

Diagnostic value of procalcitonin, C-reactive protein and leukocyte count in detecting acute appendicitis in paediatric patients - a single center experience

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ABSTRACT

Aim To evaluate diagnostic reliability of accessible laboratory findings in recognition of acute appendicitis (AA).

Methods A retrospective study included children aged 0-15 years with abdominal pain that lasted less than 5 days with at least two of the signs/symptoms - abdominal pain, tenderness of the lower right quadrant of the abdomen, "return" sensitivity of the abdomen to palpation, loss of appetite, nausea, vomiting, body temperature >37.2°C. Values of procalcitonin (PCT), C-reactive protein (CRP) and the leukocyte count were analyzed in the peripheral blood.

Results Among 114 children, 63 (58.2%) were boys and 50 (41.8%) girls; median age of 9.5 years. Elevated values of PCT were found in 74 (65.5%), CRP in 94 (83.1%), and leukocytes in 78 (69%) (65%) children. Almost uniform significance in the recognition of AA was found for pathological values of PCT and CRP with sensitivity of 65% and 83% and diagnostic accuracy of 63% and 59%, respectively, but somewhat lower sensitivity for leukocytes, 61%. A very high predictive value of 98% for PCT and CRP, and PCT with leukocytes was found; CRP with leukocytes had a negative predictive value of 100%.

Conclusion PCT values have significant sensitivity, specificity and diagnostic accuracy in recognizing AA, while CRP and leukocytes, with high sensitivity, as non-specific markers can be a significant support for clinical assessment in the timely diagnosis of AA.

Keywords: appendix, diagnosis, inflammation, predictive value of tests

INTRODUCTION

Acute appendicitis (AA) is one of the most common surgical emergencies in pediatrics, whose symptoms, signs and presentation significantly depend on the anatomical location of the inflamed appendix, the degree and intensity of the inflammatory process, but also on the age of the child, since non-specific presentations are more common in earlier age (1). As a significant number of children presents with an atypical clinical picture, the frequency

of unrecognized AA is still high, 28-57% in children up to 12 years of age, and almost 100% in children up to 2 years of age (2). Postponing the diagnosis of AA can result in the development of complications and potentially life-threatening conditions such as bacterial peritonitis, obstruction of the small intestine, formation of intra-abdominal abscesses, but also result in a greater number of deaths (3). The frequency of perforation of the appendix in case of untimely recognition of AA is about 15% in adolescents, but up to 100% in children under the age of 3 (4,5). For a timely diagnosis of AA, in addition to the anamnestic data, clinical presentation of the child, findings during the physical examination, the results of laboratory tests such as the value of procalcitonin (PCT), the value of C-reactive protein (CRP) and the total num-

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ber of leukocytes have been increasingly determined in routine work in the last few years (6).

The inflammation plays a key role in the development of AA, mediated by protein mediators, cytokines and chemokines (7). Once the translocation of bacteria from the appendix to the lymph nodes and portal vein occurs, the production of PCT is induced, and it has a half-life of 24-30 hours, while CRP does not reach high values in the first 24 hours after the onset of inflammation and takes up to 72 hours to reach the maximum level (8). However, leukocyte values increased in children with AA compared to leukocyte values of children in whom appendectomy was negative (9,10).

Given that no similar research has been conducted neither in our country nor in the neighboring countries that would determine the diagnostic value of easily accessible inflammatory markers in acute appendicitis, we decided to implement it in order to facilitate the clinical assessment of children with suspected appendicitis to pediatricians and pediatric surgeons.

The aim of this study was to evaluate diagnostic reliability of accessible laboratory findings in recognition of acute appendicitis.

PATIENTS AND METHODS

Patients and study design

This retrospective study was conducted in the period between 1 June 2018 and 30 June 2022 at the Clinic for Children's Diseases of the Tuzla University Clinical Center. The inclusion criteria were: children's age 0-15 years on the day of the examination, abdominal pain that lasts less than 5 days and the presence of at least two of the listed signs/symptoms - migratory abdominal pain, tenderness of the lower right quadrant of the abdomen, "return" sensitivity of the abdomen to palpation, loss of appetite, nausea, vomiting, elevated body temperature >37.2 °C. The exclusion criteria were: age over 15 years on the day of the examination, abdominal pain lasting longer than 5 days, children who did not have at least two of the listed signs/symptoms, children who were previously diagnosed and/or treated for acute appendicitis, children for whom no written consent from parents/guardians for inclusion in the research was received.

Based on the final outcome, the children were divided into two groups. The examined group consisted of children who required operative treatment, and the control group of children who only required observation and/or conservative treatment.

The study protocol was approved by the Ethical Committee of the University Clinical Centre of Tuzla.

Methods

For children who met the inclusion criteria, anamnestic data, age, gender, duration of illness, existence of other acute and/or chronic diseases, clinical signs and symptoms of acute abdominal disease, observations during physical examination of the child were analyzed. Data were collected from children's medical records. At the first examination, a laboratory blood analysis was performed to determine the values of PCT, CRP and the leukocytes in the peripheral blood. The PCT >0.5 ng/mL, CRP >5.0 mg/L and leukocyte $>10 \times 10^9/L$ were considered elevated, pathological values.

Based on the obtained data, the necessary further treatment of the child was assessed, whether it required further observation during 24-48 hours and other diagnostic tests, or surgical treatment of AA was required. For children who were only observed, the final outcome was noted - they were discharged. For children who were surgically treated, the removed appendix was subjected to pathohistological analysis. Postoperative complications were also recorded.

Statistical analysis

In statistical data processing, standard methods of descriptive statistics (median, minimum, maximum, Shapiro-Wilk W test for testing the distribution of variables) were used. To test the statistical significance of the difference between the groups parametric and non-parametric significance tests (χ^2 -test, Student's t-test, Fischer's test), as well as the linear correlation method were used. Depending on the conditions for examining correlations, Spearman's and Pearson's correlation coefficients were used. Variables were tested by logistic regression analysis to determine their predictive value. The hypotheses were tested at the significance level of $p < 0.05$. The difference between samples is considered significant if $p < 0.05$.

RESULTS

During the investigated time period, 3242 children were observed and/or treated in the specialist ambulance, and/or through the Day Hospital and/or at the Pediatric Surgery Department of the Clinic for Children's Diseases. A total of 1462 (45.1%) showed clinical signs of acute abdominal pain of which 326 (22.3%) children had clinical signs of acute abdominal pain with duration of less than 5 days. The presence of at least two of the listed signs/symptoms was shown 196 children, 114 (58.2%) boys, and 82 (41.8%) girls. Compared by gender, no statistically significant differences were found between the examined and control group of children with acute abdominal pain that lasted less than 5 days ($p=0.52$).

The median age of 196 children with acute abdominal pain was 9.5 years (IQR: 5-12 years) with a minimum and maximum value of 1-13.5 years. In the examined group, the median age was 10 (IQR: 5.5-14) years, and in the control group 10 (IQR: 5-13) years, respectively (p=0.42).

Elevated value of PCT was found in 65.5%, CRP in 83.1% and leukocytes in 69% of children in the examined group, compared to 33% (PCT), 60% (CRP) and 42% (leukocytes) of children in the control group (Table 1). The appearance of an elevated PCT value was 2.87 times higher in the children of the examined group than in the children of the control group. The median value of PCT in the examined group was 1.3 (IQR: 0.4-5.0; min. 0.01 and max. 29.72) ng/mL, and in the control group 0.4 (IQR: 0.04-1.05; min. 0.01 and a max. 7.2) ng/mL (p<0.0001) (Table 1).

Significantly higher CRP value with the median value higher than 50 (IQR: 15-100; min. 1 mg/L and max. 290 mg/L) compared to the CRP in the control group which was 16 (IQR: 4.9-47.5 mg/L; min. 5 and max. 114) mg/L (p<0.0001) (Table 1). Considering the diagnostic reliability of the associated parameters of acute inflammatory events, we found a very high diagnostic reliability (98%) for PCT values with CRP and PCT with elevated leukocyte values; while CRP values with elevated leukocyte values had a negative predictive value of 100%, the proportion of truly negative findings in the negative findings of the analyzed parameters (Table 2).

DISCUSSION

Acute appendicitis has a frequency in developed countries of 5.7–50 children per 100,000 inhabitants per year. A peak incidence is around 10 years of age (2,11) with predominance of boys (12–14). Our results are similar, with the median age of 9.5 years and the boys were predominant. One of the common protein markers of inflammation is PCT, which is synthesized in response to bacterial infections but also in some other clinical conditions that can strongly correlate with serious bacterial infections (15).

Despite the fact that the diagnosis of AA probably remains a clinical one, additional diagnostic tools are welcome. The results of our study support the hypothesis that inflammation markers can help in the timely diagnosis of AA. Several studies have shown that PCT has significant diagnostic accuracy in detecting complicated AA (16–19). The children of our study group had median PCT of 1.3 ng/ml, while in the control group the median was 0.4 ng/mL. Chandel et al. (20) observed that children who did not have AA, had PCT values of 0.09–0.18 ng/mL, while the median value of PCT in the group of children with AA was 0.9 ng/ml. Feng et al. (21) and Dharwal et al. (22) reported values similar to ours. Chandel et al. (20) noted sensitivity and specificity of PCT in diagnosing AA of 95.67% and 100%, respectively; our results are in line with those results, 65% and 60%, respectively and the predictive positive and negative values were 69% and 56%, respectively.

Table 1 Representation of positive findings of procalcitonin (PCT), C-reactive protein (CRP) and leukocytes in 196 children with acute abdominal pain included in the study

Patients group	Median (IQR; min. – max.)			No (%) of patients		
	PCT ng/mL	CRP mg/L	Leukocytes x10 ⁹ /L	PCT>0.5 ng/mL	CRP >5.0mg/L	Leukocytes >10x10 ⁹ /L
Examined (n=113)	1.3 (0.4-5.0; 0.01-29.72)	50 (15-100; 1-190)	13.5 (10.1-16.8; 4.0-32.0)	74 (65.5)	94 (83.1)	78 (69)
Control (n=83)	0.4 (0.04-1.05; 0.01-7.2)	16 (4.9-47.5; 5-114)	10.5 (6.0-12.4; 0.5-24)	33 (39.7)	60 (72.3)	42 (50.6)
p	<0.0001	<0.0001	<0.0001	<0.0004	0.06	0.013

Table 2 Assessment of the diagnostic value of the parameters of acute inflammatory events in the recognition of acute appendicitis in 196 children with acute abdominal pain included in the study

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
PCT	65	60	69	56	63
CRP	83	28	61	54	59
Leukocytes	61	49	62	48	56
PCT+CRP	65	60	69	56	98
PCT+Leukocytes	65	60	69	56	98
CRP+Leukocytes	69	60	65	100	60

PPV, positive predictive value; NPV, negative predictive value; PCT, procalcitonin; CRP, C-reactive protein

The difference in the diagnostic value of PCT and CRP depends on the divergence of these two inflammatory markers, and several studies showed conflicting results (23–25). In the research of Withers et al. (26), a difference was observed between elevated CRP values and the presence of AA, as well as for CRP values in complicated compared to uncomplicated appendicitis.

A prospective multicenter randomized controlled trial done by Styruud et al. (27) highlights the utility of serial determination of CRP and the sensitivity of CRP values in predicting the development of AA, CRP median value of our examined group was 3.75 times higher than in the control group. Beltrán et al. (28) found significantly higher CRP in children with AA than in those without it, as well as Zimmerman et al. (29), who reported that the value of CRP higher than 100 mg/L strongly correlated with appendix necrosis and values above 170 mg/L were a strong predictor of the presence of infection.

Our results showed higher values of leukocytes in the examined group as well as the statistically significant difference for leukocyte values between the two groups. Monsalve et al. (25) implied that the total number of leukocytes was significantly increased in children with AA compared to children with negative appendectomy. Our results are in agreement, since our diagnostic accuracy for leukocytes was 56%. An increase in the negative predictive value from 41.9% to 95.8% was found in children where the leukocyte value was combined with ultrasound findings (30). Virmani et al. (31) point out that leukocyte values had a sensitivity of 68.9%, a specificity of 60.5%, and predictive positive and negative values of 31.1% and 88.1%. The predictive positive and negative values for elevated values of leukocytes in our research were 62% and 48%. Considering the reliability of leukocyte and CRP values in recognizing AA inflammatory markers, together they had significant sensitivity and specificity while the negative predictive value was 100%.

Systemic review and meta-analysis of seven studies and 1011 patients showed that CRP had the best ability to select and recognize AA, followed by leukocyte count and PCT (32). CRP had an acceptable positive likelihood ratio, while PCT had a high positive likelihood ratio and it was therefore recognized as a reliable diagnostic marker (32). We obtained a significantly higher sensitivity of CRP compared to PCT and the value of leukocytes 83% vs 65% and 61%, however, when we considered sensitivity of the combination of parameters, very similar sensitivity was found for PCT with CRP (65%), PCT with leukocytes (65%) and CRP with leukocytes 69%, yet the high diagnostic accuracy of PCT and CRP (98%) and PCT and leukocytes 98%. PCT has been shown to have a high positive likelihood ratio in differentiating complicated forms of AA. The superiority of CRP over PCT in the diagnosis of AA can be ex-

plained by a wide range of pathological factors that can cause of AA (16). We noted high sensitivity of CRP of 83%, leukocytosis had significant sensitivity of 61%, and both parameters together showed significant sensitivity of 69%.

Newer research suggests that despite the low positive predictive value of traditional markers, by combining them the negative predictive value can be improved (24,33). We agree, since we found that the combination of leukocytes and CRP had a negative predictive value of 100%. It is necessary to add the determination of PCT values to routine tests, which can greatly improve the diagnostic assessment (34).

In conclusion, PCT values have significant sensitivity, specificity and diagnostic accuracy in recognizing acute appendicitis, while CRP and leukocyte values with high sensitivity, as non-specific markers, can be significant support for clinical observation in the timely diagnosis of acute appendicitis.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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