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(Citation)
Pediatrics International,62(6):711-715

(Issue Date)
2020-06

(Resource Type)
journal article

(Version)
Accepted Manuscript

Original Article

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Running title: Predictive factors of PA in children

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This article contains 15 pages, 2,195 words, 2 reference pages, 3 tables, and no figure legends.

Abstract

Background: To investigate the diagnostic value of objective factors present at admission for identifying predictive markers of perforated appendicitis in children.

Methods: We performed a retrospective case review of 319 children aged ≤15 years who underwent treatment for acute appendicitis at our institution over a 6-year period from January 2011 to December 2016. Univariate and multivariate analyses were performed to identify risk factors for perforation of acute appendicitis in children.

Results: In the 6-year period, 319 patients underwent treatment for acute appendicitis, of whom 72 (22.6%) had perforated appendicitis. Multivariate analysis revealed 5 independent factors predicting perforated appendicitis at admission: longer symptom duration (≥2 days), fever (axillary temperature ≥38.0°C), elevated C-reactive protein level (≥3.46 mg/dL), appendiceal fecalith on imaging, and ascites on imaging. Among patients with all 5 risk factors, 93.3% had perforated appendicitis. All patients who had none of these factors did not have perforated appendicitis.

Conclusions: Longer symptom duration (≥2 days), fever (axillary temperature ≥38.0°C), elevated C-reactive protein level, and the presence of appendiceal fecalith and ascites on imaging are independent and objective factors predicting perforated appendicitis at admission. These risk factors have the potential to be helpful as an ancillary index for physicians determining the severity of appendicitis.

Keywords acute appendicitis, perforated appendicitis, risk factor, children

Introduction

Acute appendicitis (AA) represents the most common abdominal surgical emergency in the pediatric population. Accurate diagnosis of AA is still challenging for pediatric clinicians because typical symptoms and signs are frequently absent, specific findings of AA are difficult to elicit in children, and clinical findings frequently overlap those of other conditions. There are numerous reports evaluating predictive factors and diagnostic tools for AA in children. Several clinical scoring systems have been devised and may have the potential to achieve acceptable levels of diagnostic accuracy. However, these scoring systems contained subjective factors and the results and algorithms could not clarify the severity of AA.

Perforated appendicitis (PA) is an especially severe clinical situation because delayed treatment or misdiagnosis of PA could result in unnecessary complications, including peritonitis, sepsis, bowel obstruction, abscess formation, and fertility problems. This leads to a longer hospital stay and additional expenses [1, 2]. Recently, some investigators tried to determine the predictive factors of PA in adult series. However, to date, the number of studies concerning PA in the pediatric population is extremely limited [3-8].

The aim of this study was to investigate the diagnostic value of simple and 'objective' factors present at admission as predictive markers for PA in children.

Methods

Patients

A retrospective chart review of patients, aged ≤15 years, who were diagnosed with AA at the Japanese Red Cross Society Himeji Hospital between January 2011 and December 2016 was conducted. Data gathered included patient age, gender, duration from symptom onset to admission, symptoms (vomiting and diarrhea), body temperature (axillary temperature), blood test results (white blood cell (WBC) count, neutrophil count, and C-reactive protein (CRP) level), and imaging results (maximum diameter of the appendix, presence of appendiceal fecalith, and presence of ascites on ultrasonography (US) and/or computed tomography (CT)).

Diagnosis of appendicitis and presence of appendicolith were determined by a single expert ultrasound technician and an attending-level radiologist interpreted the CT scans.

The patients were divided into 2 groups: those with PA and those with non-perforated appendicitis (NPA). The definition of PA was based on the surgeon's operative report for patients who underwent appendectomy or on the imaging report for patients who underwent non-operative management.

Statistical analysis

Normally distributed data are reported as mean ± standard deviation and categorical data are reported as frequency (percentage). Statistical comparisons between patients with and without perforation were performed using independent group Student t-tests for continuous variables and chi square tests for categorical factors. A receiver-operating characteristic curve was constructed to evaluate the predictive accuracy of the logistic regression results and to estimate cut-off points for continuous variables to maximize sensitivity and specificity. Logistic regression analysis was performed to identify risk factors for PA. Differences were considered statistically significant at $p<0.05$. Stepwise backward elimination was used to select the best model before variables were included in the multivariate models. At each step, the factor with the highest p value was removed until all factors had a p value smaller than <0.20. All data analyses were performed with Microsoft Excel and JMP 15 (SAS Institute, Cary, NC). Statistical methodology was verified by statistics experts belonging to KOBE University Hospital CTRC.

Ethics approval

This study was approved by our institutional review board (registration no.: 21). All data were collected anonymously, and patient consent was not required.

Results

There were 319 patients with AA between January 1 2011, and December 31 2016. A total of 241 patients underwent an appendectomy, of whom 47 had PA, and 78 patients underwent non-operative management, of whom 25 had PA. Patient demographic information is summarized in Table 1. A total of 67 patients were diagnosed with CT, 229 patients were diagnosed with US, and 23 patients were diagnosed with both US and CT.

Univariate and multivariate analyses of PA

A receiver-operating characteristic curve and univariate statistical analysis showed that patients with PA tended to have the following factors: younger age (<9 years, AUC=0.666), longer symptom duration (≥2 days, AUC=0.742), fever (axillary temperature ≥38.0°C), vomiting, diarrhea, elevated WBC count (≥15000 /µL, AUC=0.597), elevated neutrophil count (≥17190 /µL, AUC=0.602), elevated CRP level (≥3.46 mg/dL, AUC=0.866), greater appendiceal diameter (≥9.7 mm, AUC=0.636), presence of appendiceal fecalith on imaging, and presence of ascites on imaging.

Multivariate logistic regression after stepwise regression to determine the strength of association with PA yielded only 5 significant risk factors: longer symptom duration (≥2 days, odds ratio (OR) 3.07, 95% confidence interval (CI) 1.38-6.82), fever (≥38.0°C, OR 2.73, 95% CI 1.21-6.19), elevated CRP level (≥3.46 mg/dL, OR 8.67, 95% CI 3.32-22.65), presence of appendiceal fecalith on imaging (OR 3.73, 95% CI 1.69-8.19), and presence of ascites on imaging (OR 3.07, 95% CI 1.42-6.63) (Table 2).

Relationship between number of risk factors and perforation rate

In this study, 93.3% of patients with all 5 risk factors had PA, while all patients who had none of these factors did not have PA. Further, a receiver-operating characteristic curve showed that patients with 3 or more risk factors tend to have PA (AUC=0.906) (Table 3).

Discussion

Concerning the treatment strategy for PA, it is still debatable whether appendectomy should be performed or not. A meta-analysis showed that initial antibiotics, followed by interval appendectomy was associated with significantly fewer overall complications and no significant difference in clinical course [9]. On the other hand, a prospective, randomized trial showed that initial antibiotics followed by interval appendectomy was associated with higher overall adverse event rate, longer hospitalization, and higher cost [10]. Delayed treatment or misdiagnosis of PA could result in unnecessary complications, and perforation correlates strongly with duration of symptoms [11]. Presently, treatment for PA depends on the policy or practice of each institution, and we believe that there is no doubt that the presence of PA is one of the strongest factors determining the treatment strategy for AA. It is important to promptly distinguish PA from NPA.

In general, diagnosis of advanced appendicitis can be difficult in children because of insufficient clinical history, age-dependent communication difficulties, and a large proportion of patients with atypical and nonspecific clinical presentations. Imaging tests have played a major role in the diagnosis of AA. US has been considered as a first-choice imaging modality for children, as it is relatively inexpensive and requires no sedation, ionizing radiation, or contrast agents. Despite the benefits of US, the diagnostic utility of this modality may be greatly limited by operator ability and lack of availability at many hospitals during nights, weekends, and holidays [1, 2]. CT has several advantages over other imaging modalities, including ready availability at most institutions, rapid acquisition time, lack of operator dependency, and a relatively high sensitivity and specificity for the detection of AA [8]. However, some investigators have documented limited utility of CT for the detection and diagnosis of PA [12, 13]. There are numerous reports evaluating predictive factors and diagnostic tools of AA in children. Several clinical scoring systems have been devised and may have the potential to achieve acceptable levels of diagnostic accuracy. However, these scoring systems contained subjective factors and their results and algorithms do not predict the severity of AA. Therefore, we aimed to evaluate factors predictive of PA and to investigate the diagnostic value of simple objective factors at admission as predictive markers for PA in children.

In the present study, according to univariate analysis, younger age (<9 years), longer symptom duration (≥2 days), fever (axillary temperature ≥38.0°C), vomiting, diarrhea, elevated WBC count (≥15000 /μL), elevated neutrophil count (≥17190 /μL), elevated CRP level (≥ 3.46 mg/dL), greater appendiceal diameter (≥9.7 mm), presence of appendiceal fecalith on imaging, and presence of ascites on imaging were significant risk factors for PA. Our results show findings similar to those in previous reports that evaluated the difference between PA and NPA in children. For example, Nance et al. reported that PA increased in frequency as patient age decreased and the duration of symptoms lengthened [3]. Narsule et al. also reported that the risk of perforation increased in a linear fashion with duration of symptoms [4]. Gofrit et al. reported that children with PA were characterized by younger age, longer delay from symptom onset to correct diagnosis, higher oral and rectal temperatures, higher platelet count, and lower hemoglobin level [5]. The reasons these studies showed mixed results may be related to variations in study design, the differences in measurement method of body temperature such as rectal body temperature or axillary body temperature, quality of clinical examinations, and confounding factors among the variables examined [14]. To decrease confounding influences among variables, most recent studies tried to identify the true predictive factors for PA using multivariate analysis. However, the number of such studies is extremely limited.

A prospective cohort study by Williams et al. identified “generalized tenderness on examination”, “duration of symptoms longer than 48 hours”, “WBC >19,400 /μL”, “abscess on CT scan”, and “fecalith on CT scan” as independent predictors of PA [6]. A retrospective, single-center study by Obinwa et al. showed that “preoperative temperature ≥37.5 °C” was most discriminatory for PA and “WBC count ≥15100 /μL”, “preoperative anorexia”, and “rebound tenderness” were also significant discriminatory clinical variables [7]. Another retrospective, single-center study by Boettcher et al. showed that “CRP levels >20 mg/dL" and "free abdominal fluid on US" were the most important features to differentiate perforated from simple appendicitis [8].

In the current study, according to the multivariate model, independent predictive factors were longer symptom duration (≥2 days), fever (axillary temperature ≥38.0°C), elevated CRP level (≥3.46 mg/dL), presence of appendiceal fecalith on imaging, and presence of ascites on imaging. Our predictive factors were all relatively objective and easy to identify; therefore, we believe that these factors could be useful in determining the best course of treatment for pediatric clinicians.

We also examined the potentiality of these predictive variables as constructing factors in a scoring system. We defined these 5 independent factors as the perforated appendicitis score (PAS). Interestingly, the higher the PAS, the higher the rate of PA in this study. Over 90% of patients with all 5 risk factors had PA, while all patients who had none of these factors did not have PA. Patients with PAS 1 or more had the possibility of PA. Consequently, PA should be suspected if the score is high, especially in cases of 3 points or more. Antibiotics should be selected and surgery should be considered, taking into account the risk of panperitonitis.

Several limitations exist in our study. This study was a retrospective, nonrandomized, single-center analysis, which impedes inference of possible causalities.

The PAS was not constructed by "waiting risk factors" since we aimed to avoid complexity, which may prevent more efficient prediction of PA. Despite these limitations, we believe that the results reported herein could help physicians distinguish PA from NPA.

The current investigation is a preliminary analysis. Our next study will be to evaluate the validity and applicability of PAS, including predictive factors reported by other investigators, in a prospective and multicenter collaborative investigation.

Conclusion

Longer symptom duration (≥2 days), fever (axillary temperature ≥38.0°C), elevated CRP level (≥3.46 mg/dL), presence of appendiceal fecalith on imaging, and presence of ascites on imaging are independent and objective factors predicting PA at admission. These risk factors may potentially help physicians determine the severity of appendicitis as an ancillary index.

Author contributions:

Y.O, H.M, Y.B, and T.H conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. H.M, T.N, and Y.N were pediatric surgery residents during the study period.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the investigation.

Acknowledgements: Statistical methodology was supervised and verified by statistical experts belonging to KOBE University Hospital CTRC.

Disclosure: The authors declare no conflicts of interest

Ethical approval: Formal consent is not required for this type of study.

References

1. Velanovich V, Satava R Balancing the normal appendectomy rate with the perforated appendicitis rate: implications for quality assurance. *Am. Surg.* 1992; 58: 264-9.
2. Blomqvist PG, Andersson RE, Granath F, Lambe MP, Ekbom AR. Mortality after appendectomy in Sweden, 1987-1996. *Ann. Surg.* 2001; 233: 455-60.
3. Nance ML, Adamson WT, Hedrick HL. Appendicitis in the young child: a continuing diagnostic challenge. *Pediatr. Emerg. Care* 2000; 16: 160-2.
4. Narsule CK, Kahle EJ, Kim DS, Anderson AC, Luks FI. Effect of delay in presentation on rate of perforation in children with appendicitis. *Am. J. Emerg. Med.* 2011; 29: 890-3.
5. Gofrit ON, Abu-Dalu K. Perforated appendicitis in the child: contemporary experience. *Isr. Med. Assoc. J.* 2001; 3: 262-5.
6. Williams RF, Blakely ML, Fischer PE, et al. Diagnosing ruptured appendicitis preoperatively in pediatric patients. *J. Am. Coll. Surg.* 2009; 208: 819-25; discussion 826-8.
7. 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.
8. Boettcher M, Günther P, Breil T. The Heidelberg Appendicitis Score predicts perforated appendicitis in children. *Clin Pediatr* (Phila) 2016; doi: 10.1177/0009922816678976

9. Simillis C, Symeonides P, Shorthouse AJ, Tekkis PP. A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery* 2010; 147: 818-29.
10. Blakely ML, Williams R, Dassinger MS, et al. Early versus interval appendectomy for children with perforated appendicitis. *Arch. Surg.* 2011; 146: 660-5.
11. Rothrock SG, Skeoch G, Rush JJ, Johnson NE. Clinical features of misdiagnosed appendicitis in children. *Ann. Emerg. Med.* 1991; 20: 45-50.
12. Glass CC, Rangel SJ. Overview and diagnosis of acute appendicitis in children. *Semin. Pediatr. Surg.* 2016; 25: 198-203.
13. Gaskill CE, Simianu VV, Carnell J, Hippe DS, Bhargava P, Flum DR, Davidson GH. Use of computed tomography to determine perforation in patients with acute appendicitis. *Curr. Probl. Diagn. Radiol.* 2016; doi: 10.1067/j.cpradiol.2016.12.002
14. Craig JV, Lancaster GA, Williamson PR, Smyth RL. Temperature measured at the axilla compared with rectum in children and young people: systematic review. *BMJ*. 2000; 320: 1174-8.

Table 1. Patient demographics

	AA	PA	NPA
N (%)	319 (100%)	72 (22.6%)	247 (77.4%)
Demographics			
Age (years)	10.2±2.9 (2-15)	8.8±3.2 (2-14)	10.6±2.7 (2-15)
Sex (male)	189 (59.2)	41 (56.9)	148 (59.9)
Symptom			
Duration from symptom onset to admission (days)	1.5±1.8 (0-14)	2.6±2.1 (0-10)	1.2±1.5 (0-14)
Fever (≥38.0 ℃)	102 (32.0)	51 (70.8)	51 (20.6)
Vomiting	148 (46.4)	41 (56.9)	107 (43.3)
Diarrhea	40 (12.5)	18 (25.0)	22 (8.9)
Blood test			
WBC count (/μL)	15085±6291 (3100-71000)	16708±6265 (4400-36600)	14612±6219 (3100-71000)
Neutrophil count (/μL)	12512±5869 (1443-53108)	14272±6044 (2913-33050)	11997±5715 (1443-53108)
CRP (mg/dL)	4.23±5.78 (0.00-43.88)	10.03±7.15 (0.01-43.88)	2.52±3.93 (0.00-25.00)
Imaging test			
Maximum diameter of appendix (mm)	10.3±3.09 (4-24)	14.1±3.8 (4-22)	10.5±2.8 (4-24)
Fecalith	107 (33.5)	44 (61.1)	63 (25.5)
Ascites	111 (34.8)	46 (63.9)	65 (26.3)

AA, acute appendicitis; PA, perforated appendicitis; NPA, non-perforated appendicitis; WBC, white blood cell; CRP, C-reactive protein.

Table 2. Univariate and multivariate analyses of appendiceal perforation

			Analyses `					
	PA [n (%)]	NPA [n (%)]	Univariate	Stepwise	Multivariate			
	n=47	n=194	p	p	p	OR	CI	Intercept
Demographics								
Age (<9 years old)	21 (44.6)	40 (20.6)	<0.0001	0.0429	0.0733	2.08	0.93-4.61	0.4863
Sex (male)	29 (61.7)	120 (61.9)	0.7309					
Symptom								
Duration from symptom onset to admission (≥2 days)	25 (53.2)	44 (22.7)	<0.0001	0.0149	0.0059	3.07	1.38-6.82	0.5609
Fever (≥38.0 °C)	32 (68.1)	44 (22.7)	<0.0001	0.0171	0.0159	2.73	1.21-6.19	0.5028
Vomiting	27 (57.4)	90 (46.4)	0.0415	0.6712				
Diarrhea	10 (21.3)	13 (6.7)	0.0007	0.1551	0.1480	2.09	0.77-5.69	0.3694
Blood test								
WBC count (≥15000/μL)	18 (38.3)	40 (20.6)	0.0053	0.0825	0.1354	0.51	0.21-1.24	-0.3400
Neutrophil count (≥17190/μL)	17 (36.2)	29 (14.9)	0.0013	0.0359	0.0542	2.93	0.98-8.75	0.5373
CRP (≥3.46 mg/dl)	40 (85.1)	51 (26.3)	<0.0001	<0.0001	<0.0001	8.67	3.32-22.65	1.0797
Imaging test								
Maximum diameter of appendix (≥9.7 mm)	27 (57.4)	62 (32.0)	0.0003	0.7925				
Fecalith	34 (72.3)	60 (30.9)	<0.0001	0.0022	0.0011	3.73	1.69-8.19	0.6576
Ascites	35 (74.5)	54 (27.8)	<0.0001	0.0062	0.0043	3.07	1.42-6.63	0.5607

AA, acute appendicitis; PA, perforated appendicitis; NPA, non-perforated appendicitis; OR, odds ratio; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein.

Table 3. Correlation between number of risk factors and perforation rate

Number of risk factors	5	4	3	2	1	0
Number of AA patients	15	33	50	54	77	90
Number of PA patients	14	23	23	8	4	0
(%)	93.3	69.7	46.0	14.8	5.2	0.0
		61.2			5.4	

*Number of patients

**Number of patients with perforated appendicitis