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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Ultrasound and laboratory parameters in distinguishing complicated from uncomplicated appendicitis in children

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SUMMARY

Introduction/Objective The objective was to evaluate sonographic and laboratory findings as predictors of complicated and uncomplicated appendicitis in order to decide on further treatment options.

Methods This is a retrospective cohort study of 174 pediatric patients who had laboratory tests and ultrasound done before appendectomy during a one-year period. Results were compared with the intraoperative and histopathological findings of complicated (gangrenous or perforated) or uncomplicated (phlegmonous) appendicitis and assessed by binary logistic regression with backward elimination. The initial model included eight predictors. After backward elimination four remained: periappendiceal fluid, hyperechoic periappendiceal fat, white blood cell (WBC) count and C-reactive protein (CRP). The final model included the interaction between periappendiceal fluid and hyperechoic periappendiceal fat. Diagnostic performance of each parameter was presented with sensitivity and specificity.

Results Out of all patients, 86 had uncomplicated and 88 had complicated appendicitis (37 gangrenous, and 51 perforated). In the final model three predictors were significantly associated with complicated appendicitis: interaction between periappendiceal fluid and hyperechoic periappendiceal fat, WBC count > 11 × 10^9/l, and CRP > 100 mg/l. Inclusion of interaction between periappendiceal fluid and hyperechoic periappendiceal fat excluded them as individual predictors. The maximum outside appendiceal diameter of more than 6 mm had the highest sensitivity (93.2%), while wall thickness > 3 mm was the most specific (95.2%).

Conclusion Using periappendiceal fluid and hyperechoic periappendiceal fat as sonographic predictors and WBC and CRP as laboratory predictors can differentiate uncomplicated from complicated appendicitis in children and help a physician decide on antibiotic or surgical treatment.

Keywords: ultrasound; laboratory parameters; complicated appendicitis; uncomplicated appendicitis; children

INTRODUCTION

Appendicitis is the most common cause for emergency surgery in children. Certain laboratory parameters [white blood cell (WBC) count, C-reactive protein (CRP), total neutrophil count and procalcitonin] have predictive value, but they are considered nonspecific [1, 2]. Many other nonsurgical and surgical entities such as mesenteric adenitis, Crohn's disease, infectious enterocolitis, epiploic appendagitis, omental infarction, intussusception, ovarian torsion, and urolithiasis can cause pain in the right iliac fossa. Therefore, combining clinical, laboratory, and imaging findings remains essential for the definitive diagnosis [3].

The interest in the non-operative management of appendicitis has grown most likely due to a growing number of randomized studies showing postoperative complications and higher operative treatment costs. Additionally, when using antibiotics as first-line therapy, appendectomy can be avoided in significant number of patients [4–8]. This non-surgical approach is reserved for patients with uncomplicated appendicitis, without signs of gangrene or perforation, while complicated appendicitis treated this way leads to higher risk of surgical complications and subsequent surgery [6, 9].

Because of its noninvasive nature, availability, high diagnostic accuracy, lack of radiation and contrast administration, ultrasonography is the diagnostic modality of choice in pediatric patients [10]. Studies have shown that it is a reliable imaging method for the differentiation of perforated and non-perforated appendicitis when relying on highly specific findings such as periappendiceal fluid and the loss of the conspicuity of the echogenic submucosal layer [11, 12, 13].

The aim of our study was to evaluate sonographic and laboratory findings as predictors of complicated and uncomplicated appendicitis in order to decide on further treatment options.

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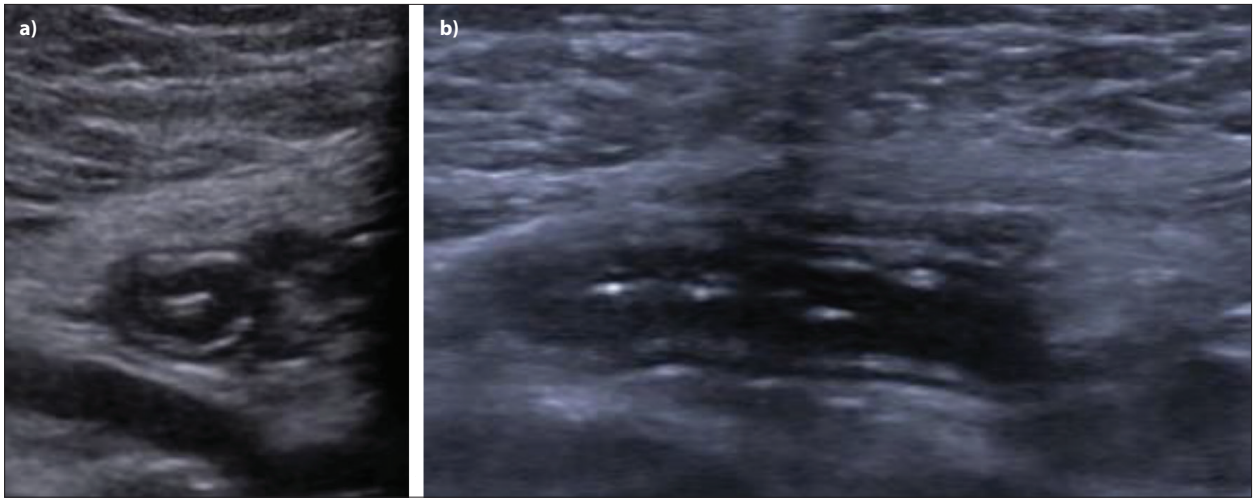

Figure 1. Acute uncomplicated appendicitis in a seven-year-old boy with a one-day history of abdominal pain, vomiting, and diarrhea; axial (a) and longitudinal (b) grayscale ultrasonography images of the right lower quadrant shows noncompressible 8 mm appendix with wall thickening and typical target sign

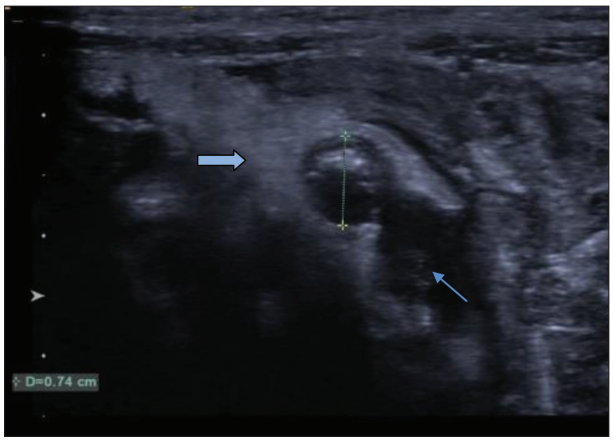

Figure 2. Grayscale axial ultrasonography images of the right lower quadrant in a five-year-old girl with a one-day history of abdominal pain shows a 7.4 mm in diameter noncompressible appendix with hyperechoic periappendiceal fat (bold arrow), wall thickening, and periappendiceal free fluid (thin arrow); complicated (perforated) appendicitis was found at appendectomy

METHODS

This is a retrospective cohort study done at a Tertiary Pediatric Institution approved by Institutional Ethics Committee. This study included 174 patients aged 2–18 years who had laboratory tests and ultrasound done by a pediatric radiologist before appendectomy between January 2022 and January 2023.

Patient population

We used our hospital's information system to review medical charts of all patients who received an ultrasound examination before the operation, had appendectomy during the same hospital admission as sonography, and had intraoperatively or histopathologically proven appendicitis. Patients who had some data missing due to incomplete data entry or had some alternative diagnosis proven (carcinoid), were excluded from the study, so the final number of the patients was 174.

Diagnostic protocol

Ultrasonography examinations were performed by one of the attending radiologists from our department on Siemens Acuson s2000 (Siemens Medical Solutions USA, Inc., Malvern, PA, USA), using convex and linear transducers (2–6 mHz and 4–9 mHz). The whole abdomen was scanned, with special interest for the right lower quadrant. The grayscale images in long and short axis were made as well as color Doppler images.

According to the previous studies we reviewed the following sonographic findings in each patient: the maximum outside diameter, wall thickness, periappendiceal fluid, periappendiceal hyperechoic fat, lymphadenitis and appendicoliths [12, 13, 14]. The maximum outside diameter was measured in short axis view and it was considered significant when it was 6 mm or more (Figure 1). Wall thickness was considered significant when measured over 3 mm. Periappendiceal fluid was diagnosed in direct proximity of the appendix, while periappendiceal hyperechoic fat was defined as increased echogenicity of the tissue adjacent to the appendix (Figure 2). Lymphadenitis was defined as sonographically detectable lymph nodes. An appendicolith was diagnosed when we identified an intraluminal hyperechogenic focus with an acoustic shadow (Figure 2). Because of the different therapeutic approach for patients with appendiceal abscess or inflammatory mass, they were excluded from this study [15]. Laboratory findings that were used as predictors were white blood cell (WBC) count over 11×10^9/l and C-reactive protein (CRP) over 100 mg/l [16].

Intraoperative and histopathological findings

Based on the intraoperative findings and histopathological findings, appendicitis was classified into three groups: phlegmonous, gangrenous, and perforated. Phlegmonous appendicitis was defined by transmural neutrophil infiltration without gangrene and perforation, gangrenous appendicitis was characterized by foci of ischemia that cause

Table 1. Distribution of age, sex, sonographic and laboratory findings

Parameters	Total (n = 174)	AUA (n = 86)	ACA (n = 88)
Age	12 (2.5–18)	9.3 (2.5–18)	8.9 (4–18)
Male	108 (62%)	54	54
Female	66 (38%)	35	31
Maximum outside diameter (mm)	9.24 ± 2.53	9.51 ± 2.58	8.97 ± 2.54
Wall thickness > 3 mm	14 (8%)	6 (7%)	8 (9%)
Periappendiceal fluid	73	20	53
Periappendiceal hyperechoic fat	117	49	68
Lymphadenitis	76	43	33
Appendicoliths	38	17	21
White blood cell count	15.5 ± 5.26	14.54 ± 5.22	18.16 ± 5.38
C-reactive protein level, med (min–max)	41.2 (0.3–225)	23.30 (0.3–225)	60.90 (2.2–225)

AUA – acute uncomplicated appendicitis; ACA – acute complicated appendicitis

gangrene. Perforation was determined by the presence of a transmural defect. Phlegmonous appendicitis was considered to be uncomplicated while gangrenous and perforated were designated as complicated [17].

Statistical analysis

All statistical analyses were calculated using the Statistical Package for Social Sciences IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Sonographic findings and laboratory parameters were compared with intraoperative and histopathological findings of complicated and uncomplicated appendicitis and assessed by binary logistic regression. A backward variable elimination was performed to determine a proper model for the regression analysis. The initial model included eight predictors: the maximum outside appendiceal diameter, wall thickness, periappendiceal fluid, hyperechoic periappendiceal fat, lymphadenitis, presence of appendicoliths, WBC count and CRP level. After backward elimination only four remained: periappendiceal fluid, hyperechoic periappendiceal fat, WBC count and CRP level. In the final step, third model was constructed by including the interaction between periappendiceal fluid and hyperechoic periappendiceal fat. In the final model there were three significant predictors: WBC count, CRP, and interaction between periappendiceal fluid and hyperechoic periappendiceal fat. The threshold for assessing statistical significance was set to 0.05. Diagnostic performance of each parameter was presented with sensitivity and specificity.

RESULTS

There were 174 patients who met the inclusion criteria, 108 male (62%) and 66 female (38%). The age range was from two years and six months to 18 years, with a mean age of 12 years. Out of all patients, 86 (49.43%) had histopathologically proven uncomplicated appendicitis, and 88 (50.57%) had complicated appendicitis (37 gangrenous (21.3%) and 51 perforated (28.73%)). Mean maximum outside diameter of appendix was 9.24 mm. Mean age of patients with complicated appendicitis was 8.9 years and was significantly younger than the mean age of patients with uncomplicated appendicitis which was 10.3 years ($p < 0.005$) (Table 1).

After the binary logistic regression was performed, the following predictors showed significant correlation with complicated appendicitis: periappendiceal fluid had odds ratio (OR) of 4.93 with $p < 0.001$, hyperechoic periappendiceal fat (OR = 2.17, $p = 0.047$), WBC count > 11×10^9/l (OR = 3.58, $p = 0.028$), CRP > 100 mg/l (OR = 3.72, $p = 0.003$). In the final model, we included interaction between periappendiceal fluid and hyperechoic periappendiceal fat which showed OR of 8.63 and $p < 0.001$. Inclusion of interaction between these two variables excluded them as individual predictors (Table 2).

Table 2. Binary logistic regression with backward elimination

Finding	OR	p value
Periappendiceal fluid	4.93	< 0.001
Hyperechoic periappendiceal fat	2.17	0.047
WBC count > 11×10^9/l	3.58	0.028
CRP > 100 mg/l	3.72	0.003
Interaction between periappendiceal fluid and hyperechoic periappendiceal fat	8.63	< 0.001

OR – odds ratio; WBC – white blood cells; CRP – C-reactive protein

The maximum outside appendiceal diameter of more than 6 mm was the most sensitive parameter of complicated appendicitis (93.2%), but it had a very low specificity (8.6%). When the diameter threshold was increased (over 6mm), the specificity values were higher, but had a concurrent decrease of sensitivity values. The most specific (95.2%) sonographic finding for the complicated appendicitis was wall thickness > 3 mm, with a lower sensitivity (16.6%) (Table 3).

DISCUSSION

Some studies have indicated antibiotic-only treatment for patients with uncomplicated appendicitis [5–9]. This has made it necessary to establish clinical, laboratory, and imaging findings that would accurately distinguish it from complicated appendicitis and ensure the complications

Table 3. Sensitivity and specificity values of sonographic and laboratory findings for acute complicated appendicitis

Finding	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MOD > 6 mm	93.2	8.6	49.7	33.3
Wall thickness > 3 mm	16.6	95.2	57.1	75
Periappendiceal fluid	61.4	76.8	75	64.7
Periappendiceal hyperechoic fat	58.1	64.9	77.3	43
Lymphadenitis	38.2	50.6	44.7	43.9
Appendicoliths	24.4	80.9	57.9	50
WBC count 11×10^9/l	84.3	28.2	55.1	63.1
CRP level > 100 mg/l	32.95	93.1	82.8	59.5

MOD – maximum outside diameter; WBC – white blood cells; CRP – C-reactive protein; PPV – positive predicted value; NPV – negative predicted value

of non-surgical treatment of perforated appendicitis are avoided. Even though computed tomography (CT) is still widely used as an imaging modality of choice for appendicitis [18, 19, 20], in our institution fewer than 5% of patients undergo CT for this diagnosis. As a radiation-free tool, operated by trained pediatric radiologists, ultrasonography is considered a method of choice in evaluating pediatric patients with suspected appendicitis [21, 22]. Additionally, some publications show poor correlation between CT reports of appendiceal perforation and intraoperative or histopathological findings [23].

In our study all 40 patients that had intraoperative or histopathological findings of perforation were classified as complicated appendicitis on ultrasonography. Moreover, we proved that all the patients that had perforation, had at least one of the following two ultrasonography parameters, periappendiceal fluid and hyperechoic periappendiceal fat. These results show high predictive value of the combination of these parameters as reported previously [11, 12]. On the other hand, when assessing the reports that were classified as uncomplicated appendicitis, we found that 43 of them had both of the aforementioned parameters negative, but only 32 of these patients (74.4%) had the diagnosis proved histopathologically. These results indicate that in order to rule out complicated appendicitis, some other factors should be included in the decision-making process. Most of the scoring systems, like the Alvarado score and appendicitis inflammatory response score, were developed to identify patients with appendicitis, discriminating it from non-appendicitis [24, 25]. Atema et al. [16] presented a scoring system based on seven clinical and ultrasonography features, with a cut-off value of six points, which showed high sensitivity of 95%, but low specificity of 45.7%. Düzgün et al. [26] presented a new scoring system based on the Alvarado score and diagnosed complicated appendicitis with sensitivity of 86.1% and specificity of 90.4% when patients had a score of 10.5 or higher.

Using the multivariate analysis, we were able to conclude that the interaction between periappendiceal fluid and hyperechoic periappendiceal fat on ultrasonography is significantly associated with complicated appendicitis. These results are consistent with the ones presented by Rawolle et al. [14] and Carpenter et al. [11]. Furthermore, we proved that two laboratory parameters, WBC count with cut-off value of 11×10^9/l and CRP of more than 100 mg/l, were also valuable predictors of complicated appendicitis as previously shown by Rawolle et al. [14]. Similarly, the sensitivity of 93.2% for appendiceal diameter greater than 6 mm, proved that it is a finding associated with complicated appendicitis, as stated in a recent paper by Bekiaridou et al. [12].

There are some limitations to our study, mostly related to its retrospective design. Because of the lack of standardization of the ultrasonography protocol, loss of the submucosal layer was not evaluated in all of our patients so we had to exclude that parameter from our statistical analysis. Due to these limitations, we are planning a prospective study with a bigger patient population where we would also include the loss of the submucosal layer as a predictive parameter. In addition, the size of our study population was affected due to the fact that patients who did not undergo appendectomy and received antibiotic-first treatment, were not included.

CONCLUSION

In conclusion, our results show that ultrasonography can be reliably used as a primary imaging modality for the differentiation between uncomplicated and complicated appendicitis in children, including gangrene and perforation. Beside the interaction between periappendiceal fluid and hyperechoic periappendiceal fat as sonographic parameters, also WBC count > 11×10^9/l and CRP > 100 mg/l proved to be significantly correlated to complicated appendicitis. Using these criteria, appendectomy can be avoided in a significant number of patients and those with uncomplicated appendicitis can be treated with antibiotics.

Conflict of interest: None declared.

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Употреба ултразвука и лабораторијских параметара у разликовању компликованог и некомпликованог апендицитиса код деце

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САЖЕТАК

Увод/циљ Циљ рада је био евалуирати ултразвучне и лабораторијске налазе као предикторе компликованог и некомпликованог апендицитиса у циљу доношења одлуке о даљим терапијским могућностима.

Методе У ову ретроспективну кохортну студију укључена су 174 педијатријска болесника у периоду од годину дана, којима су урађене лабораторијске анализе и ултразвучни преглед уочи апендектомије. Вршено је поређење резултата са интраоперативним и хистопатолошким налазом компликованог (гангренозног или перфоративног) и некомпликованог (флегмонозног) апендицитиса и рађена је процена уз помоћ бинарне логистичке регресије са елиминацијом уназад. Иницијални модел је укључивао осам предиктора. Након елиминације уназад, преостала су четири: периапендикуларна течност, хиперехогена периапендикуларна маст, број леукоцита и Ц-реактивни протеин (ЦРП). Коначни модел је укључивао и интеракцију између периапендикуларне течности и хиперехогене периапендикуларне масти. Дијагностичка вредност сваког параметра представљена је сензитивношћу и специфичношћу.

Резултати Од свих болесника, 86 је имало некомпликовани, а 88 компликовани апендицитис (37 гангренозни и 51 перфоративни). У коначном моделу три предиктора су била значајно повезана са компликованим апендицитисом: интеракција између периапендикуларне течности и хиперехогене периапендикуларне масти, број леукоцита > 11×10^9 / *l* и ЦРП > 100 *mg/l*. Укључивање интеракције између периапендикуларне течности и хиперехогене периапендикуларне масти их је искључило као индивидуалне предикторе. Највећу сензитивност од свих параметара (93,2%) показао је спољашњи дијаметар апендикса > 6 *mm*, док је најспецифичнији параметар (95,2%) била дебљина зида > 3 *mm*.

Закључак Коришћење периапендикуларне течности и хиперехогене периапендикуларне масти као ултразвучних предиктора, и броја леукоцита и ЦРП као лабораторијских предиктора, може да разликује некомпликовани од компликованог апендицитиса код деце и помогне клиничару да одлучи о терапији антибиотицима или хируршком третману.

Кључне речи: ултразвук; лабораторијски параметри; компликовани апендицитис; некомпликовани апендицитис; деца