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Original Article

Assessment of the Prognostic Power of Preoperative Laboratory Biomarkers in Predicting Pediatric Complicated Appendicitis and the Outcomes of the Relevant Surgical Intervention

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ABSTRACT

Aim: The purpose of this study was to assess the prognostic power of preoperative laboratory biomarkers in pediatric age group individuals diagnosed with appendicitis in the emergency department in distinguishing complicated appendicitis from non-complicated appendicitis and in predicting postoperative outcomes.

Materials and Methods: The population of this descriptive, cross-sectional, retrospective study consisted of children (younger than 18 years of age) who applied to our hospital's emergency department between January, 2020 and October, 2021 and underwent surgical intervention with a diagnosis of acute appendicitis. Preoperative laboratory test results, intraoperative surgical outcomes, lengths of hospital stay and postoperative complications data were recorded in the patient follow-up forms and analyzed.

Results: The intraoperative and pathological data revealed that 179 (37.8%) and 294 (62.1%) patients had complicated and non-complicated appendicitis, respectively. An analysis of the complete blood count results indicated that the C-reactive protein (CRP) level, and CRP-to-albumin ratio (CAR), neutrophil count, leukocyte count, monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) were significantly higher, whereas the sodium and albumin levels were significantly lower in those patients with complicated appendicitis than in those with non-complicated appendicitis. Among the parameters investigated, the NLR, CAR values, and the presence of hyponatremia were found to be significantly associated with the length of hospital stay and postoperative complication rates in those patients with complicated appendicitis.

Conclusion: The findings of our study show that leukocyte counts, neutrophil counts, NLR values, CRP, sodium, and direct bilirubin levels measured preoperatively in the emergency department can be used to identify pediatric patients with complicated appendicitis. In addition, MLR and CAR values, as new biomarkers, can provide guidance in emergency interventions and also predict postoperative outcomes.

Keywords: Appendicitis, complicated, pediatric, laboratory, biomarkers

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Introduction

The incidence of appendicitis is higher in developing and newly industrialized countries and in the 15-19 years old age range (1). Acute appendicitis, which is among the diagnoses to be considered in children admitted to the emergency department with abdominal pain, is the most common cause of emergency surgery in the child age group (2). The higher risk of complications such as gangrenous, necrotizing, or perforated appendicitis necessitates more prudence in the pediatric patient group, in patients under 5 years of age in particular (3,4). Both the inability of the pediatric age group to describe their symptoms well enough and delays in admission and diagnosis due to the Coronavirus disease-2019 pandemic have led to an increase in the risk of perforation in recent years (5). Given that complicated appendicitis is associated with higher complication and morbidity rates than uncomplicated appendicitis, early operative intervention is required in the treatment of complicated appendicitis, especially in the presence of a perforation (6,7).

The literature data indicate that blood tests are routinely performed in children diagnosed with acute appendicitis, which include the measurement of markers which can be potentially used to predict complicated appendicitis. Among these markers are the leukocyte and neutrophil counts and the neutrophil-to-lymphocyte ratio (NLR), which are measured within the scope of the complete blood count, and C-reactive protein (CRP) levels (8-10). In recent years, it has been reported that hyponatremia, CRP-to-albumin ratio (CAR) and monocyte-to-lymphocyte ratio (MLR) can also be used as markers for complicated appendicitis in children (11-14). There are numerous studies in the literature on new biomarkers, yet only a limited number of these studies address pediatric patients or the relationship between these biomarkers and postoperative outcomes.

In this context, the aim of this study was to assess the prognostic power of those parameters measured preoperatively within the scope of the hemogram and biochemistry tests in pediatric age group individuals diagnosed with appendicitis in the emergency department in distinguishing complicated appendicitis from non-complicated appendicitis and in predicting postoperative outcomes.

Material and Methods

This study was designed as a descriptive, cross-sectional, retrospective study. The study protocol was approved by University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Surgery Training and Research Hospital, Clinical Research Ethics Committee (decision no: 621, date: October 10th, 2021).

The study population consisted of patients younger than 18 who applied to the emergency department between January, 2020 and October, 2021 and who underwent surgical intervention at the pediatric surgery clinic with a diagnosis of acute appendicitis based on biochemical tests and ultrasonographic findings. Between January, 2020 and October, 2021, 491 of the 1,091 patients admitted to the pediatric surgery clinic with a diagnosis of acute abdomen were operated on for acute appendicitis.

Patients who underwent emergency appendectomy were taken to the ward after staying in the pediatric surgery intensive care unit for 6-8 hours. Those with metabolic, endocrine and hematological diseases and those who used drugs were excluded from this study because these can be a determinant in biochemical and hematological parameters. Those patients with metabolic and endocrine diseases, those categorized as class IV based on the American Society of Anesthesiologists (ASA) scores and negative appendectomies (n=30, 6%) were excluded from this study. A total of 473 patients were included in this study.

The patients were divided into two groups based on their histopathological data as the complicated (gangrenous, perforated) and the non-complicated (phlegmonous) appendicitis groups. The demographic characteristics of the children such as gender, age, weight, clinical characteristics such as ASA scores, laboratory test results of venous blood samples taken during admission to the emergency department, length of hospital stay, and postoperative wound infection, abscess development, coagulation disorders, and transfusion data were obtained from the files and automation system of the patients and recorded in their patient follow-up forms.

Statistical Analysis

The descriptive statistics obtained from the research data were tabulated as mean ± standard deviation values in cases of continuous variables determined to conform to the normal distribution, as median, maximum and minimum values in cases of continuous variables determined not to conform to the normal distribution, and as numbers and percentage values in cases of categorical variables. The normal distribution characteristics of the numerical variables were analyzed with Anderson-Darling, Kolmogorov-Smirnov and Shapiro-Wilk tests.

In comparisons of two independent groups, the independent samples t-test was used in cases of numerical variables which conformed to the normal distribution, and the Mann-Whitney U test was used in cases of numerical variables which did not conform to the normal distribution. In comparisons of differences between categorical variables according to groups, Pearson's chi-squared test, Fisher's exact test and Fisher-Freeman-Halton test were used.

Univariate and multiple logistic regression analyses were used to determine those variables which can predict complicated appendicitis. Those variables with a p-value of less than 0.250 were further analyzed with a multivariate model.

The prognostic powers of the NLR, MLR, and CAR variables in differentiating complicated acute appendicitis from non-complicated appendicitis were analyzed using receiver operating characteristic (ROC) curve analysis. The optimal cut-off values of the variables which can be used to predict complicated appendicitis were determined with Youden's index using the DeLong method in MedCalc Statistical Software Trial version software, along with 95% confidence interval (CI) and area under the curve (AUC) values.

All other statistical analyses were performed using the Jamovi version 2.2.5.0 (The Jamovi Project, 2021) and JASP version 0.16.1 (JASP Team, 2022) software packages. The probability (p) statistics of ≤0.05 were deemed to indicate statistical significance.

Results

The mean age of the 473 patients who were admitted to the emergency department and diagnosed with acute appendicitis and who underwent surgical procedure by the pediatric surgery clinic, of whom 151 (31.9%) were female, and 322 (68.1%) were male, was 10.1±3.7 years. The rate of the patients with a body mass index score of ≥30 (obese) was 12.9%. Based on the histopathological data, it was determined that 179 (37.8%) patients had complicated and 294 (62.1%) had non-complicated appendicitis (Table I).

There were significant differences between the groups in terms of the preoperative laboratory test results of the patients (Table II). Accordingly, neutrophil counts (p<0.001), leukocyte counts (p<0.001), NLR (p=0.021), CRP levels (p<0.001) and CAR values (p<0.001) were significantly higher, whereas lymphocyte percentage and hemoglobin and serum sodium and albumin levels were significantly lower in those patients with complicated appendicitis compared to those with non-complicated appendicitis.

The mean length of hospital stay of the pediatric patients was 3 days (minimum 2 days-maximum 39 days). The rate of complication development in the postoperative period was 9.9%. Among patients with complicated and non-complicated appendicitis, with regards to operation time, length of hospital stay, wound infection, abscess development, coagulation disorders, and the need for transfusion, no significant difference was observed.

Table I. Demographic and clinical characteristics of patients

	Total (n=473)	Groups		p-value
		Complicated appendicitis (n=179)	Non-complicated appendicitis (n=294)	
Age (years)	10.1±3.7	9.3±3.8	10.5±3.6	**<0.001†**
Gender				
Male	322 (68.1%)	119 (66.5%)	203 (69.0%)	0.632*
Female	151 (31.9%)	60 (33.5%)	91 (31.0%)	
Weight (kg)	39.8±17.2	36.0±16.1	42.2±17.4	**<0.001†**
Obesity	61 (12.9%)	20 (11.2%)	41 (13.9%)	0.465*
ASA score				
I	362 (76.5%)	142 (79.3%)	220 (74.8%)	0.172*
II	100 (21.1%)	31 (17.3%)	69 (23.5%)	
III	11 (2.3%)	6 (3.4%)	5 (1.7%)	

Descriptive statistical values are mean ± SD or number of cases (%).
*: Pearson chi-squared, Fisher's Exact or Fisher-Freeman-Halton test, †: Independent Samples t-test
ASA: American Society of Anesthesiologists

Table II. Comparison laboratory parameters according to groups

	Groups		p-value
	Complicated appendicitis (n=179)	Non-complicated appendicitis (n=294)	
WBC count (X10^9/L)	17,633.0±5,569.2	15,374.7±4,948.0	**<0.001***
Neutrophil count (X10^9/L)	14.3±5.2	12.4±4.9	**<0.001‡**
Neutrophils %	81.9 [29.4-92.6]	81.3 [30.7-94.2]	0.663*
Lymphocyte count	1.7 [0.5-5.2]	1.7 [0.4-5.3]	0.555*
Lymphocyte %	9.8 [2.9-44.5]	11.2 [2.7-57.5]	0.008*
Neutrophil/Lymphocyte ratio	8.2 [1.1-30.4]	7.3 [0.5-35.0]	0.021*
Monocyte/Lymphocyte ratio	0.1 [0.0-1.0]	0.1 [0.0-1.0]	**<0.001***
Hemoglobin (g/dL)	12.8±1.1	13.1±1.3	0.021‡
Hematocrit (%)	37.8±2.9	38.3±3.4	0.070‡
Platelet count (X10^9/L)	314.0±81.8	306.1±76.2	0.298‡
PDW (fL)	10.2 [7.6-68.3]	10.5 [7.5-66.8]	0.149*
MPV (fL)	9.4 [7.1-12.9]	9.5 [6.8-13.1]	0.869*
MPV/Platelet ratio	0.0 [0.0-0.1]	0.0 [0.0-0.1]	0.352*
Procalcitonin	0.3 [0.1-0.6]	0.3 [0.1-0.5]	0.520*
Glucose (mg/dL)	105.0 [55.0-264.0]	105.0 [44.0-162.0]	0.582*
Sodium (mEq/L)	136.0 [126.0-143.0]	138.0 [129.0-144.0]	**<0.001***
Potassium (mEq/L)	4.1 [3.1-5.4]	4.2 [3.4-5.5]	0.056*
Chloride (mEq/L)	102.0 [86.0-110.0]	104.0 [94.0-111.0]	**<0.001***
Calcium (mEq/L)	9.4 [8.0-10.4]	9.4 [7.7-10.7]	0.462*
Protein (mg/dL)	7.1 [4.9-8.2]	7.2 [5.6-8.6]	0.016*
Albumin (mg/dL)	4.3 [2.7-5.2]	4.6 [3.0-5.4]	**<0.001***
BUN (mg/dL)	9.7 [3.3-45.3]	10.0 [2.5-35.0]	0.508*
Creatinine (mg/dL)	0.6 [0.4-1.1]	0.6 [0.5-1.0]	0.104*
Alanine aminotransferase (IU/L)	12.0 [5.0-60.0]	14.0 [5.0-381.0]	**0.001***
Aspartate aminotransferase (IU/L)	19.0 [8.0-58.0]	20.0 [7.0-210.0]	0.061*
Total bilirubin (mg/dL)	0.7 [0.2-3.5]	0.6 [0.1-3.3]	0.003*
Direct bilirubin (mg/dL)	0.3 [0.1-2.1]	0.3 [0.1-1.3]	**<0.001***
CRP (mg/dL)	7.9 [0.2-32.4]	1.4 [0.1-33.0]	**<0.001***
CRP/Albumin ratio	1.8 [0.0-12.0]	0.3 [0.0-7.7]	**<0.001***
Prothrombin time (min)	14.4 [11.1-23.4]	14.0 [11.3-26.5]	0.065*
INR	1.3 [1.0-2.0]	1.2 [1.0-2.3]	0.072*
Activated partial thromboplastin time (min)	30.3±3.6	30.4±3.4	0.709‡

Descriptive statistical values are mean ± SD or number of cases (%). Number values in square brackets are minimum and maximum values.
*: Mann-Whitney U test.
†: Pearson Chi-Squared, Fisher's Exact or Fisher-Freeman-Halton test.
‡: Independent Samples t-test.
WBC: White blood cell count, PDW: Platelet distribution width, MPV: Mean platelet volume, BUN: Blood urea nitrogen, CRP: C-reactive protein, INR: International Normalized Ratio, SD: Standard deviation

The results of the univariate logistic regression analysis indicated that age, leukocyte and neutrophil counts, MLR and CAR values, sodium, direct bilirubin, hemoglobin, and CRP levels were significantly correlated with complicated appendicitis ($p<0.05$). Further analysis of these variables with multivariate logistic regression analysis revealed that leukocyte count [odds ratio (OR): 1.01, 95% CI: 1.01-1.02, $p=0.005$], CAR value (OR: 0.64, 95% CI: 0.54-0.77, $p<0.001$), and sodium levels (OR: 1.22, 95% CI: 1.11-1.35, $p<0.001$) were independent risk factors for complicated appendicitis (Table III).

The diagnostic value of these variables in predicting complicated appendicitis was analyzed using ROC analysis. Accordingly, it was determined that NLR values of >6.52, MLR values of >0.09, and CAR values of >1.12 predicted the presence of complicated acute appendicitis (Table IV). Among these variables, CAR values of >1.12 had the highest AUC value and predicted complicated acute appendicitis with a specificity of 79.25% and a sensitivity of 66.48% (AUC=0.789, 95% CI: 0.749-0.825, $p<0.001$) (Figure 1). In addition to NLR values of >6.52, and CAR values of >1.12, serum sodium levels of ≤135 were found to be significantly associated with increased postoperative complication rates and prolonged lengths of hospital stay (Table V).

Table III. Regression analysis for variables of clinical and statistical significance for the prediction of complicated appendicitis

	Univariate logistic regression		Multivariate logistic regression	
	OR [95% CI]	**p-value**	**OR [95% CI]**	**p-value**
Age	1.10 [1.04-1.16]	**<0.001**	1.05 [0.98-1.13]	0.148
Hemoglobin	1.19 [1.02-1.39]	**0.028**	1.01 [0.81-1.25]	0.961
WBC count	1.01 [1-01-1-02]	**<0.001**	1.01 [1-01-1-02]	**0.005**
Neutrophil count	0.93 [0.89-0.96]	**<0.001**	-	-
NLR	0.98 [0.95-1.01]	0.121	1.03 [0.98-1.09]	0.225
MLR	0.03 [0-01-0.16]	**<0.001**	0.39 [0.01-10.69]	0.578
Sodium	1.39 [1.28-1.51]	**<0.001**	1.22 [1.11-1.35]	**<0.001**
Direct bilirubin	0.11 [0.03-0.37]	**<0.001**	0.26 [0.05-1.25]	0.092
CRP	0.85 [0.82-0.88]	**<0.001**	-	-
CRP/Albumin	0.51 [0.43-0.60]	**<0.001**	0.64 [0.54-0.77]	**<0.001**

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, WBC: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio

Table IV. ROC curve analysis results of some parameters for the prediction of complicated appendicitis

	AUC	Sensitivity	Specificity	Cut-off values	95% CI	p-value
NLR	0.563	66.48	45.92	>6.52	0.517-0.608	**0.018**
MLR	0.659	67.04	58.84	>0.09	0.615-0.702	**<0.001**
CRP/Albumin ratio	0.789	66.48	79.25	>1.12	0.749-0.825	**<0.001**

Area under the ROC curve, CI: Confidence interval, ROC: Receiver operating characteristic, AUC: Area under the curve, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, CRP: C-reactive protein

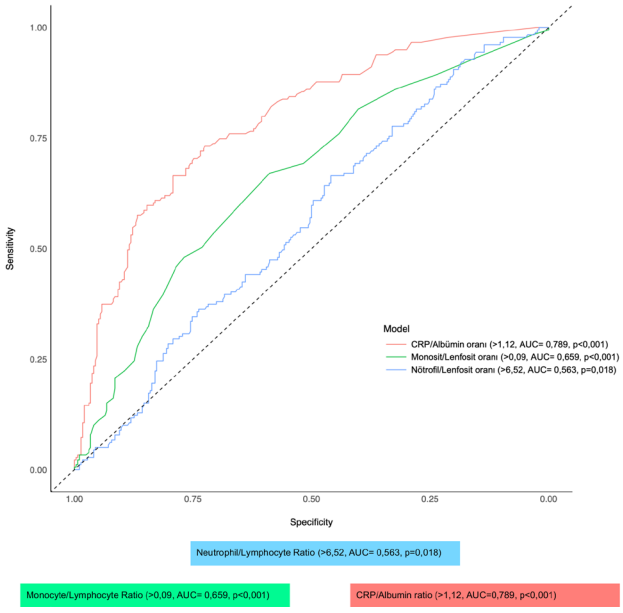

Figure 1. ROC curve analysis of NLR, MLR and CRP/Albumin ratio in the prediction of complicated acute appendicitis
ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, CRP: C-reactive protein

Table V. Relationship of ROC curve results with postoperative outcomes in the prediction of complicated acute appendicitis

	NLR >6.52	p-value	CRP/Albumin ratio >1.12	p-value
ICU stay (days)	1.24±1.17	**<0.013**	1.29±0.95	**<0.014**
Hospital stay (days)	5.09±4.62	**<0.01**	6.34±4.75	**<0.01**
Complication rate (%)	12.90	**0.005**	19.44	**<0.01**

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, ICU: Intensive care unit

Discussion

Among the variables investigated within the scope of this study, age, leukocyte counts and neutrophil counts were previously suggested as predictors for complicated appendicitis in pediatric patients (3,4). However, the findings of this descriptive, cross-sectional study indicated that complicated appendicitis was more common in younger age groups and that the rate of complicated appendicitis was significantly higher among acute appendicitis patients with higher leukocyte and neutrophil counts, NLR, CRP, CAR values, and lower sodium levels. Therefore, in addition to the commonly proposed predictors of age, leukocyte counts and neutrophil counts, the aforementioned parameters were determined as additional potential biomarkers of complicated appendicitis in the pediatric age group.

MLR, which has recently been started to be used in children, is an inflammatory marker associated with gastrointestinal and lymphoid pathologies. Hence, it has been suggested that the appendix, a lymphoid tissue located in the gastrointestinal tract, may be associated with MLR (15,16). As a matter of fact, there is evidence suggesting that MLR can be used in the diagnosis of pediatric acute appendicitis (17). Accordingly, it has been reported that MLR may be an independent predictor for complicated appendicitis. In parallel, given that increased monocyte expression is distinctive for complicated appendicitis, high MLR values have been indicated as a risk factor for complicated appendicitis (13).

CRP is an acute phase reactant mainly synthesized in liver hepatocytes. It is elevated in areas of infection or inflammation, and it plays an essential role in inflammation processes (18). CRP increase is associated with appendicitis complications such as perforation or appendix abscesses (19). CAR is a new prognostic parameter associated with the severity of inflammation. In this context, it was reported that CAR ≥1.39 might predict complicated appendicitis (20).

Stimuli such as hypovolemia, pain, nausea, vomiting and sequestration into the third space cause the release of non-osmotic vasopressin (ADH) from the posterior pituitary gland. Reabsorption of water by ADH binding to vasopressin-2 receptors in the kidney results in hyponatremia (21,22). In addition, cytokines such as IL-6 and IL-1β are associated with inflammatory conditions by taking a role in non-osmotic ADH secretion have been found to cause hyponatremia (21). Hyponatremia, which was determined to be significantly related to the level of inflammation in children, was also found to be associated with intra-abdominal sepsis, perforated appendicitis and perforated diverticulitis (23). Although the etiology of hyponatremia in appendicitis is still not clearly defined, it is thought that the processes mentioned above may be effective (24).

There are also studies which provided evidence on the use of hyponatremia as a predictor for complicated appendicitis. In a few of these studies, Pham et al. (4), Lindestam et al. (11), and Besli et al. (25) reported that sodium values of ≤135 mmol/L, ≤136 mmol/L, and ≤138 mmol/L, respectively, might predict complicated appendicitis. In a retrospective study including 1,283 pediatric patients, Walsh et al. (26) reported that serum sodium values of

<135 mmol/L predicted complicated appendicitis with a specificity of 95.7% and thus concluded that hyponatremia may be a distinctive indicator of complicated appendicitis. All these studies reveal the strong relationship between hyponatremia and complicated appendicitis in children. Similarly, serum sodium levels of ≤135 mmol/L significantly predicted complicated appendicitis in this study.

The relationship between complicated appendicitis and bilirubin levels is not as clear as with leukocytosis, CRP, and hyponatremia. Some studies reported that increased total serum bilirubin levels could be used as an indicator of perforated appendicitis in children, whereas others, e.g., Yang et al. (12), could not detect a significant relationship between perforated appendicitis and bilirubin levels (27). In fact, Bonadio et al. (28) stated that serum total bilirubin levels could not correctly distinguish those children with perforated appendicitis from those diagnosed with appendicitis. In contrast, our results of univariate logistic regression analysis reveal a significant correlation between direct bilirubin levels and the risk for complicated appendicitis.

Studies have shown that preoperative laboratory test results can be used to predict postoperative outcomes. With respect to this, it was reported that preoperative CRP values of >10 mg/dL predicted prolonged postoperative lengths of hospital stay, and preoperative NLR >10.5 and hyponatremia predicted the development of a postoperative intra-abdominal abscess in pediatric patients operated on for acute appendicitis (29-34). In addition, preoperative leukocyte counts and CRP levels have been reported as risk factors for postoperative adhesive bowel obstruction in children operated on for complicated appendicitis (35). It has also been reported that mean platelet volume and NLR can be used as biomarkers in order to reduce negative appendectomy rates (8). Furthermore, in an analysis of 35,291 pediatric patients who underwent appendectomy, hyponatremia was found to be significantly correlated with prolonged lengths of hospital stay and 30-day postoperative mortality risks (36). Additionally, NLR >6.52, CAR >1.12, and serum sodium levels of ≤135 mmol/L were found to be significantly correlated with prolonged lengths of hospital stay and postoperative complication rates in this study.

Ischemia-modified albumin (IMA), a marker used for the early detection of ischemia, has also been used in the diagnosis of pediatric appendicitis in recent studies. It was observed that the level of IMA, a protein, was higher in the complicated appendicitis group than in the control group (37,38). Pentraxin 3 (PTX3), which is an acute phase reactant, is another marker which can be used in the diagnosis of pediatric appendicitis. CRP blood values rise within 48 hours of the onset of inflammation, while PTX3 blood values rise within hours. Therefore, it is thought that PTX3 seems to be a more valuable marker (38). However, studies on IMA and PTX3 are few in the pediatric age group, and more studies are needed before they can be used as biomarkers.

Complicated appendicitis is reportedly more common in children and it is associated with higher morbidity and reoperation rates and longer lengths of hospital stay (3,4,6). The benefits of early appendectomy in pediatric perforated appendicitis cases include reduced morbidity and complication rates, shortened recovery times, reduced parental stress, and lower hospital costs (39). In a multicenter study conducted with pediatric non-perforated appendicitis cases, it was determined that each additional hour spent in an emergency department triage until appendectomy increased the perforation risk by 2%. Furthermore, it was stated that a delay of 12 hours would increase the perforation risk by approximately 25% (40). For this reason, it is vital to identify those children at risk of complicated appendicitis as early as possible, to make timely decisions about further examination and treatment, to improve perioperative care, and to take precautions by predicting any complications which may develop. In this way, the length of hospital stay can be shortened, and the related hospital costs can be reduced. In this respect, it is crucial to determine the biomarkers included in the laboratory tests which are the most easily accessible and the simple diagnostic tools used in the emergency room, the place where the patient is first intervened (9).

Study Limitations

Our study is a single-center study conducted only with pediatric patients. Its retrospective design and the number of patients are the limitations of this study. Another limitation of our study was the inability to exclude the presence of an undiagnosed inflammatory disease in the patients.

Conclusion

It is important to distinguish between complicated and non-complicated appendicitis early in children diagnosed with appendicitis in order to conduct further examinations and plan early treatment. Hence, there is a need for suitable biomarkers which can be measured simply and inexpensively within the scope of routine laboratory tests. Increased diagnostic efficiency in emergency departments will have positive effects on hospital costs as well. In addition to preoperatively measured neutrophil counts, leukocyte

counts, MLR, CAR values, CRP, sodium, and direct bilirubin levels may also be used as new biomarkers in predicting the risks of complicated appendicitis. Preoperative NLR, MLR, and CAR values may also provide information on postoperative outcomes.

Ethics

Ethics Committee Approval: The study protocol was approved by University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Surgery Training and Research Hospital, Clinical Research Ethics Committee (decision no: 621, date: October 10th, 2021).

Informed Consent: Informed consent was obtained from all of the patients' parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., Concept: C.S.Ö., K.E.Ş., Ö.A., Design: C.S.Ö., K.E.Ş., Data Collection or Processing: C.S.Ö., K.E.Ş., Analysis or Interpretation: Ö.A., Literature Search: C.S.Ö., Ö.A., Writing: C.S.Ö., K.E.Ş.

Conflict of Interest: The authors have no conflict of interest to declare.

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References

1. Ferris M, Quan S, Kaplan BS, et al. The Global Incidence of Appendicitis: A Systematic Review of Population-based Studies. Ann Surg 2017; 266:237-41.
2. Kharbanda AB, Stevenson MD, Macias CG, et al. Interrater reliability of clinical findings in children with possible appendicitis. Pediatrics 2012; 129:695-700.
3. Feng W, Zhao XF, Li MM, Cui HL. A clinical prediction model for complicated appendicitis in children younger than five years of age. BMC Pediatrics 2020; 20:401.
4. Pham XBD, Sullins VF, Kim DY, et al. Factors predictive of complicated appendicitis. J Surg Res 2016; 206:62-6.
5. Gerall CD, DeFazio JR, Kahan AM, et al. Delayed presentation and sub-optimal outcomes of pediatric patients with acute appendicitis during the COVID-19 pandemic. J Pediatr Surg 2021; 56:905-10.
6. Troester AM, Utria AF, Goffredo P, Cho E, Zhou P, Hassan I. Pediatric Appendectomy: an Analysis of 22,334 Cases from the Pediatric National Surgical Quality Improvement Program Data. J Gastrointest Surg 2021; 25:523-5.
7. Ingram MC, Harris CJ, Studer A, et al. Distilling the key elements of pediatric appendicitis clinical practice guidelines. J Surg Res 2021; 258:105-12.
8. Almaramhy HH. Acute appendicitis in young children less than 5 years: review article. Ital J Pediatr 2017; 43:15.
9. Hodge SV, Mickiewicz B, Lau M, Jenne CN, Thompson GC. Novel molecular biomarkers and diagnosis of acute appendicitis in children. Biomark Med 2021; 15:1055-65.
10. Begic-Kapetanovic S, Avdagic N, Zaciragic A, Hasic S, Babic N, Hadzimuratovic A. Could the neutrophil-to-lymphocyte ratio serve as a marker in the diagnosis and prediction of acute appendicitis complications in children? Arch Med Sci 2021; 17:1672-8.
11. Lindestam U, Almström M, Jacks J, et al. Low plasma sodium concentration predicts perforated acute appendicitis in children: A prospective diagnostic accuracy study. Eur J Pediatr Surg 2020; 30:350-6.
12. Yang J, Liu C, He Y, Cai Z. Laboratory Markers in the Prediction of Acute Perforated Appendicitis in Children. Emerg Med Int 2019; 2019:4608053.
13. Nissen M, Tröbs RB. The lymphocyte-to-monocyte ratio may distinguish complicated from non-complicated pediatric appendicitis: A retrospective study and literature review. Pediatr Neonatol 2022; 63:146-53.
14. Feng W, Yang QY, Zhao XF, Li MM, Cui HL. The use of the ratio of C-reactive protein to albumin for the diagnosis of complicated appendicitis in children. Am J Emerg Med 2022;52:148-54.
15. Yuan Y, Liu J, Zhou Y, et al. The relationship between monocyte-to-lymphocyte ratio and the risk of gastrointestinal system involvement in children with IgA vasculitis: A preliminary report. Adv Clin Exp Med 2021; 30:999-1005.
16. Tezol O, Bozlu G, Sagcan F, Daloglu FT, Citak C. Value of neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio and red blood cell distribution width in distinguishing between reactive lymphadenopathy and lymphoma in children. Bratisl Lek Listy 2020; 121:287-92.
17. Duman L, Karaibrahimoğlu A, Büyükyavuz Bİ, Savaş MÇ. Diagnostic value of monocyte-to-lymphocyte ratio against other biomarkers in children with appendicitis. Pediatr Emerg Care 2022; 38:739-42.
18. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at sites of inflammation and infection. Front Immunol 2018; 13:754.
19. Sack U, Biereder B, Elouahidi T, Bauer K, Keller T, Tröbs RB. Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. BMC Surg 2006; 6:6:15.
20. Hou J, Feng W, Liu W et al. The use of the ratio of C-reactive protein to albumin for the diagnosis of complicated appendicitis in children. Am J Emerg Med 2022;52:148-54.
21. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr 2013; 56:519-22.
22. Peri A, Thompson CJ, Verbalis JG. Disorders of Fluid and Electrolyte Metabolism. Focus on Hyponatremia. In: Mohottige D, Lehrich RW, Greenberg A (eds). Hypovolemic Hyponatremia Front Horm Res. Basel, Karger, 2019;93-103.
23. Alsaleh A, Pellino G, Christodoulides N, Malietzis G, Kontovounisios C. Hyponatremia could identify patients with intrabdominal sepsis and anastomotic leak after colorectal surgery: a systematic review of the literature. Updates Surg 2019; 71:17-20.
24. 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.

25. Besli GE, Çetin M, Durakbaşa ÇU, Özkanlı Ş. Predictive value of serum sodium level in determining complicated appendicitis risk in children. Haydarpasa Numune Med J 2019; 59:35-40.

26. Walsh A, Lala S, Wells C, Upadhyay V. Hyponatremia an indicator of complicated appendicitis in children: Starship experience. ANZ J Surg. ANZ J Surg 2022; 92:747-52.

27. 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.

28. Bonadio W, Bruno S, Attaway D, Dharmar L, Tam D, Homel P. Lack of utility of measuring serum bilirubin concentration in distinguishing perforation status of pediatric appendicitis. Am J Emerg Med 2017; 35:885-8.

29. Mizrahi N, Samuk I, Ashkenazi S, Chodick G, Freud E, Livni G. Pediatric complex appendicitis are there predictors of postoperative outcomes. Arch Pediatr Surg 2019; 3:53-8.

30. Chen CL, Chao HC, Kong MS, Chen SY. Risks factors for prolonged hospitalization in pediatric appendicitis patients with medical treatment. Pediatr Neonatol 2017; 58:223-8.

31. Obayashi J, Ohyama K, Manabe S, et al. Are there reliable indicators predicting postoperative complications in acute appendicitis? Pediatr Surg Int 2015; 31:1189-93.

32. Obinwa O, Peirce C, Cassidy M, Fahey T, Flynn J. A model predicting perforation and complications in paediatric appendicectomy. Int J Colorectal Dis 2015; 30:559-65.

33. Miguel CD, Serrano AJM, Nunez V, et al. Neutrophil-to-lymphocyte ratio as a predictor of postsurgical intraabdominal abscess in children operated for acute appendicitis. Front Pediatr 2019; 7:424.

34. Serradilla J, Bueno A, De la Torre C, et al. Predictive factors of gangrenous post-appendectomy intra-abdominal abscess. A case-control study. Cir Pediatr 2018; 31:25-8.

35. Feng W, Du XB, Zhao XF, Li MM, Cui HL. Risk factors of postoperative adhesive bowel obstruction in children with complicated appendicitis. Pediatr Surg Int 2021; 37:745-54.

36. Benzon HA, Bobrowski A, Suresh S, Wasson NR, Cheon EC. Impact of preoperative hyponatraemia on paediatric perioperative mortality. Br J Anaesth 2019; 123:618-26.

37. Ulusoy E, Çitlenbik H, Akgül F, et al. Is ischemia-modified albumin a reliable marker in accurate diagnosis of appendicitis in children? World J Surg 2020; 44:1309-15.

38. Falchi D, Bakır AC, Risteski T, et al. Diagnostic value of the ischemia modified albumin and pentraxin 3 in pediatric appendicitis: A meta analysis. J Clin Trials Exp Investig 2022; 1:1-9.

39. Howell EC, Dubina ED, Lee SL. Perforation risk in pediatric appendicitis: assessment and management. Pediatric Health Med Ther 2018; 9:135-45.

40. Meltzer JA, Kunkov S, Chao JH, et al. Association of delay in appendectomy with perforation in children with appendicitis. Pediatr Emerg Care 2019; 35:45-9.