The predictors of perforated appendicitis in the pediatric emergency department: A retrospective observational cohort study

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ABSTRACT

Objective: Appendiceal perforation has significant effects on perioperative morbidity and postoperative outcome. The present study aimed to identify possible predictive factors associated with perforated appendicitis (PA) in children at admission in the emergency department (ED).
Methods: In this retrospective observational cohort study, consecutive medical records of children <18 years old with surgically and histopathologically confirmed acute appendicitis (AA) over three years (2013–2015) were analyzed. Patients were divided into two groups: PA and non-perforated appendicitis (NPA). The differences between the two groups and potential predictors of PA were explored using univariate and multivariate analyses.
Results: During the study period, 295 patients underwent an appendectomy and had confirmatory AA diagnoses. Ninety-two patients had a PA (31.2%). In the univariate analysis, male gender, vomiting, diarrhea, fever, elevated white blood cell count (WBC) levels, and high C-reactive protein (CRP) were identified as predictors of PA. In the multivariate analysis, male gender (odds ratio [OR]: 3.133; 95% confidence interval [CI]: 1.610–6.096); vomiting (OR: 2.346; 95% CI: 1.141–4.822); diarrhea (OR: 4.549; 95% CI: 1.850–11.181); fever (OR: 3.429; 95% CI: 1.765–6.663); elevated WBC (OR: 2.962; 95% CI: 1.491–5.884) and elevated CRP (OR: 3.061; 95% CI: 1.267–7.396) were variables that predicted the PA in children.
Conclusion: Our data indicate that several clinical and biochemical parameters can reliably distinguish between pediatric PA and NPA at admission in the emergency department.

1. Introduction

Acute appendicitis (AA) is the most common abdominal surgical emergency in the pediatric and adult population, with an estimated lifetime risk of 9% in boys and 7% in girls and with the lifetime risk of appendectomy of 12% for males and 23% for females [1,2]. AA typically affects children and adolescents aged 10 to 20 years, but no age is exempt [2]. AA is uncommon in pre-school children and is often diagnosed at the perforated stage (perforated appendicitis, PA) [3]. Pediatric PA rates are ~30% but can be much higher for younger children [4,5]. Compared with non-perforated appendicitis (NPA), PA has a significant effect on the postoperative outcome, increasing the rate of complications (up to 39%) such as abdominal/pelvic abscess, bowel obstruction, and wound infections [6,7]. Increased morbidity in these patients also affected the hospital length and greater resource utilization [8]. Therefore, an accurate preoperative diagnosis of perforation is of utmost importance to enable earlier operative treatment and reduce the overall morbidity.

Previous studies have identified potential predictors of PA, including a delay in surgery [9-11], male gender [12], younger children [4,5], older adults [12], appendicoliths [13], comorbidities [14], neutrophil ratio [15], *fever, anorexia, diarrhea, and* imaging exams alterations [16]. However, prehospital or intrahospital factors that predict PA have been inconsistently identified, with the contradictory data in the current literature [17].

Table 1
White blood cell (WBC) count reference values for pediatric population (adopted from [19]).

Age	WBC x 10^9/L
6 months to 2 years	6.0–17.5
2–3 years	6.0–17.0
4–5 years	5.5–15.5
6–7 years	5.0–14.5
8–15 years	4.5–13.5
16–17 years	4.5–13.0

The present study aimed to identify factors predicting PA at admission in the pediatric emergency department (ED), comparing baseline demographic, clinical symptoms, and simple and readily available serum inflammatory markers of patients with PA and NPA.

2. Patients and methods

In this retrospective observational cohort study, consecutive medical records of children <18 years old with surgically and histopathologically confirmed AA over three years (2013–2015) were reviewed, including their medical histories, laboratory and diagnostic test results, physical examination, clinical and treatment notes.

All patients were classified into two groups as the PA group and the NPA group. The eligibility criteria were grossly positive and microscopically confirmed appendicitis. Patients were excluded when the removed appendix was not inflamed ($n = 15$).

Diagnoses were classified according to the World Health Organization International Classification of Diseases, version 9 and 10 (ICD-9 and ICD-10). The presence of fever was based on the history of fever and defined as the axillary temperature > 37.2 °C and rectal temperature > 38 °C. A C-reactive protein (CRP) level > 10 mg/dL was considered high [18]. A total white blood cell count (WBC) was considered elevated according to the age groups and cutoff values defined by Pediatric CBC Reference Values (LTR10211) (Table 1) [19].

Operative findings were classified as NPA and PA. PA was defined by a visible hole in the appendix or an appendicolith free within the abdominal cavity as well as the presence of purulent fluid (gross contamination) within the peritoneal cavity. Histological perforation was defined as a perforation confirmed by the microscopic analysis.

All patient medical records were de-identified and anonymized for the current study. This study was approved by the local institutional review board (Ethical Committee of the Clinical Center, University of Sarajevo, Number: 0901–27,723). However, the IRB waived the informed consent due to the retrospective nature of the study.

2.1. Statistical analysis

Univariate analysis was performed by comparing PA and NPA characteristics using the Mann-Whitney *U* test for numeric variables and the Fisher exact test for categorical variables. All variables in the univariate test were included in the multivariable analyses using multivariable logistic regression analysis to create a model to predict appendiceal perforation. For logistic regression analysis, the stepwise backward model was applied. *P*-values <0.05 were considered statistically significant for all statistical calculations. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) IBM Version 26 (SPSS) (UNICOM Systems, Inc.).

3. Results

During the study period, 295 patients underwent an appendectomy and had confirmatory appendicitis by histopathologic examination. Among them, 172 patients (58.3%) were male. The overall male-to-female ratio was 1.39:1. PA was found in 92 patients (31.2%). Male patients had PA significantly more frequently than females (p˜0.001). Perforation was commonly seen in young children (<5 years) with a perforation rate of 50%. There was a significant difference in the number of PA patients per age group (Table 2).

Univariate analysis of variables that may serve as possible predictors of PA, conducted between the groups (PA and NPA), is shown in Table 3. We observed a significant difference between the two groups in gender presence, vomiting, diarrhea, fever, CRP count, and WBC (Table 3). Together with the variable age below five years, these variables were entered into the initial logistic regression model. The final model included male gender, age below five years, vomiting, diarrhea, fever, WBC, and CRP (Table 4) and was characterized by a Nagelkerke R-square value of 0.441 and Hosmer and Lemeshow goodness of fit with a Chi-square value of 8.128 and a *P*-value of 0.421. This model accurately classifies 78.2% of cases. Multivariate analysis revealed that the factors significantly associated with PA were male gender (odds ratio [OR]: 3.133; 95% confidence interval [CI]: 1.610–6.096); vomiting (OR: 2.346; 95% CI: 1.141–4.822); diarrhea (OR: 4.549; 95% CI: 1.850–11.181); fever (OR: 3.429; 95% CI: 1.765–6.663); elevated WBC (OR: 2.962; 95% CI: 1.491–5.884) and elevated CRP (OR: 3.061; 95% CI: 1.267–7.396).

4. Discussion

This study revealed that patients' main demographic and clinical characteristics and commonly used laboratory tests might reliably distinguish between the NPA from PA in pediatric patients admitted to ED.

Due to the inadequate information flow with concerned parents about their children's medical history, age-related communication difficulties with sick children, and often highly atypical and nonspecific clinical presentations, PA diagnosis in children is often very challenging on admission to pediatric ED. In contrast to the numerous studies that have focused on predictors of AA [20-22], there is a relative scarcity of studies exploring the differential diagnosis (PA vs. NPA) in children.

Consistent with the previous studies [2,23-25], we also found a slight male predominance among pediatric patients with AA. Additionally, our study's PA rates were much higher in males (73.9%) (p˜0.001). This finding is consistent with a study by Guss et al., who also reported that PA's rate was significantly higher among males than females [26]. PA occurred was also substantially higher in children <5 years (50%). Our study's overall PA incidence was in line with literature data [6,26,27]. Accurate diagnosis and timely treatment of AA in children <5 years is even more challenging due to the rarity of the disease, the variable clinical presentation, less ability to articulate the clinical symptoms, the rapid development, the immaturity of omentum, and defense mechanisms [28].

This study also explored the potential value of commonly utilized biomarkers, such as WBC and CRP, in predicting PA. It has been demonstrated that WBC can be within normal limits in more than 20% of pediatric patients with AA and that WBC is not adequately sensitive and specific in the discrimination between the PA and NPA [29]; however, CRP used solely or in combination with WBC is helpful in the discrimination between PA and NPA [29]. In line with the previous studies, our data showed that elevated WBC and CRP levels evaluated together with several clinical variables were associated with a risk of perforation [30,31]. However, unlike Sack et al., who concluded that the identification of children with PA is aided by measuring IL-6 and CRP but not WBC [32], we did not use interleukin-6 (IL-6) for this purpose due to its unavailability in our pediatric ED.

The classic AA symptoms include anorexia, migration of pain, nausea, and vomiting [33]. The presence of fever with tachycardia is also a common finding in AA. Some of the mentioned symptoms in AA were especially emphasized by Rasmussen and Hoffmann, noting that the absence of nausea, vomiting, and anorexia called into question AA's diagnosis [34]. Furthermore, sustained vomiting may occur due to generalized peritonitis, while diarrhea may result from irritation of the

Table 2
Incidence of acute appendicitis and perforated appendicitis in various pediatric age groups.

Age groups	All appendicitis	Perforated appendicitis	P-value
Age group, in years (%)	295	92 (31.2%)	
<5 years	40 (13.6%)	20 (50%)	<0.005
		95% CI (33.8%, 66.2%)	
6–10 years	113 (38.3%)	27 (23.9%)	
		95% CI (16.7%, 33.4%)	
11–16 years	142 (48.1%)	45 (31.7%)	
		95% CI (24.1%, 40.0%)	

CI – Confidence interval.

Table 3
Univariate analysis of variables in non-perforated and perforated appendicitis.

Variable	Total	NPA	PA	P-value
Patients (n)[1]	295	203 (68.8%)	92 (31.2%)	X^4
Median age (years)[1]	10 (8–13)	10 (7–13.5)	10 (7–13)	0.318[4]
Age < 5 years	40 (13.5%)	20 (9.8%)	20 (21.7%)	0.143[4]
		95% CI (2.8%, 9.8%)	95% CI (8.6%, 24.2%)	
Male (n, %)[1]	172 (58.3%)	104 (51.2%)	68 (73.9%)	ˉ0.001[3]
		95% CI (38.8%, 52.9%)	95% CI (63.7%, 82.5%)	
Female (n, %)[1]	123 (41.7%)	99 (48.8%)	24 (26.1%)	X^3
		95% CI (47.1%, 61.2%)	95% CI (17.5%, 36.3%)	
Nausea (n, %)[1]	56 (19%)	37 (18.2%)	19 (20.7%)	0.633[3]
		95% CI (14.5%, 25.9%)	95% CI (10.3%, 26.7%)	
Vomiting (n)[1]	118 (40%)	99 (48.8%)	78 (84.8%)	<0.001[3]
		95% CI (38.3%, 52.4%)	95% CI (74.5%, 90.6%)	
Diarrhea (n, %)[1]	37 (12.5%)	12 (5.9%)	25 (27.2%)	<0.001[3]
		95% CI (3.5%, 10.7%)	95% CI (18.4%, 37.4%)	
Fever (n, %)[1]	82 (27.8%)	33 (16.3%)	49 (53.3%)	<0.001[3]
		95% CI (11.5%, 22.1%)	95% CI (42.6%, 63.7%)	
Median leukocyte count (WBC) (x109/L)	14.9 (5.8)	13.8 (5.3)	17.5 (6.2)	<0.001
Median C-reactive protein (CRP) level (mg/l)[2]	28.4 (9.2–69.1)	18.7 (6.7–40.4)	71.1 (36.4–120)	<0.001

NPA – Non-perforated appendicitis; PA – Perforated appendicitis; CI – Confidence interval.
Data were analyzed using a Fisher test[3] and Mann-Whitney U-test[4].
[1] Data are presented as numbers with the percentage between brackets.
[2] Data are presented as median with the P25 and P75 between brackets.

distal ileum. However, these symptoms are common in many other diseases. Either way, the diagnosis of AA is predominantly a clinical one. It should be emphasized that signs and symptoms that presented with PA vary between studies. In our study, several clinical variables, including nausea, vomiting, diarrhea, and fever, along with readily available serum inflammatory markers and some demographic characteristics, can successfully distinguish PA from NPA at the admission in emergency department. These findings are in line with the previous studies [32].

The main limitation of our study is its retrospective nature and a single institution experience. Also, the duration of symptoms was not defined precisely enough through the documentation used, so this variable could not be included. Moreover, routine ultrasound

examination at the ED was inconsistently used and reported, and therefore, it was excluded from the study. Furthermore, abdominal pain's localization was not analyzed concerning the appendix's position but was recorded in general. Thus, the possibility of monitoring the migration of pain, one of the characteristic clinical variables in patients with AA, was omitted. In addition, ultrasound examination of AA was inconsistently used and reported, and therefore, this essential variable was excluded from the study and statistical analysis. The study's additional limitation was the lack of registration of patients' prior visits to local clinics, making the clinical variable "time between the onset of symptoms to the presentation" to assess the real reason for the delayed diagnosis.

In conclusion, distinguishing PA from NPA is crucial for the decision-making process and surgical outcome. Several clinical and biochemical variables evaluated together can be helpful to distinguish between PA from NPA.

Availability of data and materials

The datasets presented in the current study are available by the corresponding author on reasonable request.

Declaration of Competing Interest

Una Glamoclija is an employee of the Bosnalijek d.d., Sarajevo, Bosnia and Herzegovina. The other authors declare no conflict of interest.

Table 4
Logistic regression model of factors that predicted perforated appendicitis. Regression coefficient and odds ratios for the male gender, vomiting, fever, diarrhea, WBC, and CRP resulting from the logistic regression model are provided

Predictor*	Odds ratio (95% CI)	Regression coefficient	P-value
Male gender	3.133 (1.610–6.096)	1.142	0.001
Age < 5 years	2.807 (0.998–7.897)	1.032	0.051
Vomiting	2.346 (1.141–4.822)	0.823	0.020
Diarrhea	4.549 (1.850–11.181)	1.515	0.001
Fever	3.429 (1.765–6.663)	1.232	0.000
WBC	2.962 (1.491–5.884)	1.086	0.002
CRP	3.061 (1.267–7.396)	1.119	0.013

CI – Confidence interval; WBC – White blood cell count; CRP – C-reactive protein.
* Significant variables are bolded.

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References

[1] Ashcraft KW, Murphy JP, Ostlie DJ. Ashcraft's Pediatric Surgery. 6th ed.. New York: Saunders/Elsevier; 2014.

[2] Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990;132(5):910–25. https://doi.org/10.1093/oxfordjournals.aje.a115734.

[3] Mallick MS. Appendicitis in pre-school children: a continuing clinical challenge. A retrospective study. Int J Surg. 2008;6(5):371–3. https://doi.org/10.1016/j.ijsu.2008.06.003.

[4] Nance ML, Adamson WT, Hedrick HL. Appendicitis in the young child: a continuing diagnostic challenge. Pediatr Emerg Care. 2000;16(3):160–2. https://doi.org/10.1097/00006565-200006000-00005.

[5] Howell EC, Dubina ED, Lee SL. Perforation risk in pediatric appendicitis: assessment and management. Pediatric Health Med Ther. 2018;9:135–45. https://doi.org/10.2147/PHMT.S155302.

[6] Ponsky TA, Huang ZJ, Kittle K, Eichelberger MR, Gilbert JC, Brody F, et al. Hospital- and patient-level characteristics and the risk of appendiceal rupture and negative appendectomy in children. JAMA. 2004;292(16):1977–82. https://doi.org/10.1001/jama.292.16.1977.

[7] Paquette IM, Zuckerman R, Finlayson SR. Perforated appendicitis among rural and urban patients: implications of access to care. Ann Surg. 2011;253(3):534–8. https://doi.org/10.1097/SLA.0b013e3182096d68.

[8] Pittman-Waller VA, Myers JG, Stewart RM, Dent DL, Page CP, Gray GA, et al. Appendicitis: why so complicated? Analysis of 5755 consecutive appendectomies. Am Surg. 2000;66(6):548–54 https://www.ncbi.nlm.nih.gov/pubmed/10888130.

[9] Bickell NA, Aufses Jr AH, Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. J Am Coll Surg. 2006;202(3):401–6. https://doi.org/10.1016/j.jamcollsurg.2005.11.016.

[10] Teixeira PG, Sivrikoz E, Inaba K, Talving P, Lam L, Demetriades D. Appendectomy timing: waiting until the next morning increases the risk of surgical site infections. Ann Surg. 2012;256(3):538–43. https://doi.org/10.1097/SLA.0b013e318265ea13.

[11] Papandria D, Goldstein SD, Rhee D, Salazar JH, Arlikar J, Gorgy A, et al. Risk of perforation increases with delay in recognition and surgery for acute appendicitis. J Surg Res. 2013;184(2):723–9. https://doi.org/10.1016/j.jss.2012.12.008.

[12] Augustin T, Cagir B, Vandermeer TJ. Characteristics of perforated appendicitis: effect of delay is confounded by age and gender. J Gastrointest Surg. 2011;15(7):1223–31. https://doi.org/10.1007/s11605-011-1486-x.

[13] Ishiyama M, Yanase F, Taketa T, Makidono A, Suzuki K, Omata F, et al. Significance of size and location of appendicoliths as exacerbating factor of acute appendicitis. Emerg Radiol. 2013;20(2):125–30. https://doi.org/10.1007/s10140-012-1093-5.

[14] Lin HR, Wang HC, Wang JH, Lu HH. Increased risk of perforated appendicitis in patients with schizophrenia and dementia: a population-based case-control study. Medicine (Baltimore). 2020;99(5):e18919. https://doi.org/10.1097/MD.0000000000018919.

[15] Sahbaz NA, Bat O, Kaya B, Ulukent SC, Ilkgul O, Ozgun MY, et al. The clinical value of leucocyte count and neutrophil percentage in diagnosing uncomplicated (simple) appendicitis and predicting complicated appendicitis. Ulus Travma Acil Cerrahi Derg. 2014;20(6):423–6. https://doi.org/10.5505/tjtes.2014.75044.

[16] Iamarino APM, Juliano Y, Rosa OM, Novo NF, Favaro ML, Ribeiro MAFJ. Risk factors associated with complications of acute appendicitis. Rev Col Bras Cir. 2017;44(6):560–6. https://doi.org/10.1590/0100-69912017006002.

[17] van Dijk ST, van Dijk AH, Dijkgraaf MG, Boermeester MA. Meta-analysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis. Br J Surg. 2018;105(8):933–45. https://doi.org/10.1002/bjs.10873.

[18] Schlenz H, Intemann T, Wolters M, Gonzalez-Gil EM, Nappo A, Fraterman A, et al. C-reactive protein reference percentiles among pre-adolescent children in Europe based on the IDEFICS study population. Int J Obes (Lond). 2014;38(Suppl. 2):S26–31. https://doi.org/10.1038/ijo.2014.132.

[19] Pediatric CBC Reference Values (LTR10211). https://www.dynalife.ca/portals/0/pdf/Lab%20procedure%20or%20protocol/Pediatric%20CBC%20reference%20values.pdf; 2021.

[20] Andersson RE, Hugander AP, Ghazi SH, Ravn H, Offenbartl SK, Nystrom PO, et al. Diagnostic value of disease history, clinical presentation, and inflammatory parameters of appendicitis. World J Surg. 1999;23(2):133–40. https://doi.org/10.1007/pl00013174.

[21] Wu HP, Lin CY, Chang CF, Chang YJ, Huang CY. Predictive value of C-reactive protein at different cutoff levels in acute appendicitis. Am J Emerg Med. 2005;23(4):449–53. https://doi.org/10.1016/j.ajem.2004.10.013.

[22] Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. Br J Surg. 2004;91(1):28–37. https://doi.org/10.1002/bjs.4464.

[23] Stein GY, Rath-Wolfson L, Zeidman A, Atar E, Marcus O, Joubran S, et al. Sex differences in the epidemiology, seasonal variation, and trends in the management of patients with acute appendicitis. Langenbecks Arch Surg. 2012;397(7):1087–92. https://doi.org/10.1007/s00423-012-0958-0.

[24] Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet. 2015;386 (10000):1278–87. https://doi.org/10.1016/S0140-6736(15)00275-5.

[25] Dahlberg MJA, Pieniowski EHA, Bostrom LAS. Trends in the Management of Acute Appendicitis in a single-Center quality register cohort of 5,614 patients. Dig Surg. 2018;35(2):144–54. https://doi.org/10.1159/000477269.

[26] Guss DA, Richards C. Comparison of men and women presenting to an ED with acute appendicitis. Am J Emerg Med. 2000;18(4):372–5. https://doi.org/10.1053/ajem.2000.7323.

[27] Church JT, Klein EJ, Carr BD, Bruch SW. Early appendectomy reduces costs in children with perforated appendicitis. J Surg Res. 2017;220:119–24. https://doi.org/10.1016/j.jss.2017.07.001.

[28] Zouari M, Abid I, Ben Dhaou M, Thamri F, Jallouli M, Mhiri R. Predictive factors of perforated appendicitis in children younger than 5 years. Pediatr Emerg Care. 2018;34(10). https://doi.org/10.1097/PEC.0000000000001632 e197-e8.

[29] Gronroos JM. Do normal leucocyte count and C-reactive protein value exclude acute appendicitis in children? Acta Paediatr. 2001;90(6):649–51 https://www.ncbi.nlm.nih.gov/pubmed/11440098.

[30] Buyukbese Sarsu S, Sarac F. Diagnostic value of white blood cell and C-reactive protein in Pediatric appendicitis. Biomed Res Int. 2016;2016:6508619. https://doi.org/10.1155/2016/6508619.

[31] 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. https://doi.org/10.1155/2019/4608053.

[32] Sack U, Biereder B, Elouahidi T, Bauer K, Keller T, Trobs RB. Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. BMC Surg. 2006;6:15. https://doi.org/10.1186/1471-2482-6-15.

[33] Pisarra VH. Recognizing the various presentations of appendicitis. Dimens Crit Care Nurs. 2001;20(3):24–7. https://doi.org/10.1097/00003465-200105000-00007.

[34] Rasmussen OO, Hoffmann J. Assessment of the reliability of the symptoms and signs of acute appendicitis. J R Coll Surg Edinb. 1991;36(6):372–7 https://www.ncbi.nlm.nih.gov/pubmed/1774704.