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Prediction of complicated appendicitis risk in children

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Abstract. – OBJECTIVE: We aimed to predict the risk of complicated appendicitis in children, constructing a risk-based prediction tool with the optimal combination of sensitivity and specificity outcomes.

PATIENTS AND METHODS: This is a prospective study on a random sample of children with acute appendicitis who underwent appendectomy. Clinical examination, history, routine laboratory tests, Alvarado and pediatric appendicitis scores, operative and histopathological findings were taken into consideration. The predictive ability of the outcome variables was assessed by the Receiver Operating Characteristics (ROC) analysis. The overall predictive ability and determination of the best cut-off value (the higher sum of sensitivity plus specificity) were calculated. A Classification and Regression Tree (CRT) was used to create a multi-level classification algorithm. The model was set to predict the outcome of complicated appendicitis, considering as potential predictors the demographic characteristics, the clinical findings, and the outcome parameters.

RESULTS: The various combinations of clinical and laboratory parameters did not improve their overall diagnostic ability. However, the CRT analysis resulted in a short classification algorithm based on the Pediatric appendicitis score, neutrophils percentage and the CRP. This model yielded a significantly better predictive ability than all the other combinations of the outcome parameters. The application of the model would predict complicated appendicitis with 90% sensitivity and 78.6% specificity.

CONCLUSIONS: The constructed predictive model may be a useful tool for daily practical use by the clinician, especially in areas where modern diagnostic imaging facilities are absent or not always available. Clinical evaluation and close follow-up remain the more accurate preoperative method to decide the performance and timing of appendectomy.

Key Words:
Complicated appendicitis, Risk prediction, Classification and regression tree, Pediatric appendicitis score.

Introduction

Appendicitis is the most common cause of acute abdomen. One third of the patients are children, and they present a higher frequency of complications compared to adults[1-4]. Early detection is important, as timely treatment affects the prognosis.

Children often present atypical symptoms[5,6]. Those under the age of five years cannot cooperate adequately or provide accurate clinical information[2,7]. False or delayed diagnosis range from 5.9% to 84%, resulting to complication rates from 5% to 51%[8-12]. Incidence of perforated appendicitis is reported up to 100% in children younger than three years old[13-15]. On the other hand, overdiagnosis and unnecessary excision of a healthy appendix is an opposite undesired reality, despite the helping aids of screening ability with ultrasonography and computed tomography[16,17].

Diagnosis of acute appendicitis is based primarily on clinical examination. The contribution of laboratory and imaging methods is considerable. However, it is often difficult to discriminate

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complicated cases in the pediatric population. Thus, the definition and discrimination of a complicated appendicitis is a field of controversy among researchers[18-21].

In the present study we aimed to evaluate the complication risk in a cohort of children with appendicitis. We assessed clinical scoring systems and laboratory examinations, operative findings, and histopathology. We combined parameters for the construction of a risk-based prediction tool that could be helpful along with the optimal combination of the sensitivity and specificity outcomes.

Patients and Methods

Study Population and Outcomes

This is a prospective study on a random sample of children with acute appendicitis. The participants underwent appendectomy between January 1st and December 31st, 2020. The standard approach on admission, included history, physical examination, and routine laboratory tests. Pediatric Appendicitis[22] (PA) and the Alvarado[23] (AL) scores were performed in all participants. Patients younger than four years of age, those with chronic disorders (respiratory, cardiovascular, renal, etc), haematological diseases or malignancies, and those who received antibiotics prior to hospital admission as well, were not included in the study. Patients without postoperative histopathological evidence of acute appendicitis were also excluded from the study. The study was approved by the Bioethics Committee of the University of Patras. Informed consent was obtained from the patients' parents prior to their enrolment.

The stage of appendicitis was initially asserted by macroscopic inspection during surgery. The macroscopic examination was confirmed by histological findings in all the cases of the study. The laparoscopic grading system of acute appendicitis was adopted for the definition of complicated cases[24]. This grading system correlates the macroscopic appearance with the histopathological examination and the biochemical analysis of the peritoneal fluid. The resulting score includes normal looking appendix (grade 0), hyperaemia and oedema (grade 1), fibrinous exudate (grade 2), segmental necrosis (grade 3A), base necrosis (grade 3B), abscess (grade 4A), regional peritonitis (grade 4B), and diffuse peritonitis (grade 5)[24]. Grades 1-2 were characterized as non-complicated appendicitis, while grades 3-5 as complicated[24,25]. Patients with grade 0 were not included in the study, as we intended to focus exclusively on patients with pathology. The predictive tool we created, aimed to compare complicated with non-complicated forms of an existing appendicitis.

The outcome variables were PA and AL scores, white blood cell count (WBC) (10^3/μL), neutrophil count (10^3/μL), neutrophils (%) and C-reactive protein (CRP) (mg/dl). The variables were assessed as separate or in combination for predicting complicated appendicitis.

Statistical Analysis

All statistical analyses were performed using the SPSS Statistical Software Package version 25 (IBM Corp., Armonk NY, USA). *p*-values less than 0.05 were considered statistically significant.

Numerical variables were expressed as mean ± SD or number of cases (%). Continuous variables were tested with *t*-test while categorical variables with chi-square test. The predictive ability of the outcome variables was assessed by the Receiver Operating Characteristics (ROC) analysis, including a calculation of the Area Under the Curve (AUC; overall predictive ability) and the determination of the best cut-off value (higher sum of sensitivity plus specificity). Positive and negative likelihood ratios (LRs) for each cut-off value were also calculated. The same cut-offs were used when more than one outcome variables were combined.

A Classification and Regression Tree (CRT) was used to create a multi-level classification algorithm[26]. A CRT model consists in successive binary splits, starting from the predictor that yields the best classification of the data (based on LRs). Subsequently, an additional split is added within each branch, based on a second predictor that improves the initial classification. The splitting process continues until no other predictors can further improve the classification. The model was set to predict the outcome of complicated appendicitis, considering (as potential predictors) the demographic characteristics (sex, age, weight, height, body mass index), the clinical findings (presence and height of fever, relevant symptoms, and signs), and the outcome parameters (PA and AL scores, WBC, neutrophil count, neutrophils % and CRP).

Table I. Characteristics of the study groups.

	Uncomplicated appendicitis	Complicated appendicitis	p
N	42	30	
Age (years)	10.8 ± 2.4	10.4±3.0	0.449
Weight (kg)	41.5 ± 13.4	41.2±15.7	0.932
Height (cm)	151.5 ± 13.7	148.7±19	0.467
BMI (kg/m^2)	17.6 ± 3.6	17.9±3.2	0.515
RLQ tenderness	41 (97.6)	30 (100)	0.583
Excessive RLQ tenderness*	21 (50)	19 (63.3)	0.262
Pain migration	18 (42.9)	14 (46.7)	0.748
Anorexia	31 (73.8)	25 (83.3)	0.338
Nausea/emesis	28 (66.7)	27 (90)	0.022
Temperature max (ºC)	37.3±0.8	38.0 ± 0.7	< 0.001
WBC (10^3/μL)	14.0±3.5	16.0 ± 4.2	0.017
Neutrophil count (10^3/μL)	11±3.6	13.5 ± 3.9	0.007
Neutrophils %	77.6 ± 8.8	83.6 ± 4,6	< 0.001
Hb (g/dL)	12.96 ± 1.02	12.93 ± 1.18	0.685
CRP (mg/dL)	3.4 ± 4.6	6.9 ± 5.9	0.015
Pediatric appendicitis score	6.6 ± 1.6	8.1 ± 1.6	< 0.001
Alvarado score	7.2 ± 1.5	8.6 ± 1.3	< 0.001

Values are mean ± SD or number of cases (%). Comparisons were performed with t-test (continuous variables) or chi-square test (categorical variables). *Cough, percusion or rebound tenderness. BMI: body mass index, RLQ: right lower quadrant, WBC: white blood cell count, Hb: hemoglobin, CRP: C-reactive protein.

Results

A total of 72 patients were included in the study (43 males, age range 7.0-13.5 years). Forty-two patients (58.3%) were classified with non-complicated appendicitis, whereas 30 of them (41.7%) with complicated appendicitis. The general characteristics of the two groups and the outcomes of interest are presented in Table I. Those with complicated appendicitis had a higher body temperature at presentation, higher PA and AL scores, and higher WBC, neutrophil count, neutrophils % and CRP (Table I).

The diagnostic characteristics of each of the outcome parameters are presented in Table II. The PA and AL scores had the higher AUC values among the tested variables (0.767 and 0.768, respectively). However, a PA score >7 resulted in a better combination of sensitivity and specificity, as compared with the AL score. The AUCs of neutrophil count (0.717) and neutrophils % (0.742) were also comparable, although they yielded poorer sensitivity-specificity combinations than the PA and AL scores. The predictive ability of WBC and CRP was lower (Table II).

The various combinations of clinical and laboratory parameters did not improve their overall diagnostic ability (Table III). The combination of PA or AL score >7, neutrophil count >10.1 10^3/μL and CRP >7.1 mg/dL yielded excellent sensitivity (96.7%) but at the price of a very low specificity (31%); as a result the AUC of both combinations was low (Table III).

Table II. Diagnostic characteristics of clinical and laboratory parameters for predicting complicated appendicitis.

	Criterion	Sensitivity %	Specificity %	+ LR	– LR	AUC (95% CI)
Pediatric appendicitis score	> 7	73.3	76.2	3.08	0.35	0.767 (0.652-0.858)
Alvarado score	> 7	83.3	59.5	2.06	0.28	0.768 (0.654-0.860)
WBC	> 14.7 10^3/μL	63.3	69	2.05	0.53	0.666 (0.545-0.773)
Neutrophil count	> 10.1 10^3/μL	90	53.4	1.89	0.19	0.717 (0.598-0.817)
Neutrophils %	> 82 %	70	71.4	2.45	0.42	0.742 (0.625-0.838)
CRP	> 7.1 mg/dL	50	83.7	3.5	0.58	0.669 (0.548-0.775)

Cut-off values were determined based on the best sensitivity-specificity combination (ROC analysis). ROC: receiver operating characteristics, LR: likelihood ratio, AUC: area under the (ROC) curve, WBC: white blood cell count, CRP: C-reactive protein.

Table III. Diagnostic characteristics of various combinations of clinical and laboratory parameters.

	Sensitivity %	Specificity %	+ LR	– LR	AUC (95% CI)
PAS + laboratory					
PAS + WBC	83.3	57.1	1.9	0.29	0.702 (0.580-0.824)
PAS + Neutrophils %	93.3	50	1.9	0.13	0.717 (0.599-0.835)
PAS + Neutrophil count	96.7	40.5	1.6	0.08	0.686 (0.564-0.807)
PAS + CRP	76.7	64.3	2.1	0.36	0.705 (0.582-0.828)
PAS + WBC + CRP	86.7	45.2	1.6	0.29	0.660 (0.534-0.785)
PAS + Neutrophils % + CRP	93.3	42.9	1.6	0.16	0.681 (0.558-0.803)
PAS + Neutrophil count + CRP	96.7	31	1.4	0.11	0.638 (0.512-0.765)
AlvS + laboratory					
AlvS + WBC	90	50	1.8	0.20	0.700 (0.579-0.821
AlvS + Neutrophils %	93.3	42.9	1.6	0.16	0.681 (0.558-0.803)
AlvS + Neutrophil count	96.7	38.1	1.6	0.09	0.674 (0.551-0.797)
AlvS + CRP	83.3	50	1.7	0.33	0.667 (0.541-0.792)
AlvS + WBC + CRP	90	40.5	1.5	0.25	0.652 (0.526-0.778)
AlvS + Neutrophils % + CRP	93.3	38.1	1.5	0.18	0.657 (0.531-0.782)
AlvS + Neutrophil count + CRP	96.7	31	1.4	0.11	0.638 (0.512-0.765)
Only laboratory					
WBC + CRP	30	100	∞	0.70	0.650 (0.515-0.785)
Neutrophils % + CRP	40	100	∞	0.60	0.643 (0.508-0.777)
Neutrophil count + CRP	46.7	97.6	19.6	0.55	0.705 (0.575-0.834)
CRT model					
(PAS - Neutrophils % - CRP)	90	78.6	4.2	0.13	0.843 (0.746-0.940)*

Cut-off values: PAS: > 7, AlvS: > 7, WBC: > 14.7 10^3/μL, Neutrophil count: > 10.1 10^3/μL, Neutrophils % > 82%, CRP: > 7.1 mg/dL.*Significantly higher (p-values between < 0.001 and 0.012) compared to all other combinations. PAS: pediatric appendicitis score, AlvS: Alvarado score, WBC: white blood cell count, CRP: C-reactive protein, CRT: classification and regression tree, LR: likelihood ratio, AUC: area under the (ROC) curve.

The CRT analysis resulted in a short classification algorithm based on the PA score, neutrophils % and CRP (Figure 1, **Supplementary Figure 1**). This model yielded an AUC of 0.843, significantly better than all combinations of the outcome parameters (Table III). The application of the model would predict complicated appendicitis with 90% sensitivity and 78.6% specificity, which again outperformed the sensitivity-specificity combination of all other parameters (Table III). A simplified version of the algorithm, outlining the steps of the two paths in a manner facilitating its clinical use, is shown in Figure 1.

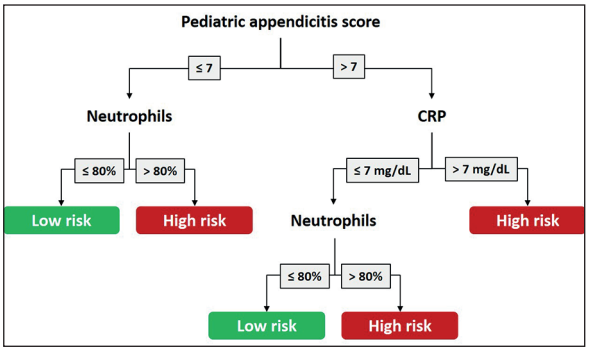

Figure 1. Classification and Regression Tree model for assessing the risk of complicated appendicitis.

Discussion

We investigated the prognostic value of clinical scoring systems and routinely used biomarkers in a cohort of children with appendicitis. An initial horizontal approach resulted in the determination of sensitivity and specificity cut-off values for each studied parameter, independently or combined with others. These parameters were incorporated in a CRT algorithm, in which the risk of complication was calculated in a stepwise manner, meaning that the effect of each parameter was appreciated separately, according to the importance of its contribution to the final model[26]. Overall, the algorithm resulted in low risk of false-negative results, while its stepwise configuration could also permit its application only up to a specific level, being however aware of the risk of false-negative results at this step.

The prognosis of complicated appendicitis is important, as it affects disease outcome and

treatment planning. Appendectomy was considered as a surgical topic of high emergency in the past. However, non-operative treatment for non-complicated appendicitis is an option that has gained much ground during the last decade. There is research supporting that non-operative management using antibiotic therapy only, is feasible for pediatric patients[27-32]. Recent international guidelines[32] recommend non-operative management for non-complicated appendicitis as safe and effective, not only for adults, but for children too, except for cases where an appendicolith is present.

Biomarkers have been used to support decision making. Inclusion of routinely used biomarkers in prediction models, such as WBC, neutrophils, CRP, has been studied[2,33-40]. Some of them were included in clinical scoring systems, such as the AL and the PA scores. Others, such as bilirubin, procalcitonin, calprotein, haptoglobin, interleukin-8, serum urokinase-type plasminogen activator receptor, and neutrophil gelatinase-associated lipocalin as well, are not used as frontline tests in the microbiology departments of most hospitals[4,36,41-44].

Diagnostic accuracy, sensitivity, and specificity of biomarkers, alone or in combination with others, or with clinical parameters, present variations. They may contribute to the diagnosis and in staging of appendicitis. Nevertheless, they cannot give straightforward answers to discriminate complicated appendicitis. There is often disagreement between researchers on this topic, especially regarding younger patients[36]. Zani et al[37] found that children under the age of five years did not present statistically significant differences of CRP, between non-complicated and complicated cases. On the contrary, Zouari et al[45] highlighted the value of CRP over 10 mg/L as a strong predictor of acute appendicitis in children under the age of six years.

Imaging methods, though of great importance in the diagnosis and staging of appendicitis, present limitations, and disadvantages[46-48]. It is well known that diagnosis with ultrasonography is strongly dependent on the experience of the operator and the analytic capacity of the method. Furthermore, ultrasonography is not always available for clinicians in primary-care hospitals, in small locations, on a continuous basis, or in low-income countries. By creating a diagnostic tool based on clinical presentation and on a minimum of biomarkers, we aimed to minimize the diagnostic failure risk especially for the clinicians who serve under these conditions.

Computed tomography must be applied with caution in children, due to the exposure to radiation. It is noteworthy that despite their large-scale use, imaging procedures have not changed the complication rate of acute appendicitis. Lee et al[13] reported that the perforation rate of 51% in children of five years and younger, was comparable to previously reported rates of 54% to 74% over the last three decades.

The use of applied mathematics in clinical diagnosis is not a novelty. Both AL and PA scores are based on statistical analysis (regression modelling) and proved to be useful tools for the first line clinician[22,23]. To our knowledge, this is the first time that CRT methodology has been used for the discrimination of complicated appendicitis on admission. We have recently applied this risk-based approach, evaluating the risk of heterotopy in children with Meckel's diverticulum[49]. Decision trees are superior to regression modelling when the relationship between features and outcome is nonlinear or when features interact with each other[50]. The parameters included in a CRT model attain their maximum predictive ability only within the decision "path" of the model[50]. Indeed, the decision tree of our study resulted in the best combination of sensitivity and specificity, overcoming all clinical and laboratory combinations taken into consideration (Table III).

Limitations

Inevitably, our study has some limitations. Firstly, the study population is small. Thus, although our sample was sufficient for a pilot, proof-of-concept study, further research is required to confirm the validity of our model in a larger population, ideally through a multicenter approach. Secondly, we must take in consideration that the age selection criteria resulted in outcomes representative of a population of the age between 8-13 years, excluding younger children (e.g., under 5 years) where complicated appendicitis is more prevalent. Finally, the definition of "low risk" cases in our CRT model was rather arbitrary. The left "path" of the model (i.e., PA $\leq$7 and neutrophils $\leq$80%, Figure 1) resulted in 7.1% false-negative cases (i.e., cases falsely predicted as uncomplicated), while the middle path (PA >7, CRP $\leq$7 mg/dL, and neutrophils $\leq$ 80%, Figure 1) in 12.5% false-negative cases. However, both percentages are at the lower levels found in literature regarding the prognosis of complicated appendicitis[8-12,18-21].

Conclusions

In this study, the use of a decision-tree (CRT) analysis for the prognosis of complicated appendicitis in children, resulted in a combination of high sensitivity and specificity, and balanced percentages of false-negative and false-positive results. Our predictive model may thus be a useful tool for daily practical use by the clinician, especially in areas where modern diagnostic imaging facilities are absent or without permanent availability. Once the high risk for complicated appendicitis has been identified, treatment may be of a more aggressive character in terms of antibiotic regimen, preoperative measures, clinical vigilance, and timing of operation. Low risk outcome may give the clinician the option to consider a more conservative approach. Clinical evaluation remains the most accurate preoperative method to decide on the performance and timing of appendectomy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed consent was obtained from the parents of all individual participants included in the study.

Ethics

The study was approved by the Bioethics Committee of the University of Patras. The planning conduct and reporting of human research are in accordance with the Declaration of Helsinki.

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