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PAN-Immune inflammation value: a new biomarker for diagnosing appendicitis in children??

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Abstract

Background This study investigates the potential of the pan-immune-inflammation values (PIV) index as a biomarker for diagnosing acute appendicitis in children and compares its performance with other systemic inflammatory markers.

Methods A retrospective analysis of 1,514 pediatric patients aged 0–18 years with abdominal pain admitted between 2019 and 2023 was conducted. Patients were categorized into complicated, non-complicated appendicitis, negative appendectomy, and non-surgical treatment groups. Demographic and laboratory data were recorded, and PIV, Systemic Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) indices were calculated. Receiver Operating Characteristic (ROC) analysis was used to assess predictive performance, with optimal cut-offs evaluated for sensitivity, specificity, and multiple logistic regression (MLR) analyses.

Results Based on Area Under the Curve (AUC), C-reactive Protein (CRP), lymphocyte, and PLR showed weak predictive value, while White Blood Cell Count (WBC), neutrophil, monocyte, NLR, SII, SIRI, and PIV demonstrated poor predictive value for appendicitis. Optimal cut-offs were 3.40 for NLR, 134.5 for PLR, 1010.3 for SII, 3.47 for SIRI, and 919.3 for PIV, with sensitivity and specificity values of 78.7%, 47.1% for NLR; 64.7%, 47.5% for PLR; 75.6%, 52% for SII; 71.5%, 57.3% for SIRI; and 72.2%, 54.1% for PIV. In the MLR model, PIV above 919.3 increased appendicitis likelihood 2.67-fold (95% Confidence Interval: 2.16–3.37).

Conclusion Although PIV demonstrated potential as a novel biomarker for pediatric appendicitis, its diagnostic utility remains limited without supplementary clinical and radiological data. Larger prospective studies are recommended to validate these findings and improve clinical decision-making. PIV may serve as a supplementary tool in diagnosing pediatric appendicitis when used alongside other markers and diagnostic methods.

Trial registration 'retrospectively registered'.

Keywords PAN-Immune inflammation value, PIV, Appendicitis, Diagnosis, Children

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Introduction

Appendicitis is the most common non-traumatic surgical issue encountered in pediatric emergency departments [1]. Early identification of the disease course in children with appendicitis and timely treatment are crucial to prevent serious adverse outcomes, such as sepsis or death [2]. Children with appendicitis often present to the emergency room with nonspecific complaints, such as fever, abdominal pain, nausea, or vomiting, which can make it challenging for clinicians to identify the underlying cause of symptoms and may result in delayed or missed diagnosis [3]. In the diagnosis of appendicitis, history-taking, physical examination, blood tests, and imaging methods are utilized. Routine blood tests aimed at assessing inflammatory processes are often helpful in the early diagnosis of various diseases [4].

Various scoring systems are used in current clinical practice to support the diagnosis of acute appendicitis. The Alvarado Score and Pediatric Appendicitis Score (PAS), which integrate symptoms, physical examination findings, and laboratory parameters, are widely used reliable tools for reducing diagnostic uncertainty [5]. However, the limited performance of these systems in predicting perforation highlights the need for new biomarkers. The recently developed Appendicitis Inflammatory Response (AIR) score, combining the neutrophil/lymphocyte ratio, C-reactive protein, and body temperature, has been shown to distinguish perforated from non-perforated appendicitis in pediatric patients with 0.80 Area Under the Curve (AUC), 89.5% sensitivity and 71.9% specificity [6].

In recent years, the role of various biomarkers in the diagnosis of acute appendicitis and the differentiation of perforation has been investigated. In addition to standard parameters such as hyperfibrinogenemia (AUC = 0.876 in perforated cases) and hyponatremia (significant decrease in serum sodium levels in children with complicated appendicitis; Weighted Mean Difference (WMD) = – 3.29, $p < 0.001$), innovative biomarkers such as Pentraxin-3 (91.8% sensitivity, 90.7% specificity), ischemia-modified albumin (Mean Difference = 0.21, $p = 0.01$), and leucine-rich α-2-glycoprotein 1 (LRG-1; AUC = 1.0 in serum, 0.85 in saliva) have shown promise in perforation differentiation [7, 8, 9, 10, 11, 12]. Inflammatory mediators such as hyperbilirubinemia (92% sensitivity at a cutoff of ≥ 15.5 µmol/L) and interleukin-6 (IL-6; 77.4% sensitivity in complicated cases) also have prognostic value [13, 14]. However, some of these biomarkers have limitations for routine use due to high costs, invasive sampling (e.g., salivary LRG-1), or methodological constraints. While these studies emphasize the diagnostic and prognostic value of these biomarkers, the role of new indices derived from easily accessible and cost-effective complete blood count parameters remains to be fully explored.

Complete blood count (CBC) is easy to perform, cost-effective, and provides information on various cell types and morphological parameters (white blood cell count, lymphocyte count, neutrophil count, monocyte count, platelet count, and mean platelet volume). For example, the diagnostic value of low-cost and routinely measured markers such as mean platelet volume (MPV) and red blood cell distribution width (RDW) has been investigated. However, meta-analyses conducted in the pediatric population have shown that MPV does not significantly differ between children with acute appendicitis and healthy controls (WMD = -0.42, $p = 0.19$), and RDW similarly lacks discriminatory power (WMD = 0.23, $p = 0.28$). These findings indicate the limited clinical utility of MPV or RDW as standalone diagnostic tools [15, 16]. Additionally, combined ratios of these parameters are used as inflammation indices, assisting in the diagnosis, progression, and risk stratification of many diseases [17]. The diagnostic value of CBC parameters is not limited to appendicitis alone; Growing evidence suggests that composite scores based on CBC can serve as prognostic biomarkers in cancer and inflammatory diseases [18]. For example, parameters such as MPV and WBC (white blood cell count), when combined with machine learning models, have achieved an accuracy of 85% in COVID-19 diagnosis [19]. Similarly, LYM (lymphocyte count) and PDW (platelet distribution width) have been used by automated algorithms to distinguish between influenza and SARS-CoV-2 infections, achieving an accuracy of 98.4% [20]. However, since many of these markers show non-specific elevations in infections, their use alone in diagnosing appendicitis is limited. In this context, several markers have been developed, including the recently introduced pan-immune-inflammation values (PIV), which encompasses levels of neutrophils, monocytes, platelets, and lymphocytes [21]. By reflecting inflammatory and immune response dynamics that cannot be captured by a single biomarker, these markers may enhance diagnostic accuracy.

The primary objective of this study is to evaluate whether the recently developed PIV index, which includes levels of neutrophils, platelets, monocytes, and lymphocytes, can be used as a biomarker for diagnosing acute appendicitis in children and to compare the performance of PIV with other commonly used systemic inflammatory markers, such as the Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Neutrophil/Lymphocyte Ratio (NLR), and Platelet/Lymphocyte Ratio (PLR).

Methods

Patients

In this retrospective study, data from 1,514 pediatric patients aged 0–18 years, admitted with abdominal pain

to Hitit University Erol Olçok Training and Research Hospital between January 1, 2019, and December 31, 2023, were analysed retrospectively.

Study design

Patients who underwent surgery with a preliminary diagnosis of appendicitis between 2019 and 2023 were classified into three groups based on their histopathological diagnoses: acute appendicitis, perforated appendicitis, and negative appendectomy. However, patients presenting with abdominal pain who could not be definitively diagnosed through physical examination, laboratory tests, and imaging methods were admitted to the pediatric surgery department for observation due to suspected appendicitis. During the follow-up period, patients who required appendectomy were operated on and classified into the appropriate group based on their histopathological diagnoses: acute appendicitis, perforated appendicitis, and negative appendectomy. Patients who remained clinically stable and were discharged without surgery were classified into the non-surgical treatment group.

Initially, patients were classified into four main groups: non-surgery treatment ($n = 624$, 41.2%), non-complicated appendicitis ($n = 630$, 41.6%), complicated appendicitis ($n = 136$, 9%), and negative appendectomy ($n = 124$, 8.2%). The complicated, non-complicated appendicitis, and negative appendectomy groups were established based on patients' pathological diagnoses. Subsequently, patients were divided into two main research groups: appendicitis (complicated and non-complicated appendicitis) and non-appendicitis (negative appendectomy and non-surgery treatment), and statistical analyses were performed.

Inclusion and exclusion criteria

Inclusion criteria: Being in the 0–18 age range, hospitalization in the pediatric surgery department for medical treatment due to abdominal pain, histopathological diagnosis after appendectomy, and availability of CBC data within 24 h before surgery were determined as inclusion criteria.

Exclusion criteria: Patients with a history of chronic inflammatory disease (e.g., Crohn's disease, ulcerative colitis), immunodeficiency, or malignancy, those who had a systemic infection or received corticosteroid/immunomodulatory treatment in the last month, and those with missing laboratory data or follow-up records were excluded from the study.

Ethical aspects

The study was approved by the Ethics Committee of Hitit University Faculty of Medicine ([Decision No: [2024-08], Approval Date: [03/04/2024]).

Study outcomes

For each patient, demographic data (age, gender) and laboratory values, including C-reactive protein (CRP), WBC, lymphocyte, neutrophil, monocyte, and platelet counts, were recorded. From these laboratory values, the PIV, SII, SIRI, NLR, and PLR indices were calculated. The formulas used were as follows: PIV = (Neutrophil × Monocyte × Platelet) / Lymphocyte, SII = (Platelet × Neutrophil) / Lymphocyte, SIRI = (Neutrophil × Monocyte) / Lymphocyte, NLR = Neutrophil / Lymphocyte, and PLR = Platelet / Lymphocyte.

Primary outcome

The primary outcome of this study was to evaluate the diagnostic performance of the PIV as a novel biomarker for acute appendicitis in children. This was assessed by comparing the predictive accuracy of PIV with other systemic inflammatory markers, including the SII, SIRI, NLR, and PLR. The diagnostic performance was measured using Receiver Operating Characteristic (ROC) analysis, with AUC, sensitivity, and specificity as key metrics.

Secondary outcomes The secondary outcomes included.

- Determining the optimal cut-off values for PIV, NLR, PLR, SII, and SIRI in diagnosing pediatric appendicitis.
- Assessing the relationship between PIV and other inflammatory markers (CRP, WBC, neutrophil, monocyte, and lymphocyte counts) in differentiating appendicitis from non-appendicitis cases.
- Evaluating the impact of demographic factors (age and gender) on the likelihood of appendicitis.
- Comparing the diagnostic performance of PIV and other inflammatory markers in distinguishing between complicated and non-complicated appendicitis cases.

Statistical analysis

Statistical analyses were performed using SPSS software (Version 22, SPSS Inc., Chicago, IL, USA, License: Hitit University). The graphics in the study were performed using the 'ggplot2' library in R Studio version 2023.06.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Descriptive statistics for categorical data were reported as frequency (n) and percentage (%). The Chi-square test was used to compare proportions between categorical variables. Descriptive statistics for normally distributed numerical data were reported as mean ± standard deviation (SD), while non-normally distributed data were reported as median (Q1-Q3). The Kolmogorov-Smirnov test, histograms, and Q-Q plots were used to test the normality assumption of

numerical data. The Levene test was used to assess the homogeneity of variances. The Student's t-test was used to compare continuous variables between two independent groups when parametric test assumptions were met; otherwise, the Mann-Whitney U test was used. The Kruskal-Wallis test was used to compare continuous variables across more than two independent groups when parametric test assumptions were not met. Following the Kruskal-Wallis test, Dunn-Bonferroni post hoc pairwise comparison tests were performed to determine the source of the differences when statistically significant results were found.

A ROC analysis was conducted to evaluate the predictive success of laboratory blood values and their derived indices, including NLR, PLR, SII, SIRI, and PIV, in diagnosing appendicitis. ROC curves, AUC, and 95% confidence intervals were calculated. AUC values were interpreted as excellent (0.9-1), good (0.8–0.9), moderate (0.7–0.8), poor (0.6–0.7), and weak (0.5–0.6). The Youden index was used to determine optimal cut-off points in the ROC analysis, and the performance of the best cut-off points was evaluated using sensitivity and specificity values. Univariate and multivariate binary logistic regression analyses were performed to assess the effect of newly created categorical variables, based on the best cut-off points, on appendicitis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for each parameter found statistically significant in both univariate and multivariate models. *P*-values < 0.05 were considered statistically significant for all statistical tests.

Results

A total of 1,514 pediatric patient records were analysed in the study. Distribution by diagnosis was as follows: non-complicated appendicitis ($n = 630$, 41.6%), complicated appendicitis ($n = 136$, 9%), negative appendectomy ($n = 124$, 8.2%), and non-surgical treatment ($n = 624$, 41.2%). The study groups were formed as appendicitis (complicated + non-complicated appendicitis) and non-appendicitis (negative appendectomy + non-surgical treatment). The appendicitis group included 766 patients (50.6%), while the non-appendicitis group had 748 patients (49.4%). Among the patients, 63.5% ($n = 961$) were male and 36.5% ($n = 553$) were female. The mean age was 10.62 ± 4.21 years (range: 0–17), and the mean hospital stay was 3.31 ± 2.3 days (range: 0–15).

Statistical findings comparing sociodemographic characteristics and laboratory blood values between the study groups are presented in Table 1. The distribution of gender ratios was significantly different between groups ($P < 0.001$). The proportion of males in the appendicitis group was 67.8%, compared to 59.1% in the non-appendicitis group. The average age and hospital stay duration were significantly higher in the appendicitis group than in the non-appendicitis group (both $P < 0.001$). Platelet values did not differ significantly between the groups ($P = 0.749$). CRP, WBC, neutrophil, monocyte, NLR, PLR, SII, SIRI, and PIV values were significantly higher in the appendicitis group compared to the non-appendicitis group ($P < 0.001$ for all comparisons). Lymphocyte values in the appendicitis group were significantly lower than those in the non-appendicitis group ($P < 0.001$).

Table 1 Statistical findings for the comparison of sociodemographic characteristics and laboratory blood values between the study groups

	Groups		*P* values
	Non-Appendicitis (*n* = 748)	**Appendicitis (*n* = 766)**	
Gender (M / F)	442 (59.1%) / 306 (40.9%)	519 (67.8%) / 247 (32.2%)	**< 0.001**[a]
Age	10.11 ± 4.486	11.13 ± 3.851	**< 0.001**[b]
Length of Stay	2.24 ± 2.011	4.35 ± 2.078	**< 0.001**[b]
CRP	6.29 (3.14-25)	14.25 (3.34–40.1)	**< 0.00**[c]
WBC	11.32 (8.26–14.79)	14.64 (11.50-18.09)	**< 0.001**[c]
Lymphocyte Count	2.08 (1.37–2.88)	1.765 (1.26–2.49)	**< 0.001**[c]
Neutrophil Count	7.69 (4.83–11.91)	11.69 (8.52–15.22)	**< 0.001**[c]
Monocyte Count	0.76 (0.56–0.99)	0.92 (0.68–1.16)	**< 0.001**[c]
Platelet Count	292 (248.2-346.7)	290.5 (245.7–346)	0.749[c]
NLR	3.76 (1.87–7.67)	6.46 (3.67–11.35)	**< 0.001**[c]
PLR	141 (101.7-212.9)	159.9 (114.9–235)	**< 0.001**[c]
SII	1072.4(564.1-2209.7)	1808.3 (1018.9-3357.7)	**< 0.001**[c]
SIRI	2.73 (1.23–6.80)	5.81 (3.00-11.21)	**< 0.001**[c]
PIV	818 (376.5-1942.5)	1687.8 (830.7-3264.1)	**< 0.001**[c]

[a]Chi-square test

[b]Student's t test

[c]Mann-Whitney U test

CRP: C-Reactive Protein, WBC: White Blood Cell Count, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, PIV: Pan-Immune-Inflammation Value, M: Male, F: Female

The findings from the ROC analysis conducted to determine the predictive success of laboratory blood values for appendicitis, as well as the sensitivity and specificity values calculated using the cut-off values identified through ROC analysis, are presented in Table 2 with 95% confidence intervals. Based on the AUC values from the ROC analysis, CRP, lymphocyte, and PLR had weak predictive value for appendicitis (AUC: 0.5–0.6; AUC = 0.589, AUC = 0.576, AUC = 0.569, respectively), while WBC, neutrophil, monocyte, NLR, SII, SIRI, and PIV demonstrated poor predictive value (AUC: 0.6–0.7) (Table 2). Optimal cut-off points calculated using the Youden index for CRP, WBC, lymphocyte, neutrophil, monocyte, NLR, PLR, SII, SIRI, and PIV were 6.32, 12.98, 1.76, 7.725, 0.88, 3.40, 134.5, 1010.3, 3.47, and 919.3, respectively. Sensitivity and specificity values for these cut-off points were 64.8%, 52.7% for CRP; 65.5%, 63.1% for WBC; 50.1%, 63.3% for lymphocyte; 79.9%, 50.7% for neutrophil; 54.5%, 65% for monocyte; 78.7%, 47.1% for NLR; 64.7%, 47.5% for PLR; 75.6%, 52% for SII; 71.5%, 57.3% for SIRI; and 72.2%, 54.1% for PIV. The ROC curves for the laboratory blood values with significant predictive success for appendicitis are presented in Fig. 1.

The results of the Univariate and Multivariate Binary Logistic Regression analysis, conducted to determine the effect of laboratory blood values on appendicitis using the new categorical variables created based on cut-off values identified by ROC analysis, are presented in Table 3. In the univariate model, the effects of gender and age were significant ($P < 0.001$ for both). The univariate model showed significant effects for CRP, WBC, lymphocyte, neutrophil, monocyte, NLR, PLR, SII, SIRI, and PIV values ($P < 0.001$ for all). Gender, age, CRP, and PIV index, which were significant in the univariate model, were included in the multivariate model; however, WBC, lymphocyte, neutrophil, monocyte, NLR, PLR, SII, and SIRI, which had significant effects in the univariate model but were highly correlated, were excluded from the multivariate model. Lymphocyte, neutrophil, monocyte, and NLR were excluded because PIV is calculated using these variables, and SII, SIRI, and PLR were excluded due to high correlation with PIV ($r = 0.920$, $r = 0.969$, $r = 0.657$, $P < 0.001$, respectively). In the final model with age, gender, CRP, and PIV parameters, all effects were significant ($P = 0.004$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively). According to the multivariate model results, the odds ratio for CRP was 1.677 (1.347–2.088) and for PIV was 2.698 (2.160–3.369). Patients with a PIV value greater than 919.3 had a 2.698 times higher likelihood of having appendicitis compared to those with a PIV value below 919.3.

Additionally, the statistical findings comparing CRP and PIV values among the complicated appendicitis, non-complicated appendicitis, negative appendectomy, and non-surgery treatment groups are presented in Table 4. CRP and PIV values were significantly different between the groups ($P < 0.001$ for both). According to the post-hoc test results, the CRP values in the complicated

Table 2 Results of ROC analysis performed to determine the success of laboratory blood values in predicting appendicitis, and sensitivity and selectivity values calculated using cut-off values determined by ROC analysis

Variables	AUC	95% CI		Cut-off	Sensitivity	Specificity
		Lower Bound	Upper Bound			
CRP	0.589	0.561	0.618	6.315	%64.8 (%61.3-%68.1)	%52.7 (%49.1-%56.2)
WBC	0.670	0.643	0.697	12.985	%65.5 (%61.9-%68.9)	%63.1 (%59.6-%66.4)
Lymphocyte Count	0.576	0.547	0.604	1.755	%50.1 (%47.3-%52.8)	%63.3 (%60.5-%66)
Neutrophil Count	0.681	0.654	0.708	7.725	%79.9 (%76.8-%82.8)	%50.7 (%47-%54.4)
Monocyte Count	0.615	0.586	0.643	0.875	%54.5 (%50.8-%58.2)	%65 (%61.3-%68.5)
NLR	0.651	0.623	0.678	3.3976	%78.7 (%75.7-%81.4)	%47.1 (%43.5-%50.7)
PLR	0.569	0.540	0.597	134.505	%64.7 (%61.2-%68.1)	%47.5 (%43.9-%51)
SII	0.645	0.617	0.672	1010.269	%75.6 (%72.5-%78.4)	%52 (%48.5-%55.4)
SIRI	0.668	0.641	0.695	3.4716	%71.5 (%68.4-%74.3)	%57.3 (%53.8-%60.6)
PIV	0.661	0.634	0.689	919.2669	%72.2 (%69.1-%75.1)	%54.1 (%50.6-%57.6)

CRP: C-Reactive Protein, WBC: White Blood Cell Count, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, PIV: Pan-Immune-Inflammation Value, AUC: Area Under Curve, CI: Confidence Interval

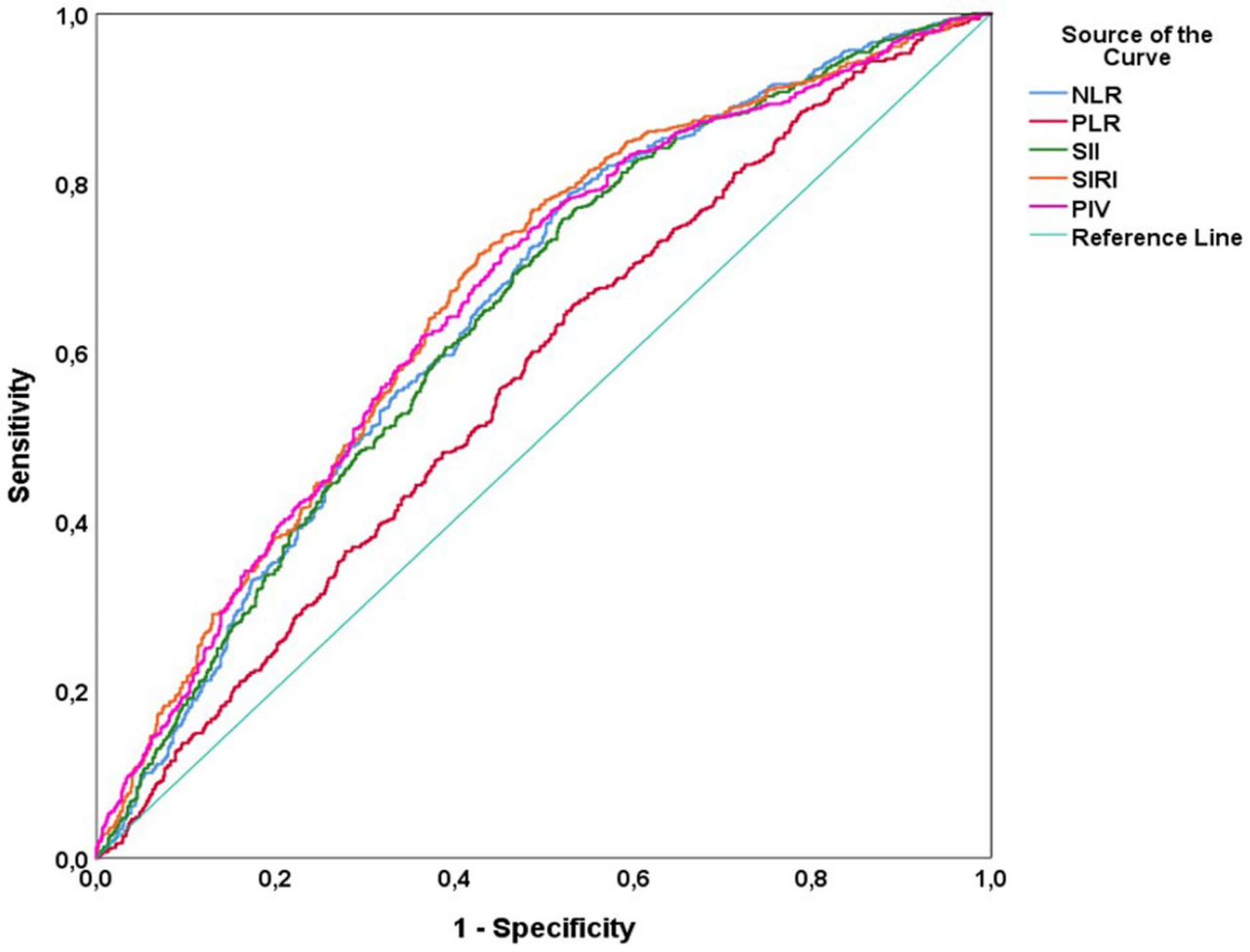

Fig. 1 ROC curves illustrating the predictive performance of statistically significant laboratory blood values indices in diagnosing appendicitis

appendicitis group were significantly higher than those in the other groups ($P<0.001$ for all comparisons). The CRP values in the non-complicated appendicitis group were significantly higher than those in the control group ($P=0.049$). No significant differences were found among the other groups ($P>0.05$). According to the post-hoc test results, the PIV values in the complicated appendicitis group were significantly higher than those in the other groups ($P<0.001$ for all comparisons). The PIV values in the non-complicated appendicitis group were significantly higher than those in the negative appendectomy and non-surgery treatment groups ($P<0.001$ for all comparisons). The PIV values in the negative appendectomy group were significantly lower than those in the non-surgery treatment group ($P=0.003$). The distribution of PIV values among the research groups is shown in Fig. 2.

Discussion

In our study, significant differences in gender and age were observed between the groups with or without appendicitis. The male gender being a risk factor for the development of appendicitis is consistent with previous studies [22, 23]. The higher average age in the appendicitis group suggests that the risk of appendicitis increases with age in children. These findings confirm, as previously highlighted in the literature, that the incidence of appendicitis is higher in males and that age may be an important factor in the development of appendicitis [22, 23].

This study evaluated the impact of inflammatory biomarkers such as CRP, WBC, lymphocyte, neutrophil, monocyte, NLR, PLR, SII, SIRI, and PIV on the prediction of appendicitis. The literature indicates that in patients with acute appendicitis, values of WBC, neutrophil count, and monocyte count are significantly higher compared to patients without acute appendicitis. However, a significant decrease in lymphocyte count has been observed in patients with acute appendicitis. Additionally, it has been stated that platelet levels show similarity between the two groups [17]. Our study presents results that support these findings in the literature.

Table 3 The results of univariate and multivariate binary logistic regression analyses performed to determine the effect of risk factors in predicting appendicitis

	Univariate		Multivariate	
	***P* values**	**OR (CI 95%)**	***P* values**	**OR (CI 95%)**
Gender (Male vs. female)	**< 0.001**	1.455 (1.179–1.795)	**0.004**	1.384 (1.108–1.729)
Age	**< 0.001**	1.060 (1.034–1.086)	**< 0.001**	1.069 (1.041–1.097)
CRP ≥ 6.315	**< 0.001**	2.045 (1.663–2.513)	**< 0.001**	1.677 (1.347–2.088)
WBC ≥ 12.985	**< 0.001**	3.252 (2.635–4.013)	ni	
Lymphocyte ≤ 1.755	**< 0.001**	1.721 (1.401–2.113)	ni	
Neutrophil ≥ 7.725	**< 0.001**	4.082 (3.251–5.125)	ni	
Monocyte ≥ 0.875	**< 0.001**	2.228 (1.812–2.740)	ni	
NLR ≥ 3.398	**< 0.001**	3.288 (2.6264.117)	ni	
PLR ≥ 134.51	**< 0.001**	1.659 (1.3502.040)	ni	
SII ≥ 1010.27	**< 0.001**	2.857 (2.2973.555)	ni	
SIRI ≥ 3.47	**< 0.001**	3.341 (2.6994.135)	ni	
PIV ≥ 919.27	**< 0.001**	3.066 (2.4763.796)	**< 0.001**	2.698 (2.160–3.369)
Multivariate model: Nagelkerke R Square = 0.136, Classification accuracy: 63.5%				

Values below $P < 0.05$ were shown bold, ni: not included, ns: not significant ($P > 0.05$),

CRP: C-Reactive Protein, WBC: White Blood Cell Count, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, PIV: Pan-Immune-Inflammation Value, OR: Odds ratio, CI: Confidence interval

Table 4 Statistical findings for the comparison of CRP and PIV laboratory blood values between research groups

	Groups					
	Non-Complicated Appendicitis (1)	**Complicated Appendicitis (2)**	**Negative Appendectomy (3)**	**Non-Surgical Treatment (4)**	***P***	**Post-hoc *P***
CRP	9.84 (3.3-26.17)	49.3 (20.47–110.7)	5.38 (3.2–20)	6.29 (3.13-25)	**< 0.001**	**1–2: < 0.001** 1–3: 0.125 **1–4: 0.049** **2–3 < 0.001** **2–4: < 0.001** 3–4: 1.000
PIV	1580.9 (758.4-3167.2)	2310.3 (1366.0-4500.1)	582.2 (277.4-1317.6)	916.4 (388.2-2028.8)	**< 0.001**	**1–2: < 0.001** **1–3: < 0.001** **1–4: < 0.001** **2–3 < 0.001** **2–4: < 0.001** **3–4: 0.003**

Kruskal-Wallis test following Dunn-Bonferroni post-hoc tests

CRP: C-Reactive Protein, PIV: Pan-Immune-Inflammation Value

According to the findings of the ROC analysis, it was determined that CRP is significant in the prediction of appendicitis; however, its discriminatory power in appendicitis classification was weak based on the AUC value. The AUC value of 0.589 for CRP on the ROC curve is consistent with previous studies [24]. However, according to the results of the ROC analysis, the sensitivity and specificity values of CRP were found to be relatively low, suggesting that these parameters alone may not be sufficient in clinical practice. This situation supports the idea that inflammatory markers like CRP are elevated in many inflammatory processes and are not specific to the diagnosis of appendicitis [25]. In a study conducted by Blok et al., the sensitivity of CRP for the diagnosis of appendicitis at a cut-off of ≥ 10 mg/L was found to be 0.87, with a specificity of 0.77 [26]. In our study, the CRP values of the

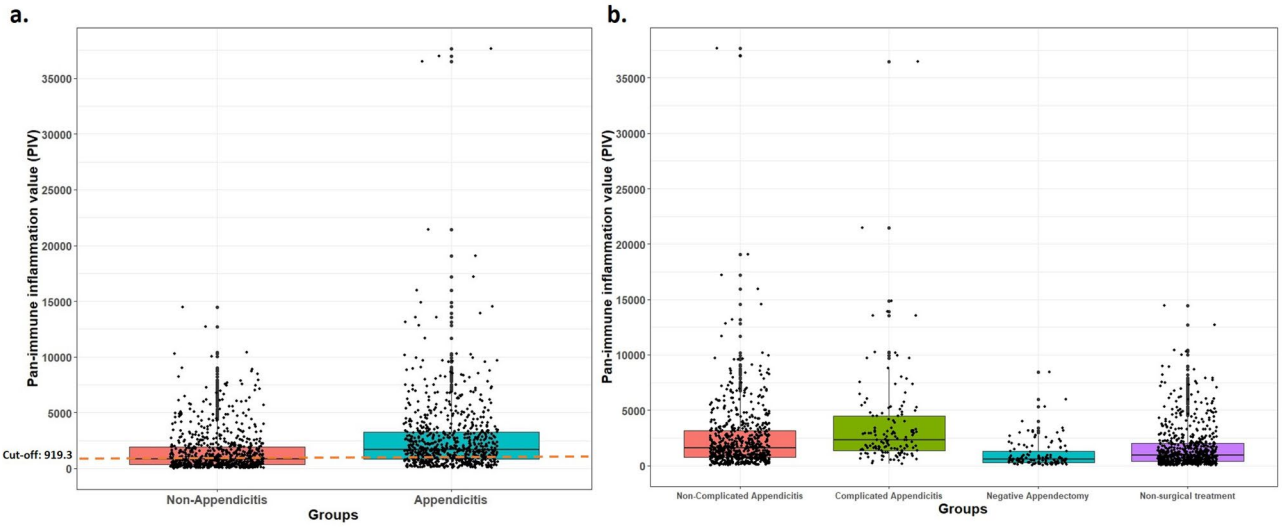

Fig. 2 Boxplot with jitter showing the distribution of pan-immune-inflammation values (PIV) among research groups

appendicitis group were found to be significantly higher compared to the non-appendicitis group; however, based on the optimal cut-off of 6.315 determined by the ROC analysis, we can say that CRP, which is a nonspecific inflammatory marker, is not sufficient alone for the diagnosis of appendicitis. Zouari et al., examined 102 children who underwent appendectomy and compared the appendicitis group with the non-appendicitis group [27]. The authors reported that a CRP level of ≥ 10 mg/L upon hospital admission ($P < 0.001$) was a predictive factor for pediatric appendicitis, and they determined an OR of 7.44 for this cut-off [27]. According to the findings of the multivariate LR model in our study, the effect of CRP on the prediction of appendicitis was significant, and it was found that each 1-unit increase above a CRP value of 6.3 increased the likelihood of appendicitis by 1.68 times. We believe that in patients with CRP values above this cut-off, clinicians should consider other laboratory and clinical information as well.

NLR is an inflammatory biomarker that can be easily calculated. Recent studies have defined its role as a predictor of peritonitis and postoperative intra-abdominal abscess in children [28]. In recent years, researchers have focused on studies that assess its utility in diagnosing appendicitis in children. A meta-analysis by Eun et al., included 19 studies comprising a total of 5,974 pediatric cases evaluating the role of NLR in pediatric acute appendicitis diagnosis [25]. This systematic review and meta-analysis reported that NLR had moderate sensitivity (0.82) and specificity (0.76) for diagnosing appendicitis in pediatric patients, with an area under the curve (AUC) of 0.86 [25]. The results of this meta-analysis demonstrate superior diagnostic performance compared to our findings. Additionally, the meta-analysis indicated that the optimal NLR cut-off values for detecting pediatric appendicitis ranged from 2.5 to 6.14. In our study, the NLR cut-off value for appendicitis diagnosis was found to be 3.4, which is consistent with this meta-analysis. In a study conducted by Delgado et al., it was reported that NLR had an AUC of 0.879, a sensitivity of 84.2%, and a specificity of 83.8% at a cut-off of 2.65, suggesting that it could be used as a predictor of negative appendectomy in children [28]. Other recent studies have similarly reported moderate diagnostic performance for NLR [29, 30]. The findings of our study support the existing data in the literature, indicating that NLR can be used as a moderate-level biomarker in pediatric acute appendicitis diagnosis. The diagnostic performance of NLR obtained with specific cut-off values may provide benefits to clinicians as an auxiliary tool in situations where clinical symptoms are uncertain. When evaluated alongside other inflammatory biomarkers, the role of NLR in appendicitis diagnosis could contribute to a more reliable diagnostic process.

High SIRI and SII values indicate the presence and severity of systemic inflammation. In a study conducted by Siki et al., the highest AUC for SIRI was 0.716 at a cut-off value of > 5.80 (95% CI, 0.691–0.741, sensitivity = 62%, specificity = 71). For SII, a cut-off value of 1630.09 predicted acute appendicitis with a sensitivity of 68% (95% CI, 65%-71) and a specificity of 61% (95% CI, 55%-67), resulting in an AUC of 0.690 (95% CI = 0.664–0.716) [17]. In a recent study by Sarıdaş et al., involving 436 patients over the age of 18, the AUC, cut-off value, sensitivity, and specificity for SII were found to be 0.742, > 1647.01, 82.6%, and 56.3%, respectively, while for SIRI, these values were 0.783, > 4.45, 78.6%, and 65.5%, respectively. The diagnostic performance of SII and SIRI in this study was higher compared to our findings [30]. In our study, the

specificity values for SII and SIRI were particularly low compared to the literature.

The literature indicates that parameters such as NLR, PLR, SII, and SIRI can be used in the diagnosis of appendicitis in children [24, 29]. However, PIV has not been addressed in previous studies and has been identified as a significant biomarker for predicting appendicitis in this study. PIV is a novel composite biomarker used to evaluate inflammatory conditions. Unlike existing biomarkers, PIV includes all four primary cell types observed in peripheral blood [31]. A study conducted on patients with rheumatoid arthritis found that PIV was associated with disease activity [32]. Additionally, it has been discovered to be a promising biomarker in individuals diagnosed with colorectal cancer [33]. Nonetheless, the connection between appendicitis and PIV remains uncertain. Although it has been evaluated in a single study involving adult patients, there are no studies assessing the utility of PIV in diagnosing appendicitis in children. In a study by Sarıdaş et al., involving 436 patients over the age of 18, the sensitivity, specificity, AUC, and cut-off value for PIV in diagnosing appendicitis were found to be 75.4%, 66.1%, 0.761, and >1179.81, respectively. This study demonstrated significant diagnostic performance for PIV in the adult population [30]. However, our study supports these findings for the pediatric population for the first time. In our study, the AUC for PIV in predicting appendicitis in children was 0.661, indicating a moderate level of predictive success. We can say that PIV is a significant predictive marker with a sensitivity of 72.2% at a cut-off value of ≥919.3, although the specificity value remained low at 54.1%. The high sensitivity but low specificity suggests that the PIV index is effective in distinguishing individuals with appendicitis but inadequate in differentiating healthy children. Furthermore, in the MLR model created considering the effects of age, gender, and CRP on the diagnosis of appendicitis in children, it was determined that patients with a PIV value of ≥919.3 were 2.69 times (2.16–3.37) more likely to have appendicitis compared to those with a PIV value below 919.3.

In comparison to other inflammatory markers like RDW, MPV, and PDW, which have been shown to have limited diagnostic value for acute appendicitis in pediatric populations [34] the PIV index demonstrated a more promising potential in our study. While traditional markers such as WBC and CRP offer limited sensitivity and specificity, PIV exhibited an improved predictive ability, with optimal cut-off values of 919.3 and a 2.67-fold increased likelihood of appendicitis in the multiple logistic regression model. However, similar to other studies, PIV's diagnostic accuracy remains constrained without adjunctive clinical and radiological evaluation, reinforcing the need for a multi-faceted approach to diagnosing pediatric appendicitis. Thus, while markers like RDW/MPV ratios have some predictive value, PIV may provide a more comprehensive inflammatory profile when used in conjunction with other diagnostic modalities.

Our study, while yielding results consistent with many studies in the literature, is innovative in that it evaluates the role of PIV in predicting appendicitis for the first time. The results of the ROC analysis indicated that the AUC, sensitivity, and specificity values of CRP, lymphocytes, and PLR in predicting appendicitis were relatively low, suggesting that these parameters alone are insufficient for clinical use. However, the AUC values for WBC, neutrophils, monocytes, NLR, SII, SIRI, and PIV in the ROC analysis were relatively higher, indicating that the combined assessment of these parameters could provide a stronger prediction for appendicitis. In terms of sensitivity values, the biomarkers demonstrating stronger positive diagnostic performance were neutrophils, NLR, SII, SIRI, and PIV.

Our study provides valuable insights into the potential of PIV and other inflammatory markers in the diagnosis of pediatric appendicitis; however, it is important to acknowledge several limitations. Due to the retrospective nature of our study, certain limitations exist. First, we had limited access to symptoms such as nausea and vomiting, as well as physical examination findings like guarding and rebound tenderness. However, the large sample size with accessible laboratory data stands out as a key advantage that strengthens our findings. Additionally, the study was based on data from a single center, which may limit the generalizability of our results to other populations or settings. Multicenter studies would further enhance the generalizability of these findings. In conclusion, while our study highlights the potential of PIV as a novel biomarker for pediatric appendicitis, these limitations indicate the need for prospective and multicenter research to validate our findings and improve the diagnostic accuracy of inflammatory markers in clinical practice.

Conclusion

Our study comprehensively evaluated the predictive power of PIV and other inflammatory parameters in diagnosing appendicitis in children. In the MLR model, the cutoff point of 919.3 for PIV showed a significant odds ratio of 2.69. This finding suggests that, based on its AUC and sensitivity values, PIV has potential as a promising new biomarker for diagnosing appendicitis in the pediatric population. However, it was concluded that PIV and other inflammatory parameters should be validated in broader, prospective studies and supported by other clinical and radiological findings in clinical practice. The identification of reliable biomarkers for acute appendicitis could improve patient management by reducing negative appendectomy rates. In this context, PIV is

recommended as a supportive tool in clinical decision-making for predicting appendicitis.

Author contributions
All authors contributed to the study conception and design. All authors read and approved the final manuscript. NÇ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. GD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. Hİ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. ED: Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ÇEA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing.

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Data availability
Data can be obtained by contacting the corresponding author.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the local ethics committee of Hitit University (date: 03.04.2024, decision number: 2024-08). The need for consent to participate was waived by the ethics committee in accordance with national regulations. The study was conducted in compliance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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