American Journal of Emergency Medicine 37 (2019) 879–883

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Diagnostic accuracy of laboratory and ultrasound findings in patients with a non-visualized appendix

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ARTICLE INFO

Article history:
Received 9 June 2018
Received in revised form 28 July 2018
Accepted 7 August 2018

ABSTRACT

Ultrasound (US) and laboratory testing are initial diagnostic tests for acute appendicitis. A diagnostic dilemma develops when the appendix is not visualized on US. Objective: To determine if specific US findings and/or laboratory results predict acute appendicitis when the appendix is not visualized. Methods: A prospective study was conducted on children (birth-18 yrs) presenting to the pediatric emergency department with suspected acute appendicitis who underwent right lower quadrant US.

Children with previous appendectomy, US at another facility, or eloped were excluded. US findings analyzed: inflammatory changes, right lower quadrant and lower abdominal fluid, tenderness during US exam and lymph nodes. Diagnoses were confirmed via surgical pathology. Results 1252 subjects were enrolled, 60.8% (762) had appendix visualized and 39.1% (490) did not. In children where the appendix was not seen, 6.7% [33] were diagnosed with appendicitis. Among patients with a non-visualized appendix, the likelihood of appendicitis was significantly greater if: inflammatory changes in the RLQ (OR 18.0, 95% CI 4.5–72.1), CRP >0.5 mg/dL (OR 2.64, 95% CI 1.0–6.8), or WBC > 10 (OR 4.36, 95% CI 1.66–11.58). Duration of abdominal pain >3 days was significantly less likely associated with appendicitis in this model (OR 0.34, 95% CI 0.003–0.395). Combined, the absence inflammatory changes, CRP < 0.5 mg/dL, WBC < 10, and pain, ≤3 days had a NPV of 94.0%. Conclusion When the appendix is not visualized on US, predictors for appendicitis include the presence of inflammatory changes in the RLQ, an elevated WBC/CRP and abdominal pain <3 days.

1. Introduction

Acute appendicitis in children is the most common condition requiring urgent abdominal surgery [1]. Ultrasound (US) and lab work are commonly used to aid in the diagnosis of appendicitis. In most academic institutions, US has become the initial imaging modality for the evaluation of acute appendicitis as it had can have a high sensitivity and specificity, lacks ionizing radiation, is cost-effective, accessible and does not require intravenous access [2,3,4]. When the appendix is visualized on US, the diagnostic accuracy is similar to that of computed tomography (CT) [1]. Studies have shown that there is little difference in outcomes when CT or US is used for the diagnosis of acute appendicitis [1-3,5]. Furthermore, the use of US in the evaluation of appendicitis has shown to decrease the incidence of negative appendectomy and decrease the number of hospital admissions for suspected appendicitis [6-9]. Although the use of magnetic resonance imaging (MRI) has been shown to be accurate in the diagnosis of appendicitis and is used in some institutions to further evaluate the appendix in equivocal cases, this is restricted to institutions that have MRI availability [10]. Additionally, the cost and potential need for sedation in younger children is a limiting factor in its use thus making ultrasound ideal as an initial imaging modality.

Diagnostic dilemmas arise when the appendix cannot be visualized on US or when the appendix is visualized but concurrent sonographic findings are inconclusive for appendicitis for a patient where there is a suspicion for appendicitis. The rates of negative appendectomy still remain high, anywhere from 5 to 10% in recent published studies [11-13]. The diagnostic accuracy of ultrasound has been shown to be dependent on US technician experience, body habitus of the child, the child's ability to tolerate the study, and the radiologist's experience in evaluating appendiceal ultrasounds [5]. There is a paucity in the literature evaluating large cohorts of patients when the appendix cannot be visualized.

The objective of this study was to determine if there are specific sonographic findings (inflammatory changes, right lower quadrant (RLQ) fluid near the appendix, lower abdominal fluid, tenderness elicited by the sonographer, and ≥1 lymph node (≥5 mm) predictive for

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https://doi.org/10.1016/j.ajem.2018.08.014
0735-6757/

appendicitis in children with a non-visualized appendix. A secondary goal was to incorporate CRP, WBC, and days of abdominal pain into predictive models that utilized ultrasound findings as variables.

2. Methods

After receiving institutional review board approval with a waiver of informed consent, a prospective study was conducted from June 2016–June 2017 at an urban pediatric emergency department located in a freestanding children's hospital (65,000 visits per year). Patients birth to 18 years of age with suspected acute appendicitis (determined by the attending physician to have sufficient concern for appendicitis) who obtained an abdominal US as part of their work up for suspected appendicitis were included. Patients were included consecutively during the hours of 7 am–midnight and enrolled via the ultrasound sonographer in the emergency department. Patients were not enrolled from midnight–7 am as US was not available during these hours at the institution. Weekly review of all emergency department appendix ultrasounds was performed by the sonographer to ensure all ultrasounds were captured. Children who eloped, had previous appendectomy, or received an appendix US at another facility were excluded. Patients with a partially visualized appendix were considered not visualized as they could not be fully evaluated for all 9 factors compared with the fully visualized appendixes. The study site has continuous pediatric surgical coverage, pediatric radiologists and dedicated pediatric sonographers. The emergency room uses a standardized approach to suspected appendicitis with ultrasound imaging and standardized laboratory markers (white blood cell count [WBC] and c-reactive protein [CRP]). Patients who had computed tomography (CT) of the abdomen imaging in addition to US were also included, although CT imaging results were not analyzed.

Sonographic findings that were analyzed included: appendix diameter, compressibility, increased vascularity, presence of appendicolith, inflammatory changes, RLQ fluid near the appendix, lower abdominal fluid, tenderness elicited by sonographer, and ≥ 1 lymph node (≥5 mm in diameter). Of ultrasounds with a non-visualized appendix, only five of the 9 findings could be analyzed: inflammatory changes, RLQ fluid near the appendix, lower abdominal fluid, tenderness elicited by the sonographer, and ≥1 lymph node (≥5 mm in diameter). The sonographic findings were chosen in collaboration with the hospital's pediatric radiologists. The sonographic factors were evaluated on every appendix US performed. The threshold for the appendiceal diameter on the sonographer study sheet was 6 mm. Lower abdominal fluid was defined as presence of any fluid noted on the sonographer exam. Inflammatory changes were defined as inflammation and edema plus or minus adjacent bowel wall thickening or relatively fixed and non-mobile structures. Laboratory results (WBC and CRP) were also analyzed. All US studies were interpreted by pediatric radiologists. The authors met prior to data abstraction to define the specific variables of interest, and data from charts were extracted into a standardized abstraction form. If notes in the chart had disagreements about the presence of abdominal pain or duration of pain, the attending physician notes were used. By-hand chart extraction was performed first by a research assistant (demographics, days of abdominal pain, sex, CRP, and WBC values via chart review) and all results were confirmed via independent review by the principle investigator. At the time of the chart review for demographic data and labs the reviewer was not aware of the patients imaging study results or diagnosis. There were no incidences of missing data in the 5 sonographic findings, demographics or days of abdominal pain. Incidences of missing data were 0 in all the US characteristics and demographics and days of pain. There were rare instances of missing data for CRP and WBC, but this was <3% of overall data. Instances of missing data were not included in the model.

All patients who met the inclusion criteria were included in the analysis. Ultrasound exams were performed using a Siemens ACUSON S3000. The linear probe 9 L4 was used for all exams. A checklist that included the nine sonographic findings being analyzed was created so that all ultrasound images in the radiology department would have a yes or no responses to each characteristic. A standard data collection form was used by the US technologists to record data at the time of the scan and the radiologist would review. Prior to study initiation study coordinators met with US technicians to ensure a process for standardized data collection. All sonographers complete a competency training as per the medical center guidelines. Study patients were divided into two groups, those in which the appendix was visualized via ultrasound and those in which the appendix was not visualized via ultrasound. These two groups were then further subdivided into those who were diagnosed with appendicitis and those who were not. In addition to the above ultrasound findings, we collected demographics, days of abdominal pain, sex, CRP and WBC values via chart review which was performed by the principal investigator.

A WBC above 10 has been shown in the literature to be helpful in the diagnosis of acute appendicitis [14-16]. Receiver operator curve (ROC) curves (using the entire group) were used to determine the cut-off points for WBC and CRP. The calculation of sensitivity and specificity of various cut-off values of WBC and CRP for predicting appendicitis were calculated using SPSS software. The corresponding empirical ROC curves were then drawn by nonparametric method using SPSS. Additionally, abdominal pain ≥3 days was chosen as the cutoff as it was assumed most children are being assessed within this time frame and prior studies have used this same period of symptoms [17-19].

For patients who underwent appendectomy, surgical pathology reports were used to confirm the clinical diagnosis of appendicitis. Patients who were discharged home from the emergency department were tracked via the electronic medical record (EMR) system to determine if they returned within seven days of their visit for suspected acute appendicitis. Since this is the major pediatric center in the region and adult hospitals typically do not perform surgery in pediatric patients, if patients did not return to the ED within 7 days they were assumed not to have appendicitis.

Descriptive statistics were calculated using IBM SPSS Statistics 22.00 and included specificity, sensitivity, positive and negative predictive values, and multivariate logistic regression to analyze calculate odd's ratio (OR) of nine sonographic findings using appendicitis as the outcome. When comparing clinical variables that did not have normal distribution the Mann Whitney *U* test was used to compare medians and the Inter Quartile Range (IQR).

3. Results

A total of 1252 patients met the inclusion criteria. Of the 1252 patients reviewed, 60.8% ($n = 762$) had their appendix visualized on ultrasound and 39.1% ($n = 490$) did not. Of the 762 patients with a visualized appendix on ultrasound, 29.5% ($n = 225$) had appendicitis which was confirmed by pathology result. Of the patients where the appendix was not seen on ultrasound, 6.7% ($n = 33$) were diagnosed with appendicitis (Fig. 1). The hospital EMR was reviewed for all patients discharged to home from the ED for the subsequent 7 days after index visits to ensure there were no missed cases of appendicitis. In this study cohort, there were no return visits to our ED within a seven-day period with a diagnosis of appendicitis.

Of patients with a non-visualized appendix 61% ($n = 299$) were female and the mean age of the study patients was 11.7 (Table 1). These patients were 49.4% ($n = 242$) white, 36.3% ($n = 178$) Hispanic or Latino, 11.2% ($n = 55$) African-American, and 3.1% ($n = 15$) identified as other. The mean number of days of abdominal pain prior to presentation was 2.4 days. Among all patients with a non-visualized appendix, 50% of patients presented within 1 day of pain, 70% within 2 days of pain and 80% within 3 days of pain or less. The median WBC was 7.6 (IQR 2.48–11.20) and CRP of 0.4 mg/dL (IQR 0.01–1.93) (Table 1).

In patients with a non-visualized appendix on US, appendicitis was confirmed on surgical pathology in 33/490 patients. The mean number

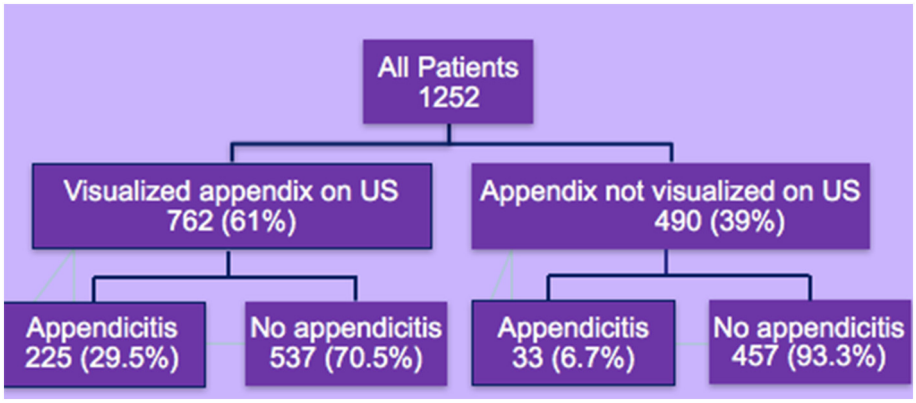

Fig. 1. Study flow chart.

days of pain was 1.6 in patients diagnosed with appendicitis vs 2.6 days in those without appendicitis ($n = 457$) ($p = 0.08$). The median WBC in patients with positive appendicitis was 13.9 (IQR 8.13–16.78) vs 7.4 (IQR 0.01–10.63) in those without appendicitis ($p < 0.001$) and the median CRP was 2.5 (IQR 0.53–9.19) in patient with appendicitis vs 0.3 (IQR 0.01–1.63) in those without appendicitis ($p < 0.001$) (Table 2). In patients with a non-visualized appendix on ultrasound who were diagnosed with appendicitis, 75% were above the 0.5 CRP cutoff. In patients with a non-visualized appendix who did not have appendicitis, 60% were below the CRP cutoff.

Logistic regression was used to evaluate the five sonographic predictors as well as laboratory results (CRP >0.5 mg/dL, WBC >10), and days of abdominal pain (≥3). Model results are shown in Table 3. Among patients with a non-visualized appendix, the likelihood of pathology positive appendicitis was significantly greater if there were inflammatory changes in the RLQ (OR 17.9, 95% CI: 4.5–72.1), CRP >0.5 mg/dL (OR 2.64, 95% CI: 1.0–6.8), or the WBC >10 (OR 4.36, 95% CI: 1.66–11.58). A duration of abdominal pain ≥3 days was significantly less likely associated with appendicitis in this model (OR 0.34, 95% CI: 0.003–0.395) (Table 3). When taken together, the absence of inflammatory changes, a CRP <0.5 mg/dL and a WBC <10 the negative predictive value (NPV) was 94.0% (95% CI: 0.92–0.96) and a negative likelihood ratio of 0.86, (95% CI: 0.75–0.99).

4. Discussion

Appendicitis remains the most common surgical emergency in children and often times establishing a correct diagnosis can be challenging [1]. The diagnosis of appendicitis using ultrasound is usually based upon a constellation of sonographic findings including a non-compressible appendix, appendiceal diameter, mesenteric fat stranding and the presence of intraabdominal fluid [20-22]. There is no current standardization for the workup of suspected appendicitis in children. Most academic pediatric emergency departments start with ultrasound as the initial choice for imaging [2]. Computed tomography has fallen out of favor, despite diagnostic precision, due to the potential risk radiation poses to children whose tissues are still growing and their likelihood of additional radiation exposure in the future [14]. In cases where the appendix is not seen on ultrasound, labs and clinical exam may drive the decision to take a child to the operating room or observe in the hospital overnight for serial abdominal examinations and repeat laboratory testing. Additional imaging such as CT or MRI may be considered for children with a high index of suspicions for appendicitis in cases where ultrasound is inconclusive as there is no single sonographic finding that is 100% sensitive or specific for the diagnosis. As a result, laboratory results such WBC and CRP are routinely used to aid in the diagnosis. There remains to be limited large detailed studies evaluating ultrasound and laboratory findings in non-diagnostic appendiceal ultrasounds.

There seems to be evolving literature evaluating sonographic findings that are most predictive for the diagnosis for acute appendicitis in children with a visualized and non-visualized appendix on US, however larger prospective studies evaluating all factors individually are lacking [2,20-26]. Larson et al. performed a study evaluating equivocal appendix ultrasounds and secondary findings and found that ultrasounds which include equivocal categories have an increase in diagnostic accuracy of appendicitis, but the study was limited by not defining which secondary findings were evaluated [27]. Another study suggested the presence or absence of periappendiceal inflammatory changes can increase US accuracy; however, this study did not evaluate which secondary factors were most predictive of appendicitis [4]. Athans et al. suggest that

Table 1
All patients demographic and laboratory results.

N (%)	All patients	Visualized appendix	Appendix not seen	*p*-Value
	1252	762	490	
Sex				0.004
Female	705 (56.3)	406 (53.3)	299 (61.0)	
Male	547 (43.7)	356 (46.7)	191 (39.0)	
Race				0.68
African American	131(10.5)	76 (10.0)	55 (11.2)	
Hispanic or Latino	434 (34.7)	259 (34.0)	178 (36.3)	
Caucasian	642 (51.3)	396 (52.0)	242 (49.4)	
Other	45 (3.6)	31 (4.0)	15 (3.1)	
Age	M 10.8; SD 4.3	M 10.2; SD 4.1	M 11.7; SD 4.4	0.05
WBC	Mdn 7.6; IQR 0.01–12.00	Mdn 7.5; IQR 0.01–12.80	Mdn 7.6; IQR 2.48–11.20	0.79
CRP	Mdn 0.5; IQR 0.01–2.67	Mdn 0.7; IQR 0.01–3.20	Mdn 0.4; IQR 0.01–1.93	0.04

CRP = C-reactive protein; IQR = interquartile range; M = mean; Mdn = median, N = number; SD = standard deviation; WBC = white blood cell.

Table 2
Univariate non-visualized appendix group.

	Appendicitis by Pathology	No appendicitis	p-value
N (%)	33	457	
Inflammatory changes	13 (39.4)	12 (2.6)	<0.001
RLQ fluid near appendix	16 (48.5)	92 (20.1)	<0.001
Lower abdominal fluid	12 (36.4)	50 (10.9)	<0.001
Tenderness by sonographer	26 (78.8)	240 (52.5)	0.002
Lymph node ≥ 5 mm	8 (24.4)	127 (27.8)	0.45
CRP > 0.5 mg/dL	Mdn 2.5; IQR 0.53–9.19	Mdn 0.3; IQR 0.01–1.63	<0.001
WBC > 10,000	Mdn 13.9; IQR 8.13–16.78	Mdn 7.4; IQR 0.01–10.63	<0.001
#days of abd pain ≥3	M 1.6; SD 1.14	M 2.6; SD 3.1	0.08

CRP = C-reactive protein; IQR = interquartile range; M = mean; Mdn = median, N = number; SD = standard deviation; WBC = white blood cell.

Table 3
Logistic regression – non-visualized appendix group.

	Odd's ratio [95% CI]	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
Inflammatory changes	18.0 [4.49–72.09]	0.43 [0.26–0.62]	0.97 [0.95–0.99]	0.52 [0.32–0.72]	0.96 [0.94–0.98]	16.0 [8.01–31.96]	0.58 [0.43–0.80]
RLQ fluid near appendix	1.6 [0.55–4.36]	0.49 [0.31–0.66]	0.80 [0.75–0.83]	0.15 [0.09–0.23]	0.95 [0.93–0.97]	2.37 [1.60–3.52]	0.65 [0.46–0.90]
Lower abdominal fluid	1.9 [0.65–5.85]	0.35 [0.20–0.54]	0.89 [0.86–0.92]	0.19 [0.11–0.31]	0.95 [0.92–0.97]	3.17 [1.88–5.35]	0.73 [0.57–0.93]
Tenderness by sonographer	2.2 [0.832–6.02]	0.79 [0.62–0.91]	0.48 [0.43–0.52]	0.10 [0.07–0.15]	0.97 [0.93–0.99]	1.52 [1.25–1.84]	0.43 [0.22–0.84]
Lymph node ≥ 5 mm	0.4 [0.13–1.04]	0.24 [0.11–0.42]	0.73 [0.69–0.77]	0.06 [0.03–0.12]	0.93 [0.89–0.95]	0.87 [0.47–1.62]	1.05 [0.87–1.27]
crp > 0.5 mg/dL	2.6 [1.02–6.82]	0.71 [0.52–0.84]	0.69 [0.65–0.73]	0.15 [0.10–0.20]	0.97 [0.94–0.98]	2.29 [1.77–2.96]	0.42 [0.25–0.72]
wbc ≥ 10,000	4.4 [1.69–11.25]	0.68 [0.49–0.82]	0.72 [0.67–0.76]	0.15 [0.10–0.22]	0.97 [0.94–0.98]	2.38 [1.81–3.14]	0.45 [0.28–0.74]
#days of abd pain ≥ 3	0.3 [0.003–0.395]	0.03 [0.001–0.17]	0.80 [0.76–0.84]	0.01 [0.0005–0.07]	0.92 [0.88–0.94]	0.15 [0.02–1.02]	1.21 [1.14–1.29]

CI = confidence interval; CRP = C-reactive protein; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; WBC = white blood cell.

equivocal ultrasounds with a low clinical score using the Pediatric Appendicitis score or Alvarado score can be used to identify patients who are low risk for an appendicitis diagnosis [28]. Prior studies have demonstrated periappendiceal fat as the only statistically significant sonographic predictor of acute appendicitis [20,21,29,30]. Other studies have evaluated color doppler ultrasonography to aid in the diagnosis of appendicitis and suggest increased blood flow in the appendiceal wall or right lower quadrant suggest appendicitis [22]. A small study of 162 equivocal appendix ultrasounds evaluated factors predictive of appendicitis showing that loss of mural stratification, peri-appendiceal fat inflammation and appendicolith were significant indicators of appendicitis [31].

A prior retrospective evaluation of the non-visualized appendix on ultrasound suggested that an equivocal US in combination with a normal WBC had a high negative predictive value of appendicitis, which our data also supports [32]. In attempts to aid the clinician with diagnostic dilemmas and improve diagnostic accuracy, laboratory results such white blood cell (WBC) and c-reactive protein (CRP) have been used in the evaluation of suspected appendicitis [14,33-37]. However, much of the prior laboratory literature evaluates laboratory results alone and does not combine it with secondary imaging findings. The literature is inconclusive regarding the sensitivity of CRP in regard to the diagnosis of appendicitis. One study found that the CRP and the Alvarado score together have an increased sensitivity in the diagnosis of appendicitis [15]. Oyetunji et al. found that patients with a normal WBC had higher rates of negative appendectomy and suggest that patients with a normal WBC can be observed when presenting early [12]. A further study suggested a CRP ≤ 6 mg/L and WBC ≤ 10 to be predictive of having a negative appendectomy [38]. Yap et al., used a different cutoff of CRP and WBC showing patients with both laboratory makers within normal range had a 100% negative predictive value for appendicitis [39]. Overall, many studies have found CRP and WBC useful in the diagnosis of appendicitis, but there are exceptions and limitations, different cutoff values used and specifically CRP elevations may not be seen until perforation [16,40-42].

Our study sought to evaluate in a large cohort of pediatric patients, for patients in whom the US did not visualize the appendix, five potential sonographic predictors of appendicitis (inflammatory changes, right lower quadrant fluid near the appendix, tenderness by sonographer, lymph node ≥ 5 mm). In our cohort, the rate of pathology positive appendicitis, when the appendix was not visualized on ultrasound was low at 6.7%. We suspect the low incidence of appendicitis in the non-visualized group due to our overall high visualization rate and lower overall likelihood of appendicitis in non-visualized ultrasounds [43]. When the appendix was not visualized by US, inflammatory changes, an increased WBC or CRP, and <3 days of abdominal pain were the strongest predictors of appendicitis. When one or more of these findings is present (inflammatory changes, an increased WBC or CRP, and < 3 days of abdominal pain), then the suspicion for appendicitis should increase. However, when all four elements are absent the likelihood of appendicitis is decreased and it may be reasonable to consider discharge home with close outpatient follow up with the pediatrician or surgeon.

Visualization of the appendix with ultrasound depends on many factors including abdominal tenderness, guarding, adipose, bowel gas and to a large degree on the proficiency of the sonographer [44,45]. Hence, the abilities and comfort of the operator can lead to non-visualization of the appendix on ultrasound and to unnecessary appendectomies, hospitalizations, or imaging [46,47]. Cases where the appendix cannot be visualized but clinical suspicion remains, present a diagnostic dilemma for the emergency physician. In our study, all ultrasounds were performed by dedicated pediatric ultrasound sonographers and interpreted by pediatric radiologists. Deliberate evaluation of specific sonographic factors seen on ultrasound are important to take into consideration when risk stratifying patients whose appendix is not seen on ultrasound. Factors such as free fluid, pericecal inflammatory fat changes and phlegmon have been shown to have high specificity in predicting appendicitis when the appendix is not visualized [17,18]. However, these data are limited both by the few overall studies that have been conducted along with the small number of patients in the studies.

There are limitations to our study. First, this was performed at a single tertiary pediatric emergency department (PED) and thus may not be reproducible in other practice settings. Our hospital is the main referring PED in the area, however, there may have been children who were sent home but diagnosed with appendicitis at another hospital. Typically, such children would be transferred to our center for care. Further, the evaluation of the appendix and other sonographic predictors seen on ultrasound may be sonographer dependent. At our institution, the percentage of visualized ultrasounds is high (60%); this may be due to well-trained pediatric sonographers whereas other institutions may not have sonographers with adequate experience to identifying these factors. Additionally, a checklist that included the 5 sonographic findings was built into all appendicitis ultrasound reads. At other institutions radiology may not comment on presence or absence of these factors thus limiting generalizability. Further, phlegmon as an independent predictor was not included in the analysis and may have added valuable information. Lastly, given that the radiology literature lacks clear and universal definitions for inflammatory changes, this finding may be subject to interobserver variability.

In conclusion, our findings suggest that in cases where the appendix is not seen on ultrasound, if inflammatory changes are seen, there is an elevation in WBC or CRP, or there are <3 days of abdominal pain the provider's suspicion for appendicitis should be raised and further evaluation may be indicated while the absence of these findings decreases the likelihood of appendicitis. Future studies to develop a scoring system based on these significant factors should be considered.

Abbreviations

(CBC) complete blood count
(CT) computed tomography
(CRP) C-reactive protein
(EMR) electronic medical record
(mg/dL) milligrams per deciliter

(OR) odds ratio
(PED) pediatric emergency department
(ROC) receiver operator curve
(US) ultrasound
(vs) versus
(WBC) white blood cell count

Presentations

Eastern Society for Pediatric Research, March 2018, Philadelphia, PA. Pediatric Academic Societies Meeting, May 2018, Toronto, Canada.

Author contributions

LM, JJS, SRS, RTB, BC and HC conceived the study. LM, JJS, TB and HC supervised the conduct of conduct of the trial and data collection. JJS provided statistical advice on study design and analyzed the data. LM drafted the manuscript and all authors contributed substantially to its revision. LM takes responsibility for the paper as a whole.

LM reports no conflict of interest.
JJS reports no conflict of interest.
SRS reports no conflict of interest.
RTB reports no conflict of interest.
BC reports no conflict of interest.
HC reports no conflict of interest.

Acknowledgments

The authors would like to thank Stephanie T. Johnson, MPH and Danielle King for their time and efforts on this project.

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