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# Factors predictive of complicated appendicitis in children

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## ABSTRACT

**Background:** The ability to predict whether a child has complicated appendicitis at initial presentation may influence clinical management. However, whether complicated appendicitis is associated with prehospital or in-hospital factors is not clear. We also investigate whether hyponatremia may be a novel prehospital factor associated with complicated appendicitis.

**Materials and methods:** A retrospective review of all pediatric patients ( $\leq 12$  y) with appendicitis treated with appendectomy from 2000 to 2013 was performed. The main outcome measure was intraoperative confirmation of gangrenous or perforated appendicitis. A multivariable analysis was performed, and the main predictors of interest were age  $< 5$  y, symptom duration  $> 24$  h, leukocytosis (white blood cell count  $> 12 \times 10^3/\text{mL}$ ), hyponatremia (sodium  $\leq 135$  mEq/L), and time from admission to appendectomy.

**Results:** Of 392 patients, 179 (46%) had complicated appendicitis at the time of operation. Univariate analysis demonstrated that patients with complicated appendicitis were younger, had a longer duration of symptoms, higher white blood cell count, and lower sodium levels than patients with noncomplicated appendicitis. Multivariable analysis confirmed that symptom duration  $> 24$  h (odds ratio [OR] = 5.5, 95% confidence interval [CI] = 3.5–8.9,  $P < 0.01$ ), hyponatremia (OR = 3.1, 95% CI = 2.0–4.9,  $P < 0.01$ ), age  $< 5$  y (OR = 2.3, 95% CI = 1.3–4.0,  $P < 0.01$ ), and leukocytosis (OR = 1.9, 95% CI = 1.0–3.5,  $P = 0.04$ ) were independent predictors of complicated appendicitis. Increased time from admission to appendectomy was not a predictor of complicated appendicitis (OR = 0.8, 95% CI = 0.5–1.2,  $P = 0.2$ ).

**Conclusions:** Prehospital factors can predict complicated appendicitis in children with suspected appendicitis. Hyponatremia is a novel marker associated with complicated appendicitis. Delaying appendectomy does not increase the risk of complicated appendicitis once intravenous antibiotics are administered. This information may help guide resource/personnel allocation, timing of appendectomy, and decision for nonoperative management of appendicitis in children.

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## Introduction

In children, acute appendicitis was responsible for more than 70,000 hospital admissions in 2012.<sup>1</sup> Appendicitis is classified as complicated when there is evidence of a perforated or gangrenous appendix, an intra-abdominal abscess, or fecal peritonitis often resulting in a longer length of stay and greater rates of morbidity and mortality. Overall, complicated appendicitis is more common in children, with rates as high as 30%.<sup>2</sup> The ability to identify children at risk for complicated appendicitis is important, as it dictates decisions regarding further workup and management. Specifically, patients with noncomplicated appendicitis may be amenable to nonoperative management with antibiotics alone.

The management of patients with complicated appendicitis differs greatly from that of acute appendicitis. The urgency of operative intervention is dependent on whether in-hospital progression of disease can convert acute appendicitis to complicated appendicitis. Previous studies have suggested age <5 y, duration of symptoms >24 h, white blood cell (WBC) count  $>12 \times 10^3/\text{mL}$ , C-reactive protein > 10 mg/L, and radiographic findings as possible predictors for complicated appendicitis.<sup>3,4</sup> Despite these studies, it is still controversial as to whether complicated appendicitis is a prehospital event or due to in-hospital progression of acute appendicitis to complicated appendicitis.<sup>5,6</sup> Thus, the purpose of this study is to investigate whether prehospital factors (age, symptom duration, and WBC count) or in-hospital factors (time from admission to appendectomy) are associated with complicated appendicitis. We will also investigate another prehospital factor, serum sodium level, to see if hyponatremia is associated with complicated appendicitis. We hypothesize that complicated appendicitis is a prehospital event and that hyponatremia will be predictive of complicated appendicitis in children.

## Materials and methods

### Study design

The study was approved by the Harbor-UCLA Medical Center Institutional Review Board. This study is a retrospective review of all consecutive pediatric patients ( $\leq 12$  y) with appendicitis treated with appendectomy from 2000 to 2013. Patients with incomplete records were excluded from this study. Recorded values included patient admission characteristics such as age, gender, race/ethnicity, insurance status, comorbidities, duration of symptoms, laboratory values, imaging findings, and time to surgery. The primary outcome was the presence of complicated appendicitis.

### Definitions

Duration of symptoms was taken from the patient's objective history of present illness and was dichotomized as to whether a patient had symptoms for 24 h or less. At our institution, hyponatremia is defined as a serum  $\leq 135$  mEq/L and leukocytosis as a WBC count  $>12 \times 10^3/\text{mL}$ . If a patient was

transferred from an outside facility, their laboratory workup from that facility was used as their admission laboratory values in the database. Time to surgery was defined as the time from first evaluation by the emergency department to time of incision and was measured in hours. We used intra-operative findings of a perforated or gangrenous appendix, an intra-abdominal abscess, or fecal peritonitis as our definitive diagnosis of complicated appendicitis.

### Statistics and data management

All data were recorded in Excel 2010 (Microsoft, Redmond, WA). Statistical analysis was performed using both SAS v9.3 (SAS Institute, Cary, NC) and Epi Info 7 v7.1.5.2 (CDC, Atlanta, GA) software. Continuous variables were analyzed using the Student's t-test, but in the presence of significant variance, the Kruskal–Wallis test was used instead. Categorical variables were analyzed using the chi-square test if all cells had expected values greater than five and a Fisher's exact test if any expected values were less than five. Statistical significance was set at a P value of less than 0.05. Clinically relevant variables and variables found to be statistically significant were included in a multivariable logistic regression for the outcome of complicated appendicitis. The multivariable model was assessed for goodness of fit using the Hosmer–Lemeshow test statistics and the area under the curve.

## Results

### Patient characteristics

A total of 503 patients were identified, but only 392 children had complete records and were included in this study. Of the 392 patients, 179 (46%) were found to have complicated appendicitis at time of surgery. Patient characteristics are summarized in Table 1. Patients with complicated appendicitis were slightly younger (8 versus 9 y,  $P < 0.01$ ). There were no significant differences with respect to gender, body mass index, race/ethnicity, comorbidities, transfer status, or type of insurance. The median duration of symptoms was longer in patients with complicated appendicitis (2 versus 1 d,  $P < 0.01$ ). There were no differences with respect to time from admission to surgery. The median serum sodium level in patients with complicated appendicitis was lower than that in patients with noncomplicated appendicitis (134 versus 137 mEq/L,  $P < 0.01$ ). There was a statistically significant difference with respect to WBC count, although the clinical value was minimal (17 versus  $16 \times 10^3/\text{mL}$ ,  $P < 0.01$ ).

### Relevant clinical cutoffs

Patients with complicated appendicitis were more likely to be aged younger than 5 y (18% versus 7.5%,  $P = 0.01$ ), have symptoms for longer than 24 h (75% versus 36%,  $P < 0.01$ ), and have a sodium  $\leq 135$  mEq/L (63% versus 33%,  $P < 0.01$ ). There were no significant differences with respect to leukocytosis. Univariate analysis of these relevant clinical cutoffs is summarized in Table 2.

**Table 1 – Comparison of patient characteristics.**

Patient factors	Complicated appendicitis (n = 179)	Noncomplicated appendicitis (n = 213)	P value
Age (y)	8 [5-11]	9 [7-11]	<0.01
Male gender	112 (63%)	148 (69%)	0.1
BMI	19 [16-22]	18 [16-22]	0.7
Race			
African-American	4 (2.2%)	5 (2.4%)	1
Asian	2 (1.1%)	8 (3.8%)	0.12
Hispanic	166 (93%)	188 (88%)	0.14
Other race	7 (3.9%)	12 (5.6%)	0.43
Comorbid disease present	21 (12%)	35 (16%)	0.19
Transferred from another facility	23 (13%)	23 (11%)	0.5
Private insurance	68 (38%)	76 (36%)	0.6
Duration of symptoms (d)	2 [2-3]	1 [1-2]	<0.01
Time from admission to operating room (h)	10 [5.8-15]	9.8 [6.5-13]	1
Serum sodium (mEq/L)	134 [132-136]	137 [135-138]	<0.01
WBC count ( $\times 10^3/\text{mL}$ )	17 [14-21]	16 [13-19]	<0.01

BMI = body mass index.

Categorical values expressed as n (%); continuous values expressed as median [interquartile range]; comorbidities included the following: diabetes mellitus, coagulopathy, and immunologic disorders.

### Multivariable analysis

The results of the multivariable analysis are summarized in Table 3. Children with symptoms >24 h were over five times more likely to have complicated appendicitis than those who did not. The next strongest predictor of complicated appendicitis was hyponatremia (odds ratio [OR] = 3.1, 95% confidence interval [CI] = 2.0-4.9,  $P < 0.01$ ). Other predictors for complicated appendicitis included age <5 y (OR = 2.3, 95% CI = 1.3-4.0,  $P < 0.01$ ) and leukocytosis (OR = 1.9, 95% CI = 1.0-3.5,  $P = 0.04$ ). There was no association between complicated appendicitis and time from admission to appendectomy. Model-fit statistics using the Hosmer–Lemeshow test demonstrated adequate fit ( $P = 0.2$ ) without overfitting. The area under the curve including all the aforementioned variables demonstrated a c-statistic of 0.8.

### Discussion

The goal of the present study was to determine whether complicated appendicitis is a prehospital occurrence or

whether inhospital progression of disease could result in progression of acute appendicitis to complicated appendicitis. We also sought to reexamine previously evaluated predictors of complicated appendicitis in children while also exploring a novel predictor, serum sodium. The primary finding of this study is that complicated appendicitis is determined by pre-hospital factors. We also propose hyponatremia be used as a novel predictor of complicated appendicitis. These two findings will help guide surgeons clinically with respect to diagnostic algorithms and clinical management of complicated appendicitis. Predicting the risk of complicated appendicitis preoperatively may also help counsel the parents regarding the anticipated postoperative course, morbidity, and length of hospitalization.

Although our results indicate that complicated appendicitis is a prehospital occurrence and noncomplicated appendicitis has minimal risk of inhospital progression, Bickell *et al.* found that before 36 h of symptoms, the risk of complicated appendicitis was less than 2%, whereas after 36 h, that risk rose to 5%. They recommended urgent surgery if any delays would push a patient's duration of symptoms over 36 h.<sup>5</sup> It is important to note although that their risk calculations were

**Table 2 – Univariate analysis of relevant clinical cutoffs.**

Patient factors	Complicated appendicitis (n = 179)	Noncomplicated appendicitis (n = 213)	P value
Age < 5 y	33 (18%)	16 (7.5%)	<0.01
Duration of symptoms >24 h	134 (75%)	77 (36%)	<0.01
Hyponatremia ( $\leq 135$ mEq/L)	112 (63%)	71 (33%)	<0.01
Leukocytosis (WBC count $> 12 \times 10^3/\text{mL}$ )	150 (84%)	170 (80%)	0.3

Categorical values expressed as n (%).

**Table 3 – Multivariate logistic regression analysis for complicated appendicitis.**

Patient factors	Odds ratio	95% confidence interval	P value
Duration of symptoms >24 h	5.5	3.5-8.9	<0.01
Hyponatremia ( $\leq 135$ mEq/L)	3.1	2.0-4.9	<0.01
Age < 5 y	2.3	1.3-4.0	<0.01
Leukocytosis (WBC $> 12 \times 10^3$ /mL)	1.9	1.0-3.5	0.04
Time from admission to operating room	0.8	0.5-1.2	0.2

No other variables were included in the model; Hosmer–Lemeshow model-fit statistic P value = 0.2; area under the curve c-statistic = 0.8.

performed in patients who had not yet received any antibiotics or supportive care. In contrast, Yardeni *et al.*<sup>6</sup> demonstrated that regardless of whether surgery was performed urgently (within 6 h) or delayed (6-24 h), there were no significant differences in operative times, complications, or rates of perforation. Thus, they concluded that delays in surgery for resuscitation, intravenous antibiotics, or simply, daytime hours, are safe and reasonable with minimal risk of progression of disease. Based on the findings of our study, we have also shown that once appropriate intravenous antibiotics are administered, the disease process appears to be halted and in many cases even treated. Thus, there is no need to rush patients with appendicitis to the operating room for fear that delaying appendectomy will increase the risk of developing complicated appendicitis.

Hyponatremia is a novel predictor of complicated appendicitis. Serum sodium levels have not been explored with respect to complicated appendicitis in children, although prior data have established strong associations between hyponatremia and other infectious disease processes. Hyponatremia is predictive of gangrenous cholecystitis and perforated colonic pathology in elderly patients who had undergone emergency general surgery.<sup>7,8</sup> It has also been established as a risk factor for mortality in patients with necrotizing soft-tissue infections (NSTI) and a tool for distinguishing an NSTI from a non-NSTI.<sup>9,10</sup> In a child with suspected appendicitis and a serum sodium level  $\leq 135$  mEq/L, one should have the possibility of complicated appendicitis on their differential, as the management strategies for these two entities can vary significantly. Our study demonstrated that hyponatremia was more helpful than WBC count in diagnosing complicated appendicitis. Thus, an electrolyte panel should be routinely obtained when working up patients for appendicitis.

Recent studies have suggested that children with noncomplicated appendicitis may be amenable to nonoperative management with antibiotics alone.<sup>11,12</sup> These studies have shown initial success rates of more than 90%. However, patients in these studies were carefully selected to have noncomplicated appendicitis. Successful nonoperative management of patients with complicated appendicitis is less likely. Thus, it is important to be able to predict which children are at risk for complicated appendicitis, as these patients should undergo immediate appendectomy and not be offered nonoperative management. Our study suggests that children with symptoms longer than 24 h, hyponatremia, and age <5 years are more likely to have complicated appendicitis and

may not be amenable to nonoperative management with antibiotics alone.

The limitations of our study include the fact that it is a retrospective design, based on results from a single institution, and only those children who were operated on were included. Data regarding other children with complicated appendicitis managed nonoperatively were thus not a part of this analysis.

## Conclusion

Prehospital factors can predict complicated appendicitis in children with suspected appendicitis. Hyponatremia is a novel marker associated with complicated appendicitis and may be more predictive than WBC count or age. Delaying appendectomy does not increase the risk of complicated appendicitis once intravenous antibiotics are administered. This information may help guide resource/personnel allocation, timing of appendectomy, and decision for nonoperative management of appendicitis in children.

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Authors' contributions: S.L.L., C.M.d.V., D.Y.K., and X.-B.D.P. contributed to study design. S.L.L., X.-B.D.P., and B.R. contributed to data collection. S.L.L., A.H.K., D.Y.K., and X.-B.D.P. contributed to data analysis. S.L.L., C.M.d.V., D.Y.K., X.-B.D.P., and V.F.S. contributed to article and critical review.

## Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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