Clinical and Laboratory Methods in Diagnosis of Acute Appendicitis in Children

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Aim To compare the diagnostic accuracy of clinical examination, white blood cell and differential count, and C-reactive protein as routine tests for acute appendicitis with that of interleukin-6 (IL-6) and ultrasonography.

Methods Eighty-two children were admitted to the Department of Pediatric Surgery and Intensive Care, Ljubljana, Slovenia because of suspected acute appendicitis. Among them, 49 children underwent surgery for acute appendicitis and 33 had abdominal pain but were not treated surgically and were diagnosed with non-specific abdominal pain or mesenteric lymphadenitis on sonography. Clinical signs of acute appendicitis were determined by surgeons on admission. White blood cell count and differential and serum concentrations of C-reactive protein and IL-6 were measured and abdominal ultrasonography was performed.

Results Ultrasonography showed the highest diagnostic accuracy (92.9%; 95% confidence interval [CI], 84.5%-98.0%, Bayes' theorem), followed by serum IL-6 concentration (77.6%; 67.1-86.1%, receiver-operating characteristic [ROC] curve analysis), clinical signs (69.5%; 59.5-79.0%, Bayes' theorem), white blood cell count (68.4%; 57.2-78.3%, ROC curve analysis), and serum C-reactive protein concentration (63.7%; 52.1-74.3%, ROC curve analysis). Ultrasonography achieved also the highest specificity (95.2%) and positive (93.8%) and negative (93.3%) predictive values, whereas clinical signs showed the highest sensitivity (93.9%).

Conclusion Ultrasonography was a more accurate diagnostic method than IL-6 serum concentration, laboratory marker with the highest diagnostic accuracy in our study, and hence it should be a part of the diagnostic procedure for acute appendicitis in children.

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Diagnosis of acute appendicitis remains a problem in pediatric surgery. Despite the fact that it is one of the most common surgical emergencies in children, the methods for diagnosing acute appendicitis have significantly not changed over the past few decades. Clinical examination and laboratory parameters, such as white blood cell, differential counts (percentage of neutrophil granulocytes and band neutrophil granulocytes), and C-reactive protein were the only diagnostic tools for many years. Perforation rate was high, as well as the number of negative appendectomies (1,2). Following the introduction of ultrasonography in the last two decades and computed tomography (CT) in the last decade, the rate of negative appendectomies in children has decreased (3-6), but the perforation rate has remained high (22%-62%) (6,7). Therefore, an ideal diagnostic method or a combination of laboratory, clinical, and imaging methods is still being sought.

A recent meta-analysis of clinical findings and laboratory tests (white blood cell and differential count and C-reactive protein) in adults showed that a combination of clinical and laboratory variables has a much higher diagnostic value for acute appendicitis than each variable alone (8). Among laboratory methods, new inflammatory markers for the detection of acute appendicitis have been most extensively studied. Interleukin-6 (IL-6) has proven to be the most promising one. Elevated concentrations of IL-6 were found in adults with acute appendicitis, especially with perforation, but their diagnostic value was controversial (9-13). Recently, similar findings have been reported in children with acute appendicitis (14,15).

Since the first description of the technique of graded compression for the visualization of the inflamed appendix in 1986 (16), ultrasonography has been gradually introduced as a diagnostic imaging procedure for acute appendicitis. Initially, it was thought to be most helpful in children with suspected acute appendicitis in whom the clinical findings were dubious (17). Later, some authors suggested the routine use of ultrasonography in all children with suspected acute appendicitis in order to decrease the negative appendectomy rate and to select the patients who do not require hospital admission (18,19). Recently, some studies have reported a delay in surgical treatment in children undergoing ultrasonography, no clear-cut improvement in diagnostic accuracy (20), and a higher rate of misdiagnosis (21), with the authors again recommending ultrasonography only for dubious cases of acute appendicitis.

There have been few prospective studies comparing ultrasonography with clinical findings or laboratory tests in children (22), and no study has so far included more recent inflammatory markers, such as IL-6. The aim of our study was to compare the diagnostic accuracy of routine diagnostic tests (clinical examination, white blood cell count, and C-reactive protein) with that of the more recent laboratory marker IL-6 and ultrasonographic examination using well-defined criteria.

Patients and methods

This prospective study was conducted in the Department of Pediatric Surgery and Intensive Care at the University Medical Center Ljubljana (tertiary care setting) between March and December, 2004.

Patients

The study included 104 consecutive children with suspected acute appendicitis who satisfied the following inclusion criteria: suspected acute appendicitis, hospital admission, and signed informed consent by the parents. Twenty-two patients were excluded from the study due to the following reasons: clinically or microbiologically diagnosed infection in 9 patients (pneumonia in 2 patients, acute tonsillopharyngitis in 4, urinary tract infection in 2, and viral enterocolitis in 1), operation for ileocolic intussusception in 1 pa-

tient, and technical problems in blood sampling and storing in 12 patients. According to the required treatment, patients were divided into two groups. One group comprised 49 patients with acute appendicitis who had surgical intervention and the other group comprised 33 children diagnosed with non-specific abdominal pain or sonographic mesenteric lymphadenitis who did not require surgery.

The study was approved by the National Medical Ethics Committee of the Ministry of Health, Republic of Slovenia, and written consent was obtained from parents before blood sampling.

Methods

Clinical signs of acute appendicitis determined by the surgeon and duration of symptoms were documented on admission. The clinical signs included direct tenderness in the right lower quadrant, percussion and rebound tenderness, localized rigidity, and diffuse rigidity of the abdominal wall. At least one clinical sign had to be present in order to consider the patient positive for clinical signs. In all operated children, in-hospital observation time until the surgical procedure was recorded. The surgeons were aware of routine laboratory and ultrasound findings but not the IL-6 concentration in the serum before making the decision to operate. None of the 33 patients with abdominal pain was readmitted in the 3 months following discharge from our institution, which is the only hospital in this region.

Blood samples for routine laboratory tests (white blood cell count, differential count, and C-reactive protein) and an additional 1.0 mL of blood for later analysis of IL-6 concentration were obtained on admission. White blood cell and differential counts were measured by the Coulter Counter (Bayer Advia 120, Bayer, Germany). C-reactive protein concentration was quantified by a routine immunochemical turbidimetric assay (Boehringer-Mannheim, Mannheim, Germany). The upper limit of the reference interval for C-reactive protein and sensitivity was 5 mg/L. Whole blood for analysis of IL-6 was centrifuged; the serum was separated and stored frozen at -80°C for later IL-6 measurements. The serum IL-6 concentration was measured by chemiluminescent sequential immunometric assay (*Immulite®IL-6*, DPC, Los Angeles, CA, USA). The sensitivity of the IL-6 assay was 2 ng/L.

Abdominal ultrasonography was performed in 56/82 (68%) of patients. It was not done in children with evident clinical signs of diffuse peritonitis (diffuse abdominal rigidity and clinical deterioration) who were taken to the operating room immediately after admission. Also, it was not done in children with mild clinical signs whose condition markedly improved within hours of admission. Diagnosis of acute appendicitis was made by an experienced sonologists. It was based on the following major criteria: visualization of a non-compressible, aperistaltic, painful appendix with an outer diameter of more than 6 mm, presenting with a "target-like" cross-sectional view and a tubular appearance with a blind-ending tip on the longitudinal scan, surrounded by echogenic inflamed fat. Additional criteria were hyperemia in the wall on color Doppler, appendicolith, and the absence of gas in the lumen. Criteria of less importance were free peritoneal fluid and enlarged regional lymph nodes. The criteria for perforation were disruption of the wall and/or presence of an abscess (23-25). The detailed procedure for ultrasonographic examination is described elsewhere (25). In non-operated patients, the diagnosis of mesenteric lymphadenitis was made if three or more enlarged lymph nodes at least 6 mm in diameter were found in the right lower quadrant and if no other abdominal or pelvic abnormalities, except terminal ileitis, were observed (17).

Removed appendices were fixed in formalin and analyzed histologically. The appendix specimens were classified as normal appendix (0 patients), mild acute appendicitis (3 patients),

moderate acute appendicitis (3 patients), severe (phlegmonous) acute appendicitis (15 patients), and gangrenous acute appendicitis (28 patients), according to the criteria described elsewhere (26,27). The finding of perforation was also noted. The final diagnosis was based on histology and, in the case of perforation, on macroscopic evaluation by the surgeon. The pathologists were not aware of the patients' clinical data, except for the surgical diagnosis.

Statistical analysis

Data were presented as median and range for numeric data and as counts (%) for categorical data. For comparison of numeric variables an unpaired *t* test was used for normal distribution and unpaired Mann-Whitney test for asymmetric distribution. Fisher exact test was used for comparison of categorical variables. All variables showing a significant difference between the groups were further analyzed. Receiver-operating characteristic (ROC) curves were drawn to define the optimum sensitivity, specificity, cut-off value, predictive values, and diagnostic accuracy, determined by the area under the ROC curve (AUC) of the studied laboratory markers (28,29). The cut-off values at which the greatest sum of sensitivity and specificity was obtained were determined by using Medcalc for Windows. Sensitivity, specificity, predictive values, and diagnostic accuracy of ultrasonography and of clinical signs were calculated using Bayes' theorem. The differences were considered to be statistically significant when *P* values were lower than 0.05. The statistical analysis was performed using Medcalc for Windows, version 5.0 (MedCalc Software, Mariakerke, Belgium) and Statistical Package for the Social Sciences for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

The male/female ratio was similar in each group, but the children with acute appendicitis were older (Table 1). There were no negative appendectomies during the study. Sixteen of 49 cases with acute appendicitis resulted in perforation. Mesenteric lymphadenitis was found in 11 of 33 children with abdominal pain.

Table 1. Characteristics of the study population*

Characteristic	Group with acute appendicitis	Group with abdominal pain
Number	49	33
Male/female†	32/17	21/12
Age (median, range) (years)‡	10.8 (4.1-13.9)	9.0 (2.8-13.6)
In-hospital observation time (median, range)	4.0 h (15 min-3 d)	/

*Acute appendicitis – children with acute appendicitis. Abdominal pain – children with diagnosis of non-specific abdominal pain or sonographic mesenteric lymphadenitis; in-hospital observation time – time until the surgical procedure.
†$P = 0.939$, χ^2 test.
‡$P = 0.019$, one-way analysis of variance.

Significant differences between acute appendicitis and abdominal pain were seen in the following diagnostic tests: clinical signs, white blood cell count, serum C-reactive protein, IL-6 concentrations, and ultrasonography (Table 2), and these were further analyzed.

The ROC curve analysis of laboratory tests showed that the IL-6 concentration had the highest diagnostic accuracy (Figure 1), but this was lower than the diagnostic accuracy of ultra-

Table 2. Duration of symptoms, clinical signs, white blood cell (WBC) count, differential count*, C-reactive protein (CRP), interleukin-6 (IL-6), and ultrasonography findings in acute appendicitis and abdominal pain†

Diagnostic method	Finding (median, range) in the group with acute appendicitis	Finding (median, range) in the group with abdominal pain	*P*
Duration of symptoms (h)	24.0 (4.0-168.0)	24.0 (2.0-120.0)	0.577‡
Clinical signs:			
positive	46	22	0.002§
negative	3	11	
WBC ($x10^9$/L)	15.1 (5.9-31.6)	10.6 (4.7-25.5)	0.008‖
Neutrophil granulocytes (%)	76 (54-91)	73 (40-93)	0.328‖
Band neutrophil granulocytes (%)	4 (0-24)	0 (0-14)	0.105‡
CRP (mg/L)	21.0 (5.0-137.0)	9.0 (5.0-148.0)	0.038‡
IL-6 (ng/L)	11.8 (5.0-1000.0)	5.0 (2.0-59.2)	<0.001‡
Ultrasonography:			
positive	32 TP	1 FP	<0.001§
negative	3 FN	20 TN	
not assessed	14	12	

*Percentage of neutrophil granulocytes and band neutrophil granulocytes.
†Abbreviations: acute appendicitis – children with acute appendicitis; abdominal pain – children with diagnosis of non-specific abdominal pain or sonographic mesenteric lymphadenitis; TP – true positive; FP – false positive; FN – false negative; TN – true negative.
‡Unpaired Mann-Whitney test.
§Fisher exact test.
‖Unpaired *t*-test.

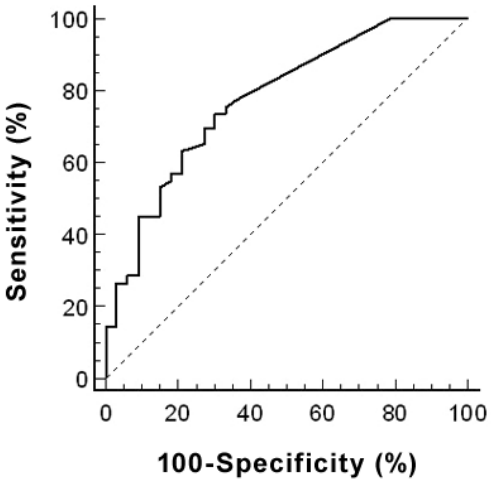

Figure 1. Receiver-operating characteristic (ROC) curve of interleukin-6 (IL-6) for prediction of acute appendicitis.

sonography. Clinical signs had the highest sensitivity of all studied diagnostic tools, while ultrasonography had the highest specificity and positive and negative predictive values (Table 3).

There were no significant differences in median (range) duration of symptoms between the children with perforated appendix (24.0 hours [4.0 hours-3.5 days]) and those with acute appendicitis without perforation (24.0 hours [4.0 hours-7.0 days]) nor in the median (range) in-hospital observation time (3.5 hours [15 minutes-3 days] vs 5.0 hours [15 minutes-27 hours]). Only median (range) IL-6 concentration was significantly higher in children with perforated appendix (33.6 ng/L [5.0-1000.0 ng/L]) compared with those with acute appendicitis without perforation (9.5 ng/L [5.0-271.0 ng/L]).

White blood cell counts, serum C-reactive protein, and IL-6 concentrations in children with acute appendicitis were dependent on the duration of symptoms (Table 4). White blood cell count and IL-6 concentration were highest in the patients with the shortest duration of symptoms (0-12 hours), while the serum C-reactive protein concentration was lowest in this group (Table 4).

Table 4. White blood cell (WBC) count, serum C-reactive protein (CRP), and interleukin-6 (IL-6) concentrations in children with acute appendicitis as functions of duration of symptoms

Duration of symptoms (hours)	Laboratory marker (median, 95% confidence intervals)		
	WBC	CRP	IL-6
0-12	16.4 (12.7-20.8)	5.0 (5.0-32.0)	12.5 (7.4-22.2)
13-24	16.3 (11.7-21.6)	24.0 (14.0-40.6)	11.8 (6.4-31.5)
25-48	12.5 (7.8-18.6)	45.0 (5.0-132.0)	11.2 (5.0-195.3)
>48	13.2 (6.4-20.4)	33.5 (12.1-57.3)	7.7 (5.0-100.0)

Discussion

This study of acute appendicitis in children compared clinical examination, routine and more recent laboratory tests and ultrasonographic examination. Ultrasonography showed the highest diagnostic accuracy, specificity, and positive and negative predictive values, and clinical signs the highest sensitivity.

In a similar adult study (30) comparing ultrasonography with routine laboratory tests (white blood cell count and C-reactive protein) and clinical findings (Ohmann score), ultrasonography showed the highest accuracy, specificity, and positive predictive value. Contrary to our results, the highest sensitivities and negative predictive values were achieved by white blood cell count

Table 3. Diagnostic accuracy (95% confidence interval), sensitivity, specificity and positive (PPV) and negative (NPV) predictive values of clinical signs, white blood cell (WBC) count, C-reactive protein (CRP), interleukin-6 (IL-6), and ultrasonography in diagnosing acute appendicitis

Diagnostic method	Indices of diagnostic values				
	diagnostic accuracy (median, 95% confidence intervals)	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
Clinical signs*	69.5 (59.5-79.0)	93.9	33.3	52.9	87.2
WBC†	68.4 (57.2-78.3)	73.5	65.6	63.1	75.6
CRP†	63.7 (52.1-74.3)	73.9	54.5	56.5	72.4
IL-6†	77.6 (67.1-86.1)	73.5	69.7	65.9	76.7
Ultrasonography*	92.9 (84.5-98.0)	91.4	95.2	93.8	93.3

*Bayes' theorem.
†Receiver-operating characteristic (ROC) curve analysis.

and C-reactive protein (30). In our study clinical signs had the highest sensitivity, but the lowest specificity and positive predictive value. Thus, relying on clinical signs alone would probably increase the negative appendectomy rate. A similar sensitivity, but much higher specificity of clinical findings, was found in a Dutch study (22), which included not only children who were actually admitted to hospital, as was the case in our study, but children referred to hospital because of suspected acute appendicitis.

Our finding that the differential count has a questionable value in diagnosing acute appendicitis because of its low specificity is in agreement with many other authors (31,32). The diagnostic accuracy of white blood cell count was higher in our study than in the Finnish study, which included children of 2 different age groups (33). In two different adult studies of acute appendicitis, Eriksson et al (9,34) found that white blood cell count can decrease to normal values during the observation period. The same result was observed in our children with acute appendicitis, as white blood cell count on admission was lower in children with a longer duration of symptoms than in those with a shorter duration of symptoms. The diagnostic accuracy of C-reactive protein in our study was within the range found in the abovementioned Finnish study (33). There was, however, a difference in the study design. Our study included all children admitted because of suspected acute appendicitis, whereas the Finnish study included only operated patients. A continuing rise in C-reactive protein concentrations was shown in two studies performed by Eriksson et al (9,34), which is concordant with the well-known C-reactive protein dynamics, ie, the rise of its concentration 6 hours after inflammation until the peak is reached in approximately 48 hours (35). Such a trend was also present in our children with acute appendicitis. We found only two studies, performed mainly in adults, which included patients suspected of having acute appendicitis as well as those operated for acute appendicitis. Their reported diagnostic accuracies of white blood cell count and C-reactive protein concentration were similar to our results (30,36).

The laboratory test for acute appendicitis in the children with the highest diagnostic accuracy in our study was the inflammatory marker IL-6. Its diagnostic accuracy in the adult population is controversial. Several studies in adults were unable to confirm the usefulness of IL-6 for diagnosing acute appendicitis (9,11,12,37), while others, including studies in children, found it to be a useful marker (10,13-15,38). The differences in the studies could be attributed to different study populations and designs. Some authors included only operated patients (9-11,13,38), while others included all admitted patients (12,14,15,37). All patients with known infection other than acute appendicitis and mesenteric lymphadenitis were excluded from our study. This could result in lower IL-6 levels in the abdominal pain group and consequently improve the diagnostic accuracy of IL-6 in our study, as IL-6 is a non- specific marker of inflammation (39). Similar to our findings, Pajaanen et al reported that the preoperative diagnostic accuracy of IL-6 in adults operated for acute appendicitis, determined by the area under the ROC curve, was higher than that of white blood cell count and C-reactive protein (13). Recently, two studies of IL-6 in children have been published. The first showed that determination of the serum IL-6 concentration on admission was of no diagnostic value. The second showed that the determination of IL-6 6 hours after admission reached the highest accuracy rate, compared with white blood cell count and tumor necrosis factor-α(TNF-α) (14). The second study showed that IL-6 correlated significantly with the severity of appendiceal inflammation, but the diagnostic usefulness of the difference between IL-6 and C-reactive protein was not significant (15). IL-6 was also the only diagnostic marker in our study that could differentiate between the children with acute appendicitis with perforation and those without perforation.

Our data confirmed the results of previous studies that the IL-6 concentration correlated well with the degree of appendix inflammation (9-13). The IL-6 concentrations in the sera of our children with acute appendicitis on admission were higher in those with a shorter duration of symptoms than in those with a longer duration of symptoms. The reason for this is probably the short half-life of IL-6 (39).

Our results of ultrasonography were similar to the results of two studies conducted on children (18,19) and to the study by Vidmar et al (25), conducted on adult patients in our institution at the same time as our study. Although one North American study on adults (40) showed the superiority of CT over ultrasonography in diagnosing acute appendicitis, a recent study reported that accuracy of ultrasonography in a mixed adult and child study was similar to that of CT (2). The advantages of ultrasonography (no radiation risk, relatively low price and 24-hour accessibility) make it the radiographic method of choice for diagnosing acute appendicitis in our institution. However, strict criteria must be used by skilled sonologists in order to avoid operator-dependent differences. Also, quick accessibility of ultrasound examination must be assured to avoid delays in surgical treatment. Some studies found that in-hospital observation time was longer in perforated appendicitis (41,42), whereas we found no differences in the median in-hospital observation time between the acute appendicitis cases with and without perforation. In addition, our median in-hospital time was shorter in both acute appendicitis cases with and without perforation than the in-hospital times in other similar studies on children and adults (41-43). We can, therefore, speculate that ultrasonographic examination did not significantly delay surgery in our patients. The data of an adult ultrasonographic study support this statement (25).

Some limitations of the study merit consideration. The first is the relatively small number of patients recruited from only one department. However, the highest accuracy of ultrasonographic examination and very low negative appendectomy rate were confirmed by the almost simultaneous study in adults at the same institution (25). Moreover, the number of patients enrolled in our study is similar to the number of patients in other studies of inflammatory marker IL-6 (10,13). The second limitation, related to the design of our study, is that in non-operated patients the diagnosis of non-specific abdominal pain could not be made with certainty without pathohistologic examination. The follow-up of 3 months after discharge ruled out the possibility of short-term relapses of acute appendicitis, but could not exclude long-term relapses, which can occur as late as one year after discharge (44), and spontaneously resolving appendicitis without relapse (45). A larger clinical study is needed to clarify some controversial issues in the diagnosis of acute appendicitis in children.

In conclusion, data from the present study showed that clinical signs were still the most sensitive diagnostic method. Among laboratory tests, IL-6 is the best laboratory marker of acute appendicitis, although it is only of medium diagnostic accuracy. White blood cell count and C-reactive protein concentration in serum are of low diagnostic accuracy and have only a supportive role in diagnosing acute appendicitis in children. Ultrasonography has the highest diagnostic accuracy of all the tests studied and should be added to clinical examination and laboratory tests in the diagnostic workup of children with acute appendicitis.

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