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ORIGINAL

Diagnostic value of serum inflammatory markers (Leucocyte count, C-reactive protein and neutrophil count) for detection of acute appendicitis in children

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Aim: to evaluate diagnostic value leucocyte count, percentage of neutrophil count and CRP levels in detection of acute appendicitis in children.

Methods: We prospectively studied 112 consecutive patients, aged 0-15 years, who were referred to the outpatient pediatric department of our hospital with symptoms and signs of acute appendicitis, with intervals of less than 7 days from the onset, between October 01, 2010 and September 30, 2011. Predictors were values of leucocyte count, percentage of neutrophil count and CRP levels. Outcome measure was the PHD confirmation of acute appendicitis. Appendicitis-specific clinical and laboratory findings were done.

Results: We found a significant difference between the values of leukocytes to the PHD group findings ($F = 17.46$, $df = 3$, $p < 0.001$). There were significant differences in the values of neutrophils by PHD diagnostic categories between groups of subjects ($F = 18.87$, $df = 3$, $p < 0.001$). Values of C-reactive protein also in comparison between groups divided according to the findings of the PHD appendectomy, showed a statistically significant difference between groups (ANOVA, $F = 13.67$, $df = 3$, $p < 0.001$).

Conclusion: In this study has been shown that Leucocyte count, C-reactive protein and neutrophil count are helpful tools to support the clinical diagnosis of all stages of appendicitis especially phlegmonous and perforated appendicitis in childhood.

Key words: acute appendicitis, neutrophils, C-reactive protein, leukocytes

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Competing interests
The authors declare no competing interests.

INTRODUCTION

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].

It is generally accepted that appendectomy is the therapy of choice in children. Conservative management, as evaluated in some studies of adult patients [3] is not established for children. A delay in diagnosis of acute appendicitis (AA) is associated with increased risk of perforation and further complications. On the other hand in young children, geriatric patients, and in adolescent females, the negative appendectomy rate may be as high as 50 % [4]. Many attempts have been made to determine ways of decreasing the negative laparotomy rate after a clinical suspicion of AA. Under this background it would be very important to differentiate mild early appendicitis from nonspecific abdominal pain. However, despite complete clinical history, physical examination, and the usual laboratory studies clear decision aids for detection of early AA are lacking.

Ultrasonography has been used increasingly in the past years with positive results and both high sensitivity and specificity rates [5]. Furthermore, the introduction of diagnostic laparoscopy and laparoscopic appendectomy in clinical pediatric surgical practice opened new horizons. One of the main question is, if laboratory tests are helpful to diagnose even early AA in Childhood. For a long time the main auxiliary test has been the leucocyte count. The diagnostic value of laboratory inflammatory markers has been studied in the past years with different and contradictory results, commonly in a heterogeneous population of adults and children [6].

A recent meta-analysis of clinical findings and laboratory tests (white blood cell and differential count and C-reactive protein) showed that a combination of clinical and laboratory variables has a much higher diagnostic value for acute appendicitis than each variable alone [3,7].

We conducted this study with intention to evaluate preoperative diagnostic value leucocyte count, percentage of neutrophil count and CRP levels in detection of acute appendicitis in children.

PATIENTS AND METHODS

Setting

The study was conducted at the Pediatric Clinic of the University Clinical Center in the town of Tuzla, Bosnia and Herzegovina.

Design

Prospective cohort study

Patients

Data were collected in a prospectiove manner on 112 consecutive patients aged 0-14 years, who were referred to outpatient department of Clinic of children's diseases Public health institution University Clinical Center Tuzla (PHI UCC) with acute right fossa pain and underwent appendectomy from October 1st 2010 until September 30th 2011.

Excluding criteria were appendicitis verified by imaging methods before the patients arrived at the first examination, duration of symptoms longer than 7 days, and patients with previously diagnosed and/or acute appendicitis.

Methods

The data for the study were entered into a dedicated form. The duration of pain rounded to 0.5 hours was recorded. It was determined the number of leukocytes and neutrophils in the peripheral blood so as the value of CRP. Achieved data and clinical examination at outpatient department were the criteria for a decision on continuation of home treatment, surgery or observation. Data on the ultrasound findings are not included in the analysis because the ultrasound examination is not routine procedure at our Department. Patient who were referred to home treatment were instructed on diet regime and rules for regular check- ups. If surgical treatment was indicated, those patients were subsequently included in the study. The final outcome - surgery or discharge home were recorded for the patients who were observed. After surgery, removed appendix was subjected to histopathologic analysis according to classified report was obtained:

1. No signs of inflammation
2. Incipient inflammation
3. Flegmonous inflammation
4. Flegmonous inflammation with a necrotic perforated appendicitis

STATISTICAL ANALYSIS

The data have been analyzed by statistical software package SPSS 18.0 (SPSS Inc. Chicago, IL, USA). They have done the basic tests and descriptive statistics with measures of dispersion and central tendency. Each variable was tested for association with a normal distribution using the Kolmogorov-Smirnov test. Quantitative variables were ordered t-test for independent samples with correction for unequal variances where they were distributed by a normal distribution. For quantitative comparison of independent variables that were not distributed by a normal distribution analysis has been made by the Mann-Whitney test. Categories of variables were analyzed $\chi 2$-test. Performance of diagnostic testing was done using Receiver Operating Characteristics (ROC) analysis. Comparison of the performance is tested by comparing the steam area under the ROC curve (AUROC). All tests were done with statistical significance level of 95% ($p < 0.05$).

RESULTS

In total, the study included 112 patients, of whom 80 (71.4%) were male and 32 (28.65) were female. The median age in the sample was 10 years (interquartile range: 8- 13 years) and range from a minimum of 1 year to a maximum of 15 years.

It was compared the length of the pain between patients' categories formed on the basis of PHD findings after appendectomy. A significant difference in duration of pain was detected between the groups with the longest duration in the group of examinees who had perforated appendix (Kruskal- Wallis; X2=10. 98; df=3; p< 0.012).

Mean values of leucocyte count, percentage of neutrophil count and CRP levels were 15, 15; 12, 46 and 46, 35 respectively.

WBC values were compared between categories of examinees according to the PHD finding. Overview of descriptive statistics is given in Table 1. It was detected a significant difference between groups using ANOVA analysis (F=17.46; df=3; p<0.001).

Table 1. The overview of leukocytes value according to PHD diagnosis

	Mean	SD	Minimum	Maximum
Flegmonous inflammation	17,04	4,71	9,10	27,20
Incipient inflammation	13,59	4,61	5,88	22,50
Necrotic perforated appendicitis	18,57	5,26	9,10	28,30
No signs of inflammation	10,31	3,48	3,80	19,70

SD - standard deviation

Post– hoc analysis of groups by reciprocal comparison is shown in Table2. Examinees with normal finding in the appendix had significantly lower values of leukocytes.

The overview of descriptive statistics of absolute neutrophil values in categories according to PHD diagnosis is given in Table 3. ANOVA analysis showed the presence of significant differences between groups (F= 18.87; df= 3; p<0.001). Post- hoc analysis, shown in Table 4, again displayed significantly lower values in patents with normal finding in the appendix.

Values of C- reactive protein (CRP), also showed statistically significant difference between groups (ANOVA; F=13.67; df=3; p<0.001) in comparison between groups divided by PHD finding after appendectomy. The overview of descriptive statistics regarding the value of CRP within compared groups is given in Table 5.

Post- hoc analysis is shown in Table 6. The values here were significantly higher within the group of examinees with histologically proven perforation.

Table2. Leukocytes count post– hoc analysis of groups by reciprocal comparison

(I) PHD	(J) PHD	Mean difference (I-J)	p	95% CI	
				Lower limit	Upper limit
Flegmonous inflammation	Incipient inflammation	3,45	,03	,25	6,64
	Necrotic perforated appendicitis	-1,54	,56	-4,61	1,54
	No signs of inflammation	6,72	,00	3,49	9,95
Incipient inflammation	Flegmonous inflammation	-3,45	,03	-6,64	-,25
	Necrotic perforated appendicitis	-4,98	,00	-8,20	-1,76
	No signs of inflammation	3,28	,06	-,09	6,64
Necrotic perforated appendicitis	Flegmonous inflammation	1,54	,56	-1,54	4,61
	Incipient inflammation	4,98	,00	1,76	8,20
	No signs of inflammation	8,26	,00	5,00	11,51
No signs of inflammation	Flegmonous inflammation	-6,72	,00	-9,95	-3,49
	Incipient inflammation	-3,28	,06	-6,64	,09
	Necrotic perforated appendicitis	-8,26	,00	-11,51	-5,00

Table 3. The overview of absolute neutrophil values according to PHD diagnosis

	Mean	SD	Minimum	Maximum
Flegmonous inflammation	14,62	4,49	7,15	23,66
Incipient inflammation	10,71	4,34	3,02	18,61
Necrotic perforated appendicitis	15,76	5,31	6,01	27,55
No signs of inflammation	7,64	3,33	1,85	16,35

Table 4. Neutrophyl count post– hoc analysis of groups by reciprocal comparison

(I) PHD	(J) PHD	Mean difference (I-J)	p	95% CI	
				Lower limit	Upper limit
Flegmonous inflammation	Incipient inflammation	3,91	,01	,81	7,02
	Necrotic perforated appendicitis	-1,13	,76	-4,12	1,85
	No signs of inflammation	6,98	,00	3,85	10,12
Incipient inflammation	Flegmonous inflammation	-3,91	,01	-7,02	-,81
	Necrotic perforated appendicitis	-5,05	,00	-8,17	-1,92
	No signs of inflammation	3,07	,07	-,20	6,34
Necrotic perforated appendicitis	Flegmonous inflammation	1,13	,76	-1,85	4,12
	Incipient inflammation	5,05	,00	1,92	8,17
	No signs of inflammation	8,11	,00	4,96	11,27
No signs of inflammation	Flegmonous inflammation	-6,98	,00	-10,12	-3,85
	Incipient inflammation	-3,07	,07	-6,34	,20
	Necrotic perforated appendicitis	-8,11	,00	-11,27	-4,96

Table 5. The overview of C-reactive protein value according to PHD diagnosis

	Mean	SD	Minimum	Maximum
No signs of inflammation	15,72	22,73	,80	75,40
Incipient inflammation	24,85	33,28	,10	126,80
Flegmonous inflammation	39,35	31,54	1,30	129,80
Necrotic perforated appendicitis	97,74	90,25	,30	301,00

SD - standard deviation

Table 6. C-reactive protein count post– hoc analysis of groups by reciprocal comparison

(I) PHD apendiksa	(J) PHD apendiksa	Mean difference (I-J)	p	95% CI	
				Lower limit	Upper limit
No signs of inflammation	Incipient inflammation	-9,13	,93	-48,04	29,79
	Flegmonous inflammation	-23,63	,35	-60,98	13,72
	Necrotic perforated appendicitis	-82,02	,00	-119,64	-44,40
Incipient inflammation	No signs of inflammation	9,13	,93	-29,79	48,04
	Flegmonous inflammation	-14,50	,74	-51,45	22,44
	Necrotic perforated appendicitis	-72,89	,00	-110,12	-35,67
Flegmonous apendicitis	No signs of inflammation	23,63	,35	-13,72	60,98
	Incipient inflammation	14,50	,74	-22,44	51,45
	Necrotic perforated appendicitis	-58,39	,00	-93,97	-22,81
Necrotic perforated appendicitis	No signs of inflammation	82,02	,00	44,40	119,64
	Incipient inflammation	72,89	,00	35,67	110,12
	Flegmonous inflammation	58,39	,00	22,81	93,97

DISCUSSION

Despite the diagnosis of AA will probably remain a clinical one, additional diagnostic tools are welcome. Generally a high index of suspicion is required to make the diagnosis and operate prior perforation and peritonitis. When the child exhibits the classical picture of the appendicitis syndrome, the diagnosis of acute suppurative appendicitis will generally be confirmed at operation. However many, if not the majority of patients do not present with this classical signs [8]. The results of our study support the hypothesis, that Leucocyte count, C-reactive protein and neutrophil count can help to diagnose advanced stages of AA.

Andersson et al. [3] and Guraya et al. [9] in their research report that the increase in leukocytes is always present in phlegmatic and perforated appendicitis. Determination of leukocytes in the blood of the patient is certainly one of the oldest and most common additional diagnostic methods in the diagnose of acute appendicitis. Determination of the number of leukocytes in the serum has a particular importance when deciding on surgery in early stage of the disease. However, leukocytosis is not a specific response to acute appendicitis, so this analysis must be complemented by other diagnostic methods. This applies in particular to a detailed clinical examination of patients that may confirm, but also exclude acute appendicitis.

Analyzing the absolute value of neutrophils in our study, we found significant difference in their number in patients whose a definitive histopathological findings showed normal appendix in relation to all forms of pathologically altered appendix. Analyzing pathologically altered appendixes, the highest mean neutrophils count was found in patients with perforated appendix (15.76×109) while the mean value of neutrophils in the initial inflammation was the lowest 10.71×109.

The authors of most studies cited high predictive value of the absolute number of neutrophils in the diagnosis of acute appendicitis in children[9,10]. Ng and Lai [11] suggested that the increased absolute number of neutrophils in patients with clinical suspicion to acute appendicitis increases the likelihood of making good diagnosis so that absolute number of neutrophils could be a good parameter for the diagnosis of acute appendicitis, which we confirmed in our study. Multivariate regression analysis in mentioned study showed no significant association between acute appendicitis and elevated CRP and increased the number of leukocytes, while increasing absolute neutrophils count was the only significant associated factor. Other authors suggest a combination of mentioned laboratory parameters has a better predictive value in diagnosis of acute appendicitis [9,10].

Mikaelsson and Arnbjornsson [12] for the first time published a study in which they demonstrated a correlation between elevated CRP values and acute appendicitis. They stated that 156 pediatric patients whose CRP was in normal value before surgery, the definitive histopathological diagnosis after surgery showed a normal appendix, while in patients with elevated CRP was found mesenteric lymphadenitis or acute appendicitis. They also concluded that if the degree of inflam-

mation was greater, duration of the disease was longer and CRP value was higher as well.

CRP values in our study, divided according to the histopathologic findings, were the lowest in patients with normal appendix, while the highest values were found in patients whose appendix was perforated. We found a statistically significant difference in CRP values in patients with normal appendix in relation to all examined forms of pathologically altered appendix.

The sensitivity of CRP in the diagnosis of acute appendicitis was between 40-87%, while specificity was between 53-82% in several studies [13]. In study Moon et al. [14] there are significantly elevated CRP values in patients with pathologically altered appendix, which is similar to the results of our study.

Park et al. [15] published results similar to ours and stated that in patients with severely elevated CRP level was found a high degree of inflammation. Mean CRP value in patients with gangrenous or perforated appendix was 9.76mg/dl as the slightly lower mean value found in our study.

According to the research of Chung JL et al. [16] diagnostic values of CRP in children have great significance, especially in the case of acute perforated appendicitis. This study shows that defining limits of CRP 25 mg/L and its increase above this figure indicate the greater probability of acute appendicitis (LR, 5.2; 95% CI 1.7-16). A similar result confirmed the study Rodriguez et al. [17] of CRP marginal value greater than 17 mg/L. The concentration of CRP lower than the selected marginal values reduces the probability of acute appendicitis.

Numerous studies have been conducted to evaluate the diagnostic value of leukocyte count and CRP in predicting acute appendicitis and confirmed the high sensitivity of mentioned inflammation markers [18].

Results of the study Siddique et al. [19] reported a higher diagnostic value of CRP in the diagnosis of acute appendicitis compared with the values of leukocytes, which we did not confirm in our study. The authors also reported high sensitivity of these markers in the diagnosis of perforated appendix. The combination of these markers increases the sensitivity to 95-100% in the diagnosis of acute appendicitis, which confirms an excellent diagnostic value of these markers of inflammation as we showed in our study.

In a meta- analysis Andesson [3] states that a combination of clinical signs and laboratory tests (WBC, CRP) can quite likely establish correct diagnosis of acute appendicitis. This analysis showed that WBC and CRP are equally important parameters in diagnose so as clinical signs i.e. higher values of WBC and CRP with a higher probability point to acute appendicitis, which confirmed Siddique et al. [19] in their study.

Comparing our results with the results of other studies, we noticed higher sensitivity if we combine both markers (WBC and CRP) not only in diagnose of acute but perforated appendicitis also [20].

Bikel et al. [21] in study conducted on patients 5-80 years reported that if the time interval between pain onset and surgery was longer than 36 hours, the risk of appendix perforation was higher, as the results we obtained in our study. Moon at al. [14] found no correlation between duration of pain and surgery with complications of appendicitis, which explain with a higher number of children of younger age included in the study and problems in communicating with those examinees.

We presented the results of a pediatric study focusing on the diagnostic value of a spectrum of acute phase reactants for the diagnosis of acute appendicitis. It has been shown, that Leucocyte count, C-reactive protein and neutrophil count are helpful tools to support the clinical diagnosis of all stages of appendicitis especially phlegmonous and perforated appendicitis in childhood.

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