Original Article

DOI: 10.4274/haseki.galenos.2025.44153
Med Bull Haseki 2025;63(5):236-244

Diagnostic Value of Hematological and Biochemical Markers in Pediatric Appendicitis: A ROC-Based Retrospective Evaluation

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Abstract

Aim: Acute appendicitis is the most common surgical emergency in children; however, its diagnosis often remains challenging due to non-specific clinical features and overlapping laboratory results with other abdominal conditions. We aimed to evaluate the diagnostic accuracy of routine hematological and biochemical markers as accessible and reliable tools to support early and precise diagnosis of pediatric appendicitis.

Methods: This retrospective study included pediatric patients aged 0-18 years who were evaluated in the pediatric surgery department between April and June 2025. Patients were divided into three groups based on clinical, radiological, and histopathological findings: histopathologically confirmed acute appendicitis (n=63), right lower quadrant pain with appendicitis excluded (n=71), and healthy controls (n=74). Laboratory parameters analyzed at admission included white blood cell, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, mean corpuscular volume, red cell distribution width, mean platelet volume (MPV), platelet count, C-reactive protein (CRP), albumin, total bilirubin, direct bilirubin, sodium, and phosphorus. Diagnostic performance was evaluated using receiver operating characteristic curve analysis and multivariable logistic regression.

Results: Multivariable logistic regression identified seven independent predictors of acute appendicitis: direct bilirubin, albumin, CRP, MPV, sodium, NLR, and total bilirubin. Among these, direct bilirubin [odds ratio (OR)=8.34, p=0.0006) and albumin (OR=0.42, p=0.0021) were the strongest independent predictors, while CRP, MPV, and sodium also remained significant (p<0.05). Although NLR and total bilirubin were included in the model, their associations did not reach statistical significance. The final seven-parameter PediACS model demonstrated excellent discriminative performance (area under the curve=0.903; 95% confidence interval: 0.86-0.94). Using the optimal cut-off value (0.214) determined by the Youden Index, the model achieved 85.7% sensitivity, 89.7% specificity, and an overall diagnostic accuracy of 87.9%.

Conclusion: The PediACS model, derived from routine laboratory parameters, reliably distinguishes acute appendicitis from non-specific abdominal pain in children. It represents a practical, reproducible, and cost-effective diagnostic tool, particularly beneficial when imaging resources are limited or radiological results are inconclusive.

Keywords: Appendicitis, child, biomarkers, serum albumins, bilirubin, C-reactive protein, logistic models, ROC curve, sensitivity and specificity, nomograms

Introduction

Acute appendicitis is one of the most frequent indications for emergency surgical intervention in children. Delayed or missed diagnoses can lead to serious complications, such as perforation, abscess formation, and peritonitis, resulting in increased morbidity and prolonged hospital stay (1,2). In pediatric patients, diagnostic accuracy is often hindered by atypical clinical manifestations, limited communication abilities, and non-specific physical findings (3,4). Therefore, prompt and accurate diagnosis is crucial to reduce complications and avoid unnecessary surgical procedures (5).

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Received: 08.08.2025 **Accepted:** 28.10.2025 **Publication Date:** 28.11.2025

Cite this article as: Buyukbese Sarsu S. Diagnostic value of hematological and biochemical markers in pediatric appendicitis: a ROC-based retrospective evaluation. Med Bull Haseki. 2025;63(5):236-244

Recent studies have explored the diagnostic value of routinely available laboratory biomarkers in pediatric appendicitis. Conventional inflammatory indicators such as white blood cell (WBC) count, C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) are widely used because they are simple, inexpensive, and accessible (6,7). Moreover, biochemical parameters including mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), albumin, bilirubin fractions, and electrolytes such as sodium and phosphorus have been proposed as complementary diagnostic tools (8-10). These easily obtainable and cost-effective markers are especially useful in clinical settings where imaging resources are limited or radiological findings remain inconclusive.

We hypothesized that combining hematological and biochemical parameters would improve diagnostic accuracy for pediatric acute appendicitis compared with the use of individual markers. Accordingly, this study aimed to evaluate the diagnostic performance of routine laboratory parameters, determine optimal cut-off values through receiver operating characteristic (ROC) analysis, and construct a multivariable predictive model—the PediACS model—based on seven readily available indicators: direct bilirubin, albumin, CRP, MPV, sodium, total bilirubin, and NLR. By integrating these parameters into a single scoring system, the PediACS model is expected to serve as a practical, reliable, and cost-effective decision-support tool that enhances diagnostic precision and contributes to improved clinical management, particularly in resource-limited settings.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Türkiye, Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (approval no.: 243/2025, date: 16.07.2025). Given the retrospective nature of the study, the requirement for informed consent was waived by the committee. All patient data were anonymized prior to analysis.

Study Design

This retrospective cross-sectional study included pediatric patients aged 0-18 years admitted to the tertiary pediatric surgery clinic between April and June 2025. Based on clinical, radiological, and histopathological findings, the patients were categorized into three groups: (1) The appendicitis group (n=63), consisting of children with acute appendicitis confirmed by surgical and histopathological examination; (2) the abdominal pain group (n=71), including children presenting with right lower quadrant pain in whom appendicitis was clinically and radiologically excluded; and (3) the healthy control group (n=74), comprising children with normal clinical and laboratory findings who presented for routine health evaluations.

The inclusion criteria included pediatric patients aged 0-18 years who presented with acute abdominal pain. Eligible participants included those with a preliminary diagnosis of acute appendicitis who underwent appendectomy and had histopathological confirmation. Patients with abdominal pain due to other conditions, such as mesenteric lymphadenitis or gastroenteritis, managed conservatively during the same period, were also included. Healthy individuals in the same age range with complete blood count results and basic biochemical test results served as the control group. Only cases with complete medical records, laboratory data, and pathology reports were included in the final analysis.

Patients older than 18 years; those with incomplete laboratory data for any of the analyzed hematological or biochemical parameters (n=6); or those without histopathological confirmation of acute appendicitis (n=3) were excluded from the study. In addition, individuals who underwent surgical procedures other than appendectomy and patients with chronic systemic diseases that could affect biomarker levels (such as malignancy, immunodeficiency, chronic liver or kidney disease, or systemic infection; n=7) were excluded. After all exclusions were applied, 208 patients with complete medical and laboratory data were included in the final analysis. Laboratory inconsistencies arising from preanalytical or postanalytical errors (n=2) were also excluded. For patients with repeated admissions for the same diagnosis, only the first admission was analyzed.

Demographic characteristics (age, sex) and laboratory results were obtained from the hospital's electronic medical database. The analyzed hematological and biochemical parameters included WBC count, neutrophils, lymphocytes, NLR, PLR, mean corpuscular volume (MCV), red cell distribution width (RDW-CV), MPV, platelet count, CRP, albumin, total bilirubin, direct bilirubin, sodium, and phosphorus. Among these parameters, NLR, CRP, albumin, MPV, sodium, and total and direct bilirubin demonstrated the strongest diagnostic potential and were incorporated into the final multivariable diagnostic model, termed PediACS.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 20.0 (MedCalc Software Ltd., Ostend, Belgium). Data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were

expressed as medians (interquartile ranges) and compared among groups using the Kruskal-Wallis test, whereas categorical variables were analyzed using the chi-square or Fisher's exact test, as appropriate. Receiver operating characteristic curve analysis was performed to evaluate the diagnostic performance of each parameter. The area under the curve (AUC) was calculated, and sensitivity, specificity, and optimal cut-off values were determined using the Youden Index. Variables showing statistical significance in ROC analysis were subsequently included in a multivariable logistic regression model to identify independent predictors of acute appendicitis. Model performance was assessed using odds ratios (ORs) with 95% confidence intervals (CIs), the Hosmer–Lemeshow goodness-of-fit test for calibration, and the AUC for discrimination.

A diagnostic scoring system, the PediACS model, was constructed from seven parameters that remained significant in the multivariable regression analysis (direct bilirubin, albumin, CRP, MPV, sodium, total bilirubin, and NLR). Each variable was assigned a weighted score according to its regression coefficient, and a nomogram was developed to facilitate individualized risk estimation. The clinical utility of the model was further evaluated using decision curve analysis (DCA). A two-tailed p-value <0.05 was considered statistically significant.

Results

Comparison of baseline laboratory parameters among the study groups revealed statistically significant differences across multiple hematological and biochemical variables (Table 1). NLR, CRP, and albumin showed the strongest statistical differences (p<0.001), whereas MPV, phosphorus, and MCV also differed significantly (p<0.05).

Receiver operating characteristic analysis identified NLR as the most accurate biomarker (AUC=0.845, sensitivity=83%, specificity=75%), followed by CRP (AUC=0.815) and albumin (AUC=0.810) (Table 2).

Multivariable logistic regression identified seven independent predictors of acute appendicitis: direct bilirubin, albumin, CRP, MPV, sodium, NLR, and total bilirubin (Table 3). Among these, direct bilirubin (OR=8.34, p=0.0006) and albumin (OR=0.42, p=0.0021) were the strongest predictors, while CRP, MPV, and sodium also remained significant (p<0.05). The PediACS model demonstrated excellent discrimination (AUC, 0.903; 95% CI, 0.86-0.94; sensitivity, 85.7%; specificity, 89.7%) (Figure 1). No significant multicollinearity was detected among the predictors (all variance inflation factors <2.5; Table 4).

A nomogram was generated to visualize the scoring structure of the PediACS model (Figure 2). Each variable contributed proportionally to the total diagnostic score according to its β coefficient, and the relative contribution of each variable is illustrated in Figure 3, where direct bilirubin and albumin accounted for the largest diagnostic weights.

Table 1. Baseline laboratory parameters showing significant differences (Kruskal–Wallis test)

Parameter	H Statistic	p-value
NLR	102.73	p<0.000001
NEU	72.55	p<0.000001
LYM	63.59	p<0.000001
PLR	59.78	p<0.000001
CRP	49.53	p<0.000001
RDW-CV	25.45	≈ 0.000003
WBC	25.09	≈ 0.000004
Phosphorus	10.16	≈ 0.0062
MCV	9.27	≈ 0.0097
MPV	8.17	0.017
Albumin	72.55	p<0.0001
PLT	6.65	0.036

Statistical tests: Kruskal-Wallis test for continuous variables, chi-square or Fisher's Exact test for categorical variables
NLR: Neutrophil-to-lymphocyte ratio, NEU: Neutrophil, LYM: Lymphocyte, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, RDW-CV: Red cell distribution width, WBC: White blood cell count, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PLT: Platelet count

Table 2. Diagnostic performance of single biomarkers (ROC analysis)

Parameter	AUC	Cut-off	Sensitivity	Specificity
NLR	0.845	2.87	0.83	0.75
CRP	0.815	5.50	0.71	0.81
NEU	0.808	7.00	0.79	0.79
PLR	0.754	134.35	0.81	0.66
Albumin	0.810	4.15	0.77	0.72
MPV	0.709	7.85	0.68	0.71
Total bilirubin	0.701	0.80	0.65	0.76

Abbreviations and tests: Table 1 plus ROC analysis for diagnostic accuracy
NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, NEU: Neutrophil, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, ROC: Receiver operating characteristic, AUC: Area under the curve

Table 3. Optimal cut-off and overall model performance (PediACS model)

Metric	Value
AUC	0.903
Optimal cut-off (Youden Index)	0.214
Sensitivity	85.7%
Specificity	89.7%
Accuracy	87.9%
F1 score	0.87

Abbreviations and tests: Same as Table 1 plus ROC and Youden Index analysis
ROC: Receiver operating characteristic, AUC: Area under the curve

Calibration analysis demonstrated strong agreement between predicted and observed probabilities (Table 5). The Hosmer-Lemeshow goodness-of-fit test (p>0.05) and the calibration curve (Figure 4) confirmed accurate probability estimation across the entire prediction range.

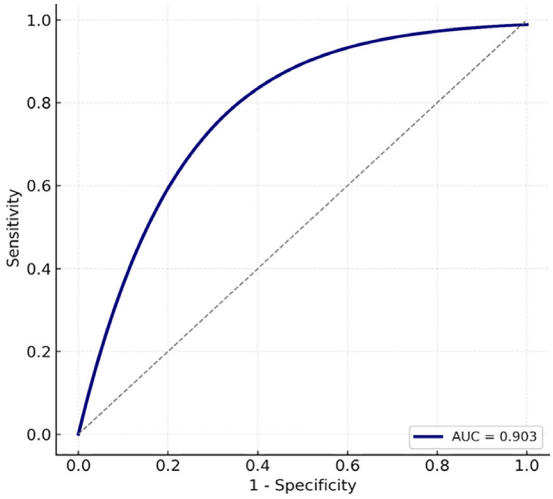

Figure 1. Receiver Operating Characteristic (ROC) Curve for the PediACS Model

The ROC curve illustrates excellent discrimination between acute appendicitis and control groups (AUC=0.903, 95% CI 0.86-0.94). The optimal cut-off determined by the Youden Index (0.214) yielded 85.7% sensitivity and 89.7% specificity. The curve confirms strong diagnostic performance of the model across all evaluated biomarkers

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

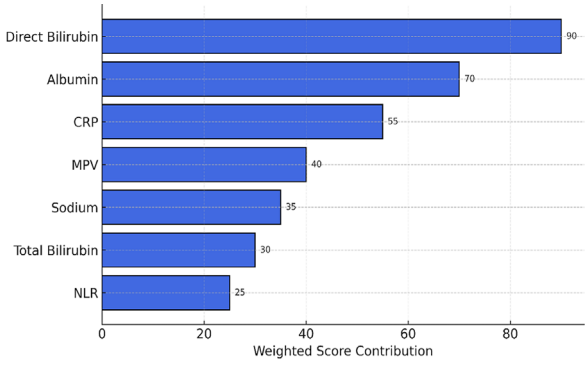

Figure 2. Nomogram-based scoring algorithm for the PediACS model (7-parameter model)

Nomogram-based scoring algorithm for the PediACS model showing the relative contribution of seven laboratory parameters to the total diagnostic score. Direct bilirubin and albumin had the highest predictive weights, followed by CRP, MPV, and sodium. The weighted points correspond to each parameter's β coefficient derived from the multivariable logistic regression model

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio

The optimal cut-off value determined by the Youden Index (0.214) yielded a sensitivity of 85.7%, a specificity of 89.7%, an overall diagnostic accuracy of 87.9%, and an F1 score of 0.87. A comparative ROC analysis indicated that the PediACS model achieved a significantly higher AUC than that of the best-performing single biomarker, NLR (ΔAUC=+0.058, p=0.031; Table 6). Decision curve analysis (Figure 5) demonstrated greater net clinical benefit across a broad range of threshold probabilities, confirming the model's clinical utility in accurately distinguishing pediatric appendicitis.

Discussion

The present study assessed the diagnostic performance and clinical applicability of the PediACS model, a seven-parameter framework that combines biochemical and inflammatory markers to improve the diagnostic accuracy for pediatric acute appendicitis. The model demonstrated excellent discrimination (AUC=0.903, 95% CI: 0.86-0.94), good calibration (Hosmer-Lemeshow p>0.05), and a clear net clinical benefit across probability thresholds from 0.2 to 0.7 in the DCA. These results indicate that the model not only performs well statistically but also has significant potential as a practical tool for supporting individualized clinical decision-making in pediatric emergency settings.

Each biomarker incorporated into the PediACS model reflects a distinct physiological mechanism underlying appendiceal inflammation. Among these, direct (conjugated) bilirubin was identified as the strongest independent predictor (OR=8.34). Its increase is most likely attributable to cytokine-mediated hepatocellular cholestasis induced by interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These pro-inflammatory cytokines impair both bile excretion and conjugation during the early stages of inflammation, thereby interfering with hepatocellular bile transport processes (11,12). In line with these observations, several previous studies have reported significantly elevated serum bilirubin levels in patients with appendicitis (13-16). Taken together, these findings support the hypothesis that hepatic metabolic alterations are closely associated with the systemic inflammatory response.

Conversely, hypoalbuminemia represents a classic negative acute-phase response, primarily resulting from cytokine-mediated suppression of hepatic protein synthesis and an increase in vascular permeability (17). In our study, reduced serum albumin levels were significantly associated with appendicitis and remained an independent inverse predictor in the multivariable analysis (OR=0.42; p=0.0021), consistent with its progressive decline under elevated inflammatory stress.

C-reactive protein is rapidly synthesized by hepatocytes in response to IL-6 and IL-1β signaling (18,19). Its plasma

Table 4. Multivariable logistic regression analysis (PediACS 7-parameter model)					
Parameter	β	**SE**	**p-value**	**OR (Exp)**	**95% CI (Lower-upper)**
Direct bilirubin	2.121	0.613	0.0006 ★	8.34	2.51-27.75
Albumin	-0.868	0.273	0.0021 ★	0.42	0.25-0.73
MPV	0.554	0.257	0.031 ★	1.74	1.05-2.87
CRP	0.030	0.012	0.0049 ★	1.03	1.01-1.06
Sodium	0.174	0.081	0.028 ★	1.19	1.02-1.40
NLR	0.174	0.133	0.181	1.19	0.92-1.55
Total bilirubin	0.385	0.348	0.269	1.47	0.74-2.89

Abbreviations and tests: As above; multivariable logistic regression used for independent predictors; Hosmer-Lemeshow test for model calibration
SE: Standard error, OR: Odds ratio, CI: Confidence interval, MPV: Mean platelet volume, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio
★ Statistically significant at the 0.05 level (p<0.05)

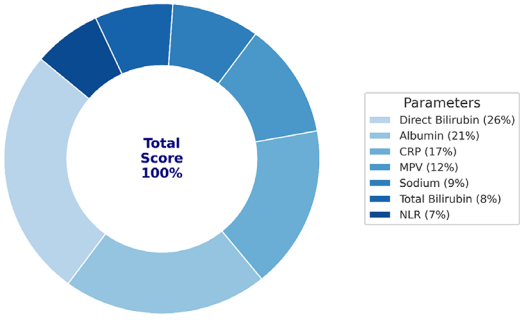

Figure 3. PediACS nomogram: score contribution distribution (7-parameter model)

Distribution of the relative contribution of seven laboratory parameters to the PediACS diagnostic model, expressed as percentage of total score. Direct bilirubin and albumin accounted for the highest proportions, followed by CRP, MPV, and sodium. The model composition demonstrates balanced weighting across inflammatory and biochemical markers

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio

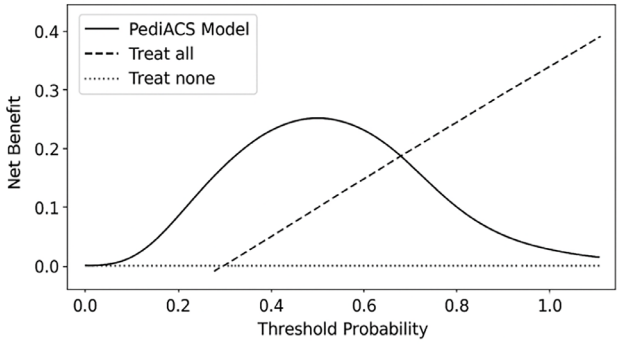

Figure 4. Calibration curve for the PediACS model

Calibration curve for the PediACS model showing strong agreement between predicted and observed probabilities of acute appendicitis. The blue line represents the model's performance, while the dashed gray line indicates perfect calibration. The model demonstrates excellent calibration with Hosmer-Lemeshow goodness-of-fit test (p>0.05)

concentration rises markedly during inflammatory conditions, thereby making CRP both a key component of the innate immune response and a clinically valuable marker for assessing the severity of systemic inflammation (20-24). The plasma CRP level shows a positive correlation with the intensity of inflammation, which explains its widespread clinical use as a non-specific but highly sensitive biomarker in various infectious and inflammatory diseases (25,26). Accordingly, the CRP-to-albumin ratio (CAR) serves as a sensitive indicator of inflammatory intensity and disease progression. As CRP levels rise and albumin concentrations decrease during inflammation, an elevated CAR value reflects a greater systemic inflammatory burden and has been associated with poorer clinical outcomes (27).

In appendicitis, hyponatremia is commonly attributed to the non-osmotic release of antidiuretic hormone (ADH, vasopressin) triggered by systemic inflammation. Circulating pro-inflammatory cytokines, including IL-6 and IL-1β, can cross the blood–brain barrier and activate the hypothalamic supraoptic and paraventricular nuclei. This cytokine-mediated stimulation leads to ADH hypersecretion, excessive renal free-water reabsorption, and ultimately dilutional or inflammation-related hyponatremia (28). In our cohort, lower sodium levels demonstrated a modest but statistically significant association with appendicitis (OR=1.19), supporting this proposed pathophysiological mechanism. Consistent with previous evidence, hyponatremia has also been suggested as a potential indicator of complicated appendicitis, and recent reports further reinforce this association (29).

Inflammatory laboratory markers—including CRP, NLR, and MPV—serve as important indicators of the systemic inflammatory response (6,7). C-reactive protein remains the primary acute-phase reactant in humans and reliably reflects the degree of inflammation.

The NLR, derived easily and inexpensively from routine differential counts, provides additional insight into subclinical inflammation. By integrating stress-related neutrophilia with relative lymphopenia, the NLR

Table 5. Model calibration and multicollinearity assessment		
Variable	**VIF**	**Tolerance**
CRP	1.82	0.55
Albumin	1.49	0.67
Direct bilirubin	1.36	0.73
Sodium	1.24	0.80
MPV	1.21	0.82
NLR	2.11	0.47
Total bilirubin	1.40	0.71
Hosmer–Lemeshow	p>0.05	Good fit

VIF: Variance inflation factor, CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio

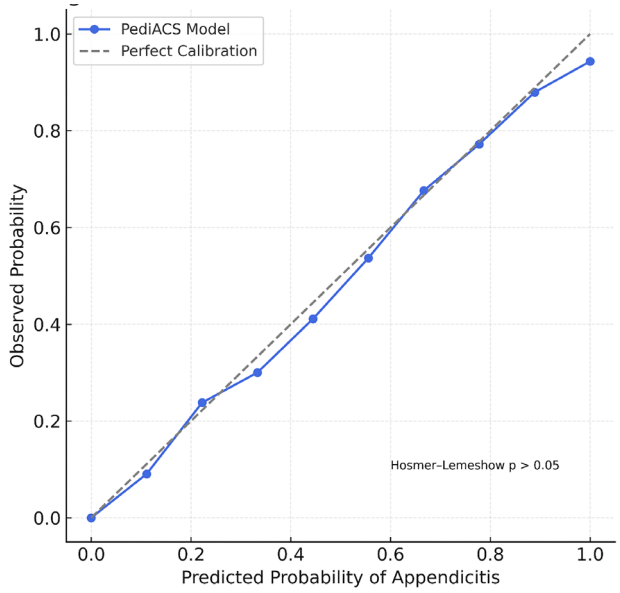

Figure 5. Decision Curve Analysis (DCA) for the PediACS Model (7-Parameter Version)

Decision curve analysis demonstrates that the PediACS model (solid line) provides a higher net benefit across a wide range of threshold probabilities compared with the "treat-all" (dashed line) and "treat-none" (dotted line) strategies. The model achieves the greatest clinical benefit between threshold probabilities of approximately 0.2 and 0.7, supporting its utility for individualized surgical decision-making in pediatric appendicitis

quantitatively reflects the imbalance between innate and adaptive immune activity. Through this mechanism, NLR may contribute meaningful supplementary information regarding both the onset and severity of appendicitis, thereby supporting clinical decision-making (30).

Mean platelet volume, an indicator of platelet size and activation, has frequently been investigated as a biomarker of systemic inflammation. Previous studies have shown that MPV correlates with inflammatory burden, and that elevated MPV levels in complicated appendicitis (e.g., perforated or gangrenous cases) may help identify high-risk patients who require urgent surgical intervention (31).

Table 6. Comparative ROC analysis (best single marker vs PediACS model)			
Model	**AUC**	**ΔAUC vs best single marker**	**p-value**
Best single marker (NLR)	0.845	–	–
PediACS model	0.903	+0.058	0.031

Abbreviations and tests: As in Table 1 plus ROC comparison between curves (DeLong test). NLR: Neutrophil-to-lymphocyte ratio

The elevation of MPV in acute appendicitis can be explained by the systemic inflammatory response and the accompanying increase in platelet activation (32). Under inflammatory conditions, thrombopoiesis accelerates, resulting in the release of larger, immature platelets into the circulation. These platelets are metabolically more active and exhibit greater proinflammatory potential, which accounts for the higher MPV values observed in acute inflammation, including appendicitis (33,34). In complicated forms such as perforated or gangrenous appendicitis, the inflammatory response is particularly intense, leading to a more pronounced increase in MPV. Ishizuka et al. (34) have shown that cytokines—especially IL-6—play a pivotal role in modulating megakaryocyte proliferation and platelet activation during severe inflammation. This cytokine-mediated stimulation promotes the release of larger platelets, reinforcing the value of MPV as a marker of inflammatory severity, particularly in complicated appendicitis.

When considered collectively, these hematologic and biochemical markers reflect the multidimensional inflammatory profile underlying appendiceal disease. Reactive oxygen species play a central role in inflammation-related tissue injury; free radicals released from polymorphonuclear leukocytes promote lipid peroxidation, increase microvascular permeability, and contribute to cellular damage. Evidence from the literature indicates that oxidative stress markers—such as malondialdehyde, thiobarbituric acid–reactive substances, and superoxide dismutase—are significantly elevated in advanced or gangrenous appendicitis (35). Overall, these observations suggest that systemic inflammation and oxidative stress jointly contribute to appendiceal tissue damage and metabolic dysregulation, which may further explain the biochemical alterations observed in bilirubin and albumin levels within the PediACS model.

The diagnostic potential of classical inflammatory biomarkers such as WBC count, neutrophil count, and CRP has been extensively investigated (6). Although these parameters often demonstrate moderate to high diagnostic accuracy when assessed individually, they typically lose independent predictive strength in multivariable analyses.

This finding underscores the rationale for using multivariate modeling in the PediACS framework, which integrates biomarkers with complementary biological relevance. The early stage of infection is typically characterized by neutrophilia and relative lymphopenia (36); consequently, the NLR has recently been proposed as a useful biomarker for detecting bacterial infections (37). Previous studies have shown that leukocyte count and NLR are markedly higher in complicated appendicitis compared to uncomplicated cases, with particularly elevated NLR values observed in perforated appendicitis (38).

Although individual biomarkers such as the (NLR, AUC=0.845), (CRP, AUC=0.815), and albumin (AUC=0.810) demonstrated strong univariate diagnostic accuracy, their predictive power diminished when analyzed together, suggesting overlapping biological variance. This pattern aligns with previous reports in the literature. Buyukbese and Sarac (6) reported similarly high diagnostic accuracy for CRP (AUC=0.887) and WBC count (AUC=0.845), whereas Birben et al. (39) observed moderate diagnostic performance for bilirubin-based indices (AUC ≈ 0.77-0.79). Similarly, diagnostic models based on the NLR have demonstrated high discriminative ability in pediatric populations, emphasizing the clinical relevance of inflammatory biomarkers in appendicitis. In addition, several investigations have suggested that NLR and bilirubin levels may aid in establishing the diagnosis or assessing disease severity. However, reported diagnostic performance varies widely across studies, largely due to methodological differences and heterogeneity in patient populations.

While Zhang et al. (8) also identified CRP, NLR, and direct bilirubin as significant biomarkers associated with complicated appendicitis, our findings further highlight the pivotal role of direct bilirubin as the most specific and independently predictive parameter within the multivariate diagnostic framework.

Beyond classical inflammatory markers such as CRP, NLR, and MPV, the PediACS model also incorporates biochemical indicators including direct and total bilirubin, sodium, and albumin, thereby reflecting the multifactorial nature of appendiceal inflammation. Although CRP and sodium individually exhibited limited diagnostic discrimination, their inclusion enhanced the model's overall diagnostic accuracy through synergistic interactions between inflammatory and biochemical pathways. This integrative structure outperformed the best single biomarker (ΔAUC=0.058, p=0.031). In contrast to previous studies that evaluated isolated parameters such as NLR in small or heterogeneous pediatric cohorts-which consequently reported variable diagnostic performance and limited generalizability (40). The present analysis demonstrates that combining inflammatory and biochemical markers yields superior diagnostic performance with robust internal calibration. Similarly, earlier studies focusing on a limited set of biochemical markers, particularly bilirubin and CRP, in selective cohorts with normal WBC counts have shown inconsistent diagnostic accuracy.

The nomogram visualization further supports these findings, illustrating how biochemical and inflammatory markers are integrated into a clinically applicable framework for individualized risk estimation. This multivariable synergy reflects the dynamic interaction between biochemical and inflammatory processes, as hepatic, hematologic, and electrolyte alterations co-evolve throughout the course of appendiceal inflammation. In the nomogram analysis, direct bilirubin showed the greatest contribution to the overall risk score, whereas low albumin levels acted as a negative predictor, consistent with previous biochemical evidence on the suppressive effects of systemic inflammation on hepatic protein synthesis (17). Collectively, these findings confirm that the nomogram effectively captures the integrated diagnostic value of biochemical and inflammatory parameters. Among the available inflammatory indicators, MPV is one of the markers that has shown the greatest variability across studies. While some investigations have reported lower MPV values in acute appendicitis, others have described higher values, resulting in inconsistent diagnostic performance. These discrepancies limit the utility of MPV as a reliable standalone biomarker. Nevertheless, when combined with other hematological and biochemical parameters that reflect different components of the inflammatory response, MPV can contribute meaningfully within a multivariable diagnostic framework.

This pattern is consistent with the findings of our study: although MPV demonstrated limited independent diagnostic power, it enhanced the overall performance of the multivariate PediACS model by complementing other markers. Similarly, parameters such as total bilirubin and the NLR may show strong performance in ROC analyses but lose statistical significance once overlapping biological pathways are accounted for in multivariable modeling. These observations highlight the importance of integrating multiple indicators rather than relying on any single biomarker in the diagnostic assessment of pediatric appendicitis.

At the Youden-optimized cut-off value of 0.214, the PediACS score achieved 85.7% sensitivity and 89.7% specificity, yielding an overall diagnostic accuracy of 87.9%. Decision-curve analysis (Figure 5) demonstrated a consistent net clinical benefit across threshold probabilities between 0.2 and 0.7, outperforming both the "treat-all" and "treat-none" strategies.

In practical terms, when ultrasonography provides inconclusive results, a high PediACS score may warrant early surgical consultation or short-interval reassessment, whereas a low score may support conservative management and reduce unnecessary imaging.

Because the model is based solely on routinely available laboratory parameters, it can be implemented across diverse clinical environments without additional cost or specialized training.

Most pediatric studies evaluating bilirubin fractions, CRP, or albumin individually have reported AUC values between 0.70 and 0.85, often without calibration or decision-curve validation. By achieving an AUC of 0.903, the PediACS model demonstrates superior diagnostic performance and clinical applicability.

Moreover, its nomogram-based visualization provides a user-friendly framework for estimating patient-specific risk, thereby bridging the gap between statistical modeling and bedside decision-making.

Future external validations should explore age-specific physiological adaptations, taking into account developmental differences in bilirubin metabolism, albumin synthesis, and sodium regulation.

In addition, large-scale multicenter prospective studies are warranted to assess the model's ability to reduce unnecessary imaging and negative appendectomy rates, particularly when integrated with ultrasonography or existing clinical scoring systems.

Study Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings to broader pediatric populations. Second, although the sample size was statistically adequate, the study period was relatively short; therefore, future research involving larger, multicenter cohorts is warranted for external validation. Third, imaging interpretations and surgical decision-making were based on clinical judgment, potentially introducing interobserver variability. Finally, only routinely available laboratory parameters were analyzed, and the potential diagnostic contribution of emerging biomarkers or advanced imaging modalities was not assessed.

Despite these limitations, the study has notable strengths. It is among the few pediatric appendicitis investigations to integrate both inflammatory and biochemical parameters into a unified multivariate diagnostic model. By relying exclusively on routine, low-cost laboratory data, the PediACS model enhances clinical feasibility and accessibility, particularly in resource-limited settings. Moreover, its excellent discriminatory capacity (AUC=0.903) and strong calibration (Hosmer–Lemeshow $p>0.05$) confirm its reliability as a practical, objective, and cost-effective decision-support tool for the early diagnosis of acute appendicitis in children.

Conclusion

The PediACS model, which integrates seven routinely available biochemical and inflammatory parameters, demonstrated excellent diagnostic accuracy (AUC=0.903) for detecting acute appendicitis in children. Its multivariable design provides a practical, accessible, and low-cost clinical decision-support tool, particularly valuable when ultrasonographic findings are inconclusive. The model's strong calibration and high overall performance underscore its potential for routine implementation in pediatric emergency settings. Nonetheless, prospective multicenter studies involving diverse pediatric populations are needed to confirm and externally validate its diagnostic reliability and generalizability.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Türkiye, Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (approval no.: 243/2025, date: 16.07.2025).

Informed Consent: Given the retrospective nature of the study, the requirement for informed consent was waived by the committee. All patient data were anonymized prior to analysis.

Footnotes

Financial Disclosure: This study received no financial support.

References

1. Shannon LC, Smith J, Brown A, et al. Postoperative antibiotics, outcomes, and resource use in children with gangrenous appendicitis. JAMA Surg. 2024;159:1-7.
2. Cameron DB, Anandalwar SP, Graham DA, et al. Development and implications of an evidence-based and public health-relevant definition of complicated appendicitis in children. Ann Surg. 2020;271:962-8.
3. Echevarria S, Rauf F, Hussain N, et al. Typical and atypical presentations of appendicitis and their implications for diagnosis and treatment: a literature review. Cureus. 2023;15:e37024.
4. Li D, Zhang Z, Wan J, et al. Clinical features and perforation predictors of appendicitis in infants and toddlers under 3: a retrospective two-center study. Sci Rep. 2025;15:14338.
5. Almaramhy HH. Acute appendicitis in young children less than 5 years: review article. Ital J Pediatr. 2017;43:15.
6. Buyukbese Sarsu S, Sarac F. Diagnostic value of white blood cell and C-reactive protein in pediatric appendicitis. Biomed Res Int. 2016;2016:6508619.
7. Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M. Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: a systematic review and meta-analysis. Am J Surg. 2020;219:154-63.
8. Zhang Q, Zhao H, Wang F, Li W, Zhang P. Diagnostic value of laboratory parameters for complicated appendicitis: a two center study. Biomed Rep. 2024;20:77.

9. Assiri AM, Alrowabah NA, Alobaidi AA. Using neutrophil-lymphocyte ratio, mean platelet volume, and hyponatremia to diagnose appendicitis in children. IJMDC. 2023;7:867-73.
10. Feng W, Yang Q, Zhao X, Li M, Cui H. C-reactive protein and albumin ratio for the diagnosis of complicated appendicitis in children. Res Square. 2020.
11. Ikeda S, Mitaka T, Harada K, Sato F, Mochizuki Y, Hirata K. Tumor necrosis factor-alpha and interleukin-6 reduce bile canalicular contractions of rat hepatocytes. Surgery. 2003;133:101-9.
12. Kosters A, Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. Semin Liver Dis. 2010;30:186-94.
13. Brienza N, Dalfino L, Cinnella G, Diele C, Bruno F, Fiore T. Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Med. 2006;32:267-74.
14. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl. 2011;93:213-7.
15. Hong YR, Chung CW, Kim JW, et al. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soc Coloproctol. 2012;28:247-52.
16. Pogorelić Z, Lukšić AM, Mihanović J, Đikić D, Balta V. Hyperbilirubinemia as an indicator of perforated acute appendicitis in pediatric population: a prospective study. Surg Infect (Larchmt). 2021;22:1064-71.
17. Li Y, Chen L, Yang X, et al. Dynamic association of serum albumin changes with inflammation, nutritional status and clinical outcomes: a secondary analysis of a large prospective observational cohort study. Eur J Med Res. 2025;30:679.
18. Wang MY, Zhang CM, Zhou HH, et al. Identification of a distal enhancer that determines the expression pattern of acute phase marker C-reactive protein. J Biol Chem. 2022;298:102160.
19. Singh SK, Prislovsky A, Ngwa DN, et al. C-reactive protein lowers the serum level of IL-17, but not TNF-α, and decreases the incidence of collagen-induced arthritis in mice. Front Immunol. 2024;15:1385085.
20. Rajab IM, Majerczyk D, Olson ME, et al. C-reactive protein in gallbladder diseases: diagnostic and therapeutic insights. Biophys Rep. 2020;6:49-67.
21. Wang Q, Shi Y. Photoacoustic viscoelasticity imaging for the detection of acute hepatitis: a feasibility study. Biophys Rep. 2020;6:1-8.
22. Jimenez RV, Wright TT, Jones NR, Wu J, Gibson AW, Szalai AJ. C-reactive protein impairs dendritic cell development, maturation, and function: implications for peripheral tolerance. Front Immunol. 2018;9:372.
23. Cottin V, Valenzuela C. C-reactive protein as a candidate biomarker in fibrotic interstitial lung disease. Respirology. 2024;29:195-8.
24. Zhang SC, Wang MY, Feng JR, Chang Y, Ji SR, Wu Y. Reversible promoter methylation determines fluctuating expression of acute phase proteins. Elife. 2020;9:e51317.
25. Plebani M. Why C-reactive protein is one of the most requested tests in clinical laboratories? Clin Chem Lab Med. 2023;61:1540-5.
26. Zhou HH, Tang YL, Xu TH, Cheng B. C-reactive protein: structure, function, regulation, and role in clinical diseases. Front Immunol. 2024;15:1425168.
27. Symeonidis NG, Pavlidis ET, Psarras KK, et al. Preoperative hyponatremia indicates complicated acute appendicitis. Surg Res Pract. 2022;2022:1836754.
28. Shuaib A, Alhamdan N, Arian H, Sallam MA, Shuaib A. Hyperbilirubinemia and hyponatremia as predictors of complicated appendicitis. Med Sci (Basel). 2022;10:36.
29. Anand S, Krishnan N, Birley JR, Tintor G, Bajpai M, Pogorelić Z. Hyponatremia-a new diagnostic marker for complicated acute appendicitis in children: a systematic review and meta-analysis. Children (Basel). 2022;9:1070.
30. Sidharth RG, Gunasekaran G, Kishore A, Jeffrey RS, Paramsivam S. Predictive value of neutrophil-to-lymphocyte ratio in differentiating perforated from non-perforated appendicitis: a cross-sectional study in a tertiary care hospital, Tamil Nadu. Cureus. 2024;16:e62030.
31. C A S, Vincent A. Mean platelet volume as an emerging biomarker for diagnosing acute appendicitis: a retrospective study. Cureus. 2024;16:e75247.
32. Aydogan A, Akkucuk S, Arica S, et al. The analysis of mean platelet volume and platelet distribution width levels in appendicitis. Indian J Surg. 2013;77:495-500.
33. Tullavardhana T, Sanguanlosit S, Chartkitchareon A. Role of platelet indices as a biomarker for the diagnosis of acute appendicitis and as a predictor of complicated appendicitis: a meta-analysis. Ann Med Surg (Lond). 2021;66:102448.
34. Ishizuka M, Shimizu T, Kubota K. Neutrophil-to-lymphocyte ratio has a close association with gangrenous appendicitis in patients undergoing appendectomy. Int Surg. 2012;97:299-304.
35. Koltuksuz U, Uz E, Ozen S, Aydinç M, Karaman A, Akyol O. Plasma superoxide dismutase activity and malondialdehyde level correlate with the extent of acute appendicitis. Pediatr Surg Int. 2000;16:559-61.
36. Takahashi J, Shono Y, Hirabayashi H, et al. Usefulness of white blood cell differential for early diagnosis of surgical wound infection following spinal instrumentation surgery. Spine (Phila Pa 1976). 2006;31:1020-5.
37. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. Infection. 2017;45:299-307.
38. Ribeiro AM, Romero I, Pereira CC, et al. Inflammatory parameters as predictive factors for complicated appendicitis: a retrospective cohort study. Ann Med Surg (Lond). 2022;74:103266.
39. Birben B, Akkurt G, Akın T, Surel AA, Tez M. Efficacy of bilirubin values in diagnosing acute appendicitis in patients with normal white blood cell count and predicting complicated appendicitis. Ulus Travma Acil Cerrahi Derg. 2021;27:50-4.
40. Marjanović V, Zečević M, Budić I, et al. Percentage of neutrophils and neutrophil-to-lymphocyte ratio in distinguishing late from early prehospital presentation of perforated appendicitis in children. Niger J Clin Pract. 2024;27:1435-40.