratio, SIRS: systemic inflammatory response syndrome.

For SIRS detection, ROC curves showed markedly superior discrimination for PCT and presepsin; CRP and leukocyte count remained statistically significant but at lower AUC values (Figure 3A). For sepsis diagnosis, the same hierarchy was observed: presepsin and PCT led, with CRP and leukocyte count playing a supportive but secondary role (Figure 3B).

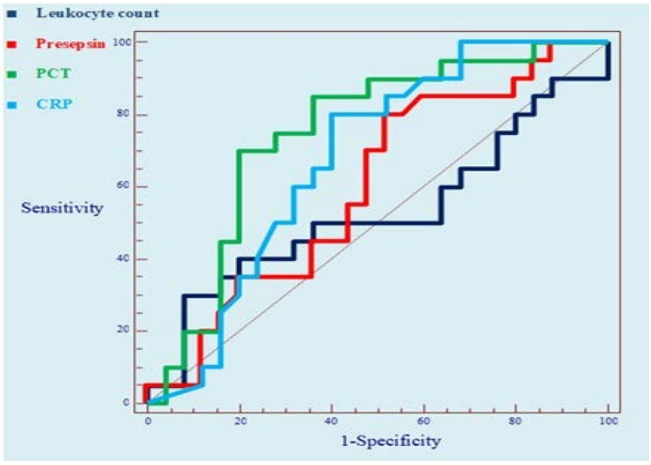

Figure 3. (A) ROC curves of Leukocyte count, CRP, PCT, and Presepsin for detecting SIRS, (B) ROC curves of Leukocyte count, CRP, PCT, and Presepsin for detecting Sepsis.

Biomarker performance for separating SIRS from sepsis was substantially more limited. PCT achieved the highest, though still modest, discriminatory capacity; CRP showed only intermediate performance; and leukocyte count and presepsin did not reach statistical significance (Table 3). The corresponding ROC curves in Figure 4 are consistent with this pattern.

Table III: Area Under the Curve (AUC) and cut-off values for leukocyte count, CRP, PCT and presepsin in distinguishing SIRS from sepsis

Parameter	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	+LR	−LR	p
Leukocyte count (K/uL)	>28600	0.528(0.374-0.678)	30.00	92.00	3.75	0.76	0.7492
CRP (mg/L)	>100	0.677(0.521-0.808)	76.19	60.00	2.52	0.53	0.0264
PCT (ng/mL)	>0.67	0.750(0.599-0.867)	70.00	80.00	3.50	0.38	0.0005
Presepsin (pg/mL)	>526	0.596(0.439-0.739)	80.00	48.00	1.54	0.42	0.2587

CRP: C-reactive protein; PCT: procalcitonin.

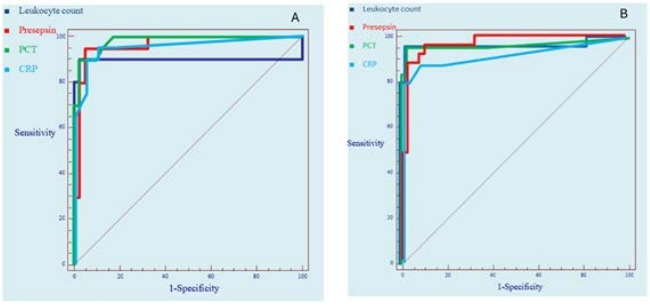

Figure 4. ROC curves of leukocyte count, CRP, PCT, and presepsin for distinguishing SIRS from sepsis.

Sepsis-3 Reclassification Analysis Given the limitations of the 2001 SCCM classification, a secondary analysis was performed in which all 46 patients were re-evaluated against Sepsis-3 definitions. Thirty-four patients satisfied the organ-dysfunction threshold and were included in this analysis; 12 were excluded for insufficient data or sub-threshold organ dysfunction. Controls (n=40) were carried forward unchanged, producing a secondary cohort of 74 individuals (Table 4).

Table IV: Comparison of Demographic, Laboratory, and Culture Results Between Sepsis-3 and Control Groups

Parameter	Sepsis-3 n=34	Control n=40	p value
Age (months)[£]	20 (2–172)	75 (1–192)	0.001
Sex Girls Boys	19 (55.9%) 15 (44.1%)	19 (47.5%) 21 (52.5%)	0.627
Leukocyte count (K/μL)[£]	19,355 (5,980–34,720)	8,630 (4,700–14,670)	<0.001
CRP (mg/L)[£]	97.5 (3–387)	3.0 (3–17)	<0.001
PCT (ng/mL)[£]	1.35 (0.01–75)	0.01 (0.01–0.24)	<0.001
Presepsin (pg/mL)[£]	514.5 (146.1–935)	122.8 (1–495.5)	<0.001
Blood culture Negative Positive	23 (67.6%) 11 (32.4%)	NA	NA
Microorganisms *E. coli* *S. pneumoniae* *S. aureus* *K. pneumoniae*	7 (20.6%) 2 (5.9%) 1 (2.9%) 1 (2.9%)	NA	NA

CRP: C-reactive protein; NA: not applicable; PCT: procalcitonin.
£Numeric variables are presented as median (minimum–maximum).

Male sex was recorded in 15/34 (44.1%) Sepsis-3 patients and 21/40 (52.5%) controls, a non-significant difference (p=0.627). Patients were substantially younger than controls (median 20 months, range 2–172 vs. 75 months, range 1–192; p=0.001). All four biomarkers were significantly higher in the Sepsis-3 group (all p<0.001): leukocyte count 19,355 vs. 8,630 K/μL; CRP 97.5 vs. 3.0 mg/L; PCT 1.35 vs. 0.01 ng/mL; presepsin 514.5 vs. 122.8 pg/mL. Blood culture positivity reached 32.4% (11/34) in the Sepsis-3 group; the most frequently recovered organism was Escherichia coli (7/11; 63.6%), with Streptococcus pneumoniae (2/11; 18.2%), Staphylococcus aureus (1/11; 9.1%), and Klebsiella pneumoniae (1/11; 9.1%) accounting for the remainder.

Within the Sepsis-3 cohort, ROC analysis demonstrated robust and broadly comparable discriminatory performance across all four biomarkers for separating sepsis from controls (Table 5, Figure 5). PCT and presepsin again achieved the highest AUC values (0.976 each), followed closely by leukocyte count (0.972) and CRP (0.951). Optimal cut-off values and associated performance metrics are detailed in Table 5. These results closely mirror the primary analysis findings, confirming that PCT and presepsin retain their strong discriminatory capacity under the more stringent Sepsis-3 framework.

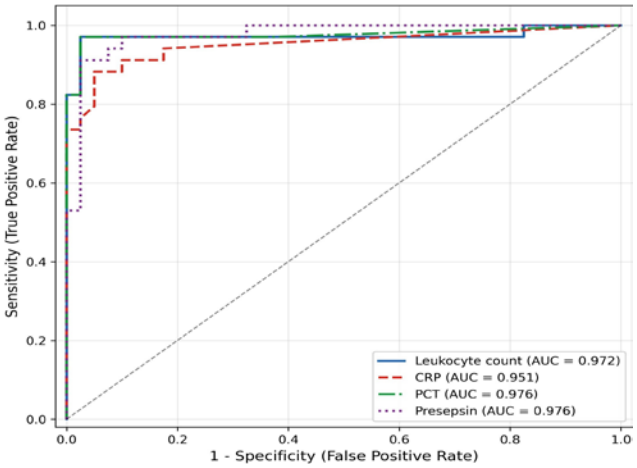

Figure 5. ROC curves of leukocyte count, CRP, PCT, and presepsin for detecting sepsis under the Sepsis-3 reclassification (Sepsis-3 group vs. controls).

Table V: Diagnostic performance of biomarkers for identifying sepsis under the Sepsis-3 reclassification (Sepsis-3 group vs. controls)

Parameter	Cutoff	AUC (95% CI)	Sens (%)	Spec (%)	+LR	-LR	p
Leukocyte count (K/μL)	>12,640	0.972 (0.895–0.996)	97.1	97.5	38.82	0.030	<0.001
CRP (mg/L)	>8	0.951 (0.866–0.989)	88.2	95.0	17.65	0.124	<0.001
PCT (ng/mL)	>0.16	0.976 (0.903–0.997)	97.1	97.5	38.82	0.030	<0.001
Presepsin (pg/mL)	>276	0.976 (0.903–0.997)	91.2	97.5	36.47	0.090	<0.001

AUC: area under the receiver operating characteristic curve (95% confidence interval); CRP: C-reactive protein; LR: likelihood ratio; PCT: procalcitonin.

DISCUSSION

Despite decades of research, sepsis and SIRS remain major drivers of morbidity and mortality in the paediatric population, and the timely establishment of an accurate diagnosis with reliable risk stratification continues to be a significant clinical challenge. The identification of laboratory parameters that can meaningfully support bedside decision-making therefore remains a research priority. In this study, we evaluated the diagnostic utility of leukocyte count, CRP, PCT, and presepsin in children presenting with SIRS or sepsis.

In our series, leukocyte count, CRP, PCT, and presepsin were each markedly elevated in both patient groups relative to healthy controls (p<0.001 for all; Table 1). As shown in Figure 1, values followed an ascending gradient from controls through SIRS to sepsis, consistent with the role of these parameters as indicators of systemic inflammatory activation in childhood. Comparable findings have been documented in

critically ill children, where PCT and presepsin concentrations rise substantially in SIRS/sepsis relative to healthy peers[10]. The particularly pronounced elevations of CRP, PCT, and presepsin in the sepsis group suggest that these markers capture both the severity of systemic inflammation and the degree of infectious burden.

Leukocyte counts were comparable between the SIRS and sepsis groups yet substantially exceeded control values, consistent with the view that total white cell count reflects inflammatory activity without infection specificity. Paediatric literature confirms that leukocyte and neutrophil counts may rise in noninfectious conditions and are therefore insufficient as standalone markers to exclude sepsis when used in isolation kers to rule out sepsis[15,16]. CRP was elevated in both SIRS and sepsis but more markedly so in sepsis, in keeping with the meta-analysis by Ruan et al., which documented moderate diagnostic accuracy for CRP and lower performance relative to PCT and presepsin[8]. The substantially elevated PCT and presepsin concentrations in our patient groups versus controls are consistent with published data indicating these biomarkers outperform CRP in childhood sepsis[4,9,11]. Yoon et al.[5] showed that presepsin outperformed both CRP and PCT in terms of diagnostic accuracy in a paediatric cohort, a finding consistent with the presepsin elevations we observed across our SIRS and sepsis groups.

When SIRS and sepsis were compared directly, only CRP and PCT were significantly higher in the sepsis group, suggesting these markers more accurately capture the infectious burden superimposed on systemic inflammation. This aligns with recent literature identifying PCT as a superior predictor of sepsis and septic shock in children, where it has become a cornerstone of early risk stratification; presepsin, by contrast, showed limited additional discriminatory value between closely related inflammatory conditions[17].

Among biomarker correlations, the most notable association was between presepsin and leukocyte count (R^2=0.251; p<0.001; Figure 2), with comparatively weaker relationships observed among CRP, PCT, and presepsin. The uniformly modest R^2 values confirm that no single marker fully characterises the inflammatory response, supporting combined multimarker strategies, consistent with earlier studies reporting broadly comparable rather than clearly superior diagnostic accuracy for presepsin over CRP and PCT[1,2].

ROC analysis confirmed that PCT and presepsin are powerful discriminators of SIRS and sepsis from healthy controls, with AUC values near 1.0 and favourable likelihood ratios, while leukocyte count and CRP also reached significance at comparatively lower AUC values. The AUC data reported by Yoon et al.[5] and Khera et al.[10], who documented high AUC values for presepsin in paediatric and neonatal cohorts, lending further support to integrating these markers into structured diagnostic approaches. Collectively, these data reinforce the case for PCT and presepsin as central components of multimarker diagnostic algorithms for paediatric SIRS/sepsis, though age and context specific threshold values will require prospective multicentre validation before routine clinical adoption.

When the analysis focused on separating SIRS from sepsis, discriminatory performance was substantially more limited. PCT achieved only moderate capacity; CRP, leukocyte count, and presepsin fared even less well, and none provided reliable stand-alone differentiation of the two groups. Similar moderate to high AUC values for PCT have been reported across neonatal and paediatric settings[3,9,16]. CRP (AUC 0.68; +LR 2.0) offers limited stand-alone discriminatory value; its combination with PCT has been advocated to enhance specificity for

SIRS–sepsis differentiation in this distinction[3,12]. The modest presepsin performance in the SIRS–sepsis comparison reinforces the view that its primary strength lies in separating infected or inflamed children from healthy peers rather than resolving closely related inflammatory states.

Several clinical and methodological considerations merit discussion. Patient classification followed the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions[18]. This may limit direct comparability with more recent investigations applying alternative criteria. To address this concern, we performed a secondary analysis in which all patient-group subjects were retrospectively reclassified according to the Sepsis-3 definitions; 34 patients met Sepsis-3 criteria and were compared with the original 40 controls. All four biomarkers remained significantly elevated in the Sepsis-3 group compared with controls (all $p<0.001$), and PCT and presepsin again achieved the highest AUC values (both 0.976), confirming the robustness of the primary findings across classification systems (Table 5, Figure 5). In addition, blood culture results showed that all SIRS patients were culture-negative, whereas blood culture positivity in the primary sepsis group was 44% (11/25) and in the Sepsis-3 group was 32.4% (11/34). Negative blood cultures should not be interpreted as excluding sepsis; bacteraemia is confirmed in only a fraction of sepsis cases even under optimal conditions, so group assignment in the primary analysis was guided by the overall clinical presentation rather than microbiological findings alone. The predominance of E. coli and Gram negative organisms mirrors national and international epidemiological trends, underscoring the value of biomarker assessment as an adjunct to culture in childhood, with biomarkers playing a complementary role to culture[19-22].

From a practical clinical standpoint, the strong discriminatory performance of presepsin and PCT—confirmed under both 2001 SCCM and Sepsis-3 criteria—suggests that these markers could usefully complement standard parameters within structured paediatric triage protocols. In settings where blood culture results are unavailable for 24–48 hours following admission, a combination of presepsin, PCT, and CRP measured at presentation may help clinicians identify children at elevated risk of bacterial sepsis and guide early empirical antibiotic decisions, potentially limiting both under-treatment and unnecessary antimicrobial exposure. Prospective evaluation of these biomarkers within validated clinical decision-support tools or paediatric early warning systems is warranted.

Several limitations must be acknowledged when interpreting these findings. The sample was relatively small and drawn from a single tertiary institution, restricting generalisability to broader populations and settings. Biomarkers were measured at a single time point only, so dynamic changes across the clinical course were not captured. This is a particularly important caveat because CRP, PCT, and presepsin are known to reach peak concentrations at different intervals after infection or inflammatory stimulus onset. The absence of information on the duration of symptoms prior to sampling therefore limits the comparability of these markers and must be considered when interpreting their relative performance. A further limitation is that primary patient classification employed the 2001 SCCM/ESICM consensus criteria, which represented the applicable standard when data were collected in 2015. Although the Sepsis-3 definitions introduced in 2016 — which replaced SIRS-based criteria with SOFA score-based organ dysfunction assessment — were applied in a retrospective secondary analysis,

the post-hoc nature of this reclassification and the consequent exclusion of 12 patients with incomplete data introduce unavoidable methodological constraints. Additionally, negative blood cultures do not preclude a diagnosis of sepsis; bacteraemia is microbiologically confirmed in only a subset of sepsis cases, even under ideal conditions. Accordingly, group allocation in the primary analysis reflected the overall clinical presentation rather than culture results in isolation. The substantial age gap between Sepsis-3 patients and controls (median 20 vs. 75 months; p=0.001) warrants attention: all four biomarkers showed a significant inverse relationship with age in this cohort (Spearman r: −0.273 to −0.399; all p<0.05), implying that the younger age profile of sepsis patients may have independently inflated biomarker concentrations, and residual age-related confounding cannot be dismissed. Culture positivity rates were modest across both analyses, and confounding factors including prior antibiotic use and pre-existing comorbidities could not be fully controlled for. Prospective multicentre studies enrolling patients under Sepsis-3 criteria, collecting serial biomarker measurements anchored to symptom onset, and examining the additive utility of presepsin within composite instruments such as the paediatric Sequential Organ Failure Assessment (pSOFA) score are needed to validate and extend these findings.

CONCLUSION

This study confirms that leukocyte count, CRP, PCT, and presepsin are responsive to systemic inflammatory activation in paediatric SIRS and sepsis. PCT and presepsin offered greater incremental diagnostic value than conventional parameters for identifying diseased children relative to healthy controls, while their capacity to differentiate SIRS from sepsis remained limited. These results support a multimarker approach incorporating PCT, CRP, and presepsin, calibrated for age and context specific thresholds, over reliance on any single “ideal” biomarker. This integrated panel-based strategy based approach may represent a clinically sound and practically feasible approach for supporting clinical decision making, both in recognizing culture negative sepsis and in early risk stratification in pediatric SIRS and sepsis. From a clinical practice standpoint, these findings suggest that presepsin and PCT could be incorporated alongside CRP and leukocyte count into structured triage protocols for febrile children presenting to the emergency department, helping to prioritize patients who require empirical antibiotic treatment or intensified monitoring prior to culture result availability. Prospective multicentre studies enrolling patients under Sepsis-3 criteria, collecting serial biomarker measurements anchored to symptom onset, and examining the additive utility of presepsin within composite instruments such as the paediatric Sequential Organ Failure Assessment (pSOFA) score are needed to validate and extend these findings.

Ethics Committee Approval: The study was carried out prospectively at the Department of Paediatrics, Kahramanmaraş University Faculty of Medicine, over the period from 1 January to 15 December 2015. Ethical approval was obtained from the the local ethics committee on 09 March 2015 (decision no: 2015/04-07).

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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