

Can C-Reactive Protein and White Blood Cell Count Predict Complicated Appendicitis in Children?

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Objective and summary of background data: Acute appendicitis remains a challenging diagnosis in pediatrics, and inflammatory markers are helpful in the management of these patients. Our purpose is to evaluate the prediction potential of specific laboratory parameters (total white blood cell count and C-reactive protein) regarding complicated appendicitis and to highlight the need for a careful interpretation of their levels.

Methods: A retrospective study was performed on a population of children who underwent appendectomy between January and December 2014. Patients were clustered in 2 groups according to severity of disease: group I, uncomplicated appendicitis; and group II, complicated appendicitis. Data regarding total white blood cell count and C-reactive protein levels were obtained. Variables were compared using χ^2 , Student *t*-tests, and Pearson correlation.

Results: A total of 128 pediatric patients (age <18 years) with a mean age of 10.2 ± 3.9 years were included (76 males). Complicated appendicitis occurred in 27 patients. Age of patient was statistically different in groups I (10.6 ± 3.8 years) and II (8.5 ± 3.7 years; $P = 0.011$). CRP is a parameter statistically correlated to severity of appendicitis ($P < 0.001$), but white blood cell count is not ($P = 0.295$). A CRP level (above 4.3 mg/dL) was 74% sensitive and 77% specific for complicated appendicitis.

Conclusions: The authors emphasize the role of CRP value in the prediction of the severity of appendicitis in children and present a potential usable cutoff value of 4.3 mg/dL, as a marker of complicated appendicitis.

Key words: C-reactive protein – Leukocytosis – Biomarkers – Perforated appendicitis – Child

Acute appendicitis is the most common abdominal surgical emergency in the pediatric age group. Complicated acute appendicitis (perforation, abscess, plastron formation, and generalized peritonitis) may be detected in 20% to 50% of all appendicitis in children,¹ a higher percentage than in adults. Those younger than 3 years have a higher risk of complications.² In order to prevent them it is necessary to undertake an early diagnosis of acute appendicitis.

Several works have evaluated the diagnostic accuracy of different inflammatory markers in appendicitis [C-reactive protein (CRP), interleukin-6, leucocyte elastase, serum amyloid A, neutrophil count, procalcitonin, and white blood cell (WBC) count] and also its behavior in disease staging (early or advanced appendicitis, perforated or unperforated appendix), some reporting different and contradictory results.³⁻⁸ Only a few of those reports were performed in pediatric patients, including those studying the role of the biomarkers in the severity of acute appendicitis (uncomplicated versus complicated appendicitis).

Some studies in adults support that CRP levels alone are not sufficient to make the diagnosis of acute appendicitis, although they represent the most accurate marker for the diagnosis.⁹ In a previous study,⁴ identification of children with severe appendicitis was supported by interleukin-6 or CRP, but not by WBC count. It is generally agreed that more studies are needed to evaluate the accuracy of these markers, mainly in children, to provide surgeons with complementary information in discerning the necessity for urgent operation.

The present study comprises only patients of the pediatric age group and reflects its pathophysiologic characteristics. The aim of our study is to understand how specific inflammatory marker (total WBC count and CRP) values relate to the severity of appendicitis.

Patients and Methods

A retrospective study was performed on a population of children (age <18 years) who underwent surgery for suspected acute appendicitis at a tertiary children's hospital between January and December 2014. The diagnosis was established preoperatively by a pediatric surgeon on the basis of clinical history and physical observation. Abdominal ultrasound scan was used when the clinical diagnosis of appendicitis was uncertain. Laboratory tests were prescribed by

the surgeon or the pediatrician at hospital admission when a suspicious diagnosis existed.

Data regarding total WBC count and CRP were collected. Reference intervals for WBC count were considered according to patient age and dichotomized into groups based on the presence or absence of leukocytosis. The upper reference limit for CRP was 0.5 mg/dL for all age groups.

Depending on surgical findings (and histologic confirmation) appendicitis was defined as uncomplicated if there were no signs of perforation or abscess (group I), and complicated if either diffuse peritonitis, sealed perforation, or abscess with perforated appendix was found (group II).

Data collection and statistical analysis were performed using SPSS software (21.0), and results are shown as mean and SD and compared as appropriate. Pearson correlation was also performed to compare continuous variables. A 2-tailed *P* value of <0.05 was considered significant for all tests. Receiver-operator characteristic curves were obtained only for CRP values.

Results

A total of 128 pediatric patients had an appendicitis and underwent an appendectomy during the study period.

There were 76 males (59.4%) and 52 females (40.6%), with a mean age of 10.2 ± 3.9 years. A total of 27 appendixes had pathologic findings consistent with complicated appendicitis (corresponding to 21.1%).

In the studied population, 33.6% of children with confirmed diagnosis of appendicitis had a normal WBC count and 30.71% had a normal CRP value. Normal levels of WBCs were present in 36.7% of patients in group I and in 25.9% of patients in group II. The mean value of CRP in each group is shown in Table 1.

When comparing the sexes of the patients in groups I and II no significant differences were found ($P = 0.649$). Age of patient was statistically different in groups I (10.6 ± 3.8 years) and II (8.5 ± 3.7 years), as can be seen in Fig. 1 ($P = 0.011$).

Age does not seem to have been related to the CRP ($P = 0.975$), but it was found to have an association with leukocytosis ($P = 0.045$).

A significant association between CRP value and severity of disease ($P < 0.001$) was also verified, with higher values in complicated cases. No difference was found when comparing the 2 groups for the presence of leukocytosis ($P = 0.295$).

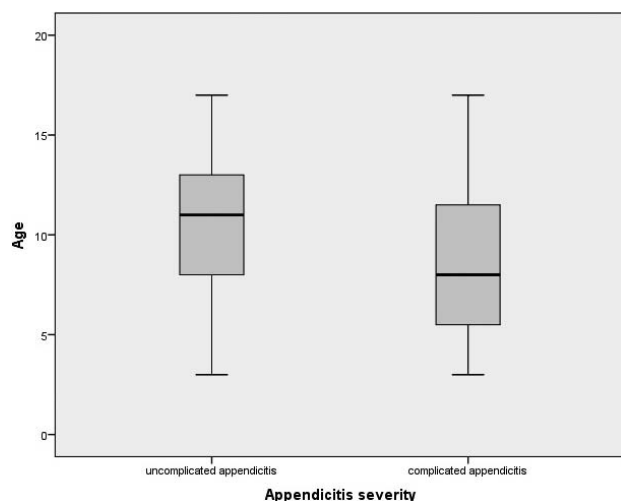


Fig. 1 Difference in mean age according to acute appendicitis severity.

A CRP value higher than 4.3 mg/dL was predictive for complicated appendicitis with a 74% sensitivity and 77% specificity. The area under curve was 0.812 (Fig. 2).

Discussion

Acute appendicitis represents a diagnostic challenge for a pediatric surgeon because clinical findings are usually nonspecific in children compared with the adult population. In fact, WBC count and CRP are the most widely used inflammatory markers to investigate this diagnosis, in spite of their low specificity in adults as well as in children.¹⁰ In adults, when normal values of WBC count and CRP are present, acute appendicitis is highly unlikely and reliably excluded. However, the same has not been verified in children.¹¹ For children, the most frequent scenario is an elevated WBC count, CRP, or both.

However, in the studied population, 33.6% of the children with a confirmed diagnosis of appendicitis had normal WBC count and 30.7% had a normal

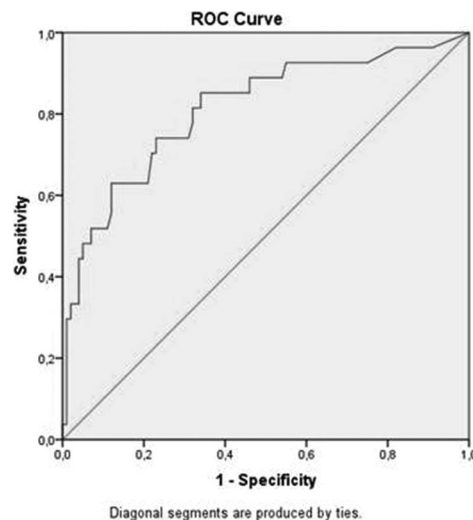


Fig. 2 Receiver-operating characteristic analysis of CRP value.

CRP value. Normal WBC counts were present in 36.7% of patients of group I and in 25.9% of group II patients, which are significant numbers. Similar results were found in a previous study.

WBC counts rise in the early phases of the inflammatory response,¹¹ which explains the presence of leukocytosis in most of the population before surgery (probably the 36.7% in group I had not had the necessary time to increase it). Nevertheless, it does not explain the significant percentage of patients with normal WBC counts in group II (25.9%), where theoretically, because they had advanced appendicitis, enough time had passed for the WBC count to be elevated. As was suggested in a previous study in adults, this is probably related to a phenomenon of rapid decrease in WBC count when perforation of the appendix occurs.¹¹ The other results that may support this idea are: no differences between the 2 groups were found regarding the presence of leukocytosis ($P = 0.295$), and in group II leukocytosis was absent in a significant number of patients.

CRP levels increase over time as the inflammatory response evolves. Our results confirm a close association between CRP and the severity of appendicitis ($P < 0.001$), which is consistent with the results reported in other studies.¹¹ Previous studies also concluded that CRP was a significant predictor of perforation.¹¹

In this study, according to receiver-operator characteristic analysis, the authors suggest that CRP levels may have an important role in predicting

Table 1 Values of WBC count and CRP according to pathologic findings at surgery

	Group I	Group II	P value
CRP, mean $\pm$ SD ^a	3.041 $\pm$ 4.37	11.267 $\pm$ 8.41	<0.001
Leukocytosis, n (%)	62 (63)	20 (74.1)	0.295

^aData were compared by χ^2 and Student *t*-test.

the severity of appendicitis. A possible cutoff CRP value of 4.3 mg/dL is proposed, reporting a 74% sensitivity and 77% specificity to predict disease severity. Although this is of limited clinical relevance because its specificity and sensitivity values are lower comparing those of ultrasonography and computed tomography (CT) scan for this diagnosis, the authors believe this may serve as an important additional orientation for the surgeon. This is the first study to propose a cutoff value of CRP for prediction of complicated appendicitis in the pediatric population.

Regarding the other studied inflammatory marker (WBC count), the association with severity is not observed, once leukocytosis reaches its highest level in gangrenous appendicitis and subsequently decreases in perforated appendicitis.

Distinguishing between perforated (complicated) and nonperforated (uncomplicated) appendicitis becomes more important because some authors claim that these are different conditions requiring different approaches: perforated appendicitis requires emergent surgery, whereas surgery for non-perforated appendicitis can be accurately delayed for some hours.^{12,13}

Sex does not seem to be a risk factor for complicated appendicitis, because there were no differences in the 2 groups for this parameter. This conclusion differs from the results of a previous work in an adult population that reported a higher complicated appendicitis rate in males.

Moreover, authors found an association between children's age and severity of appendicitis ($P = 0.011$), with the youngest presenting a greater probability of having a complicated appendicitis at the time of diagnosis. This can be explained by a slight delay in diagnosing younger children, because of their nonspecific presentation and increased probability of perforation.

Conclusion

These findings corroborate previous studies highlighting the importance of CRP as an inflammatory marker in surgical decision-making. Moreover, this is the first study to present a cutoff value of CRP for the prediction of complicated appendicitis in children. In addition, the authors suggest that when discordant laboratory data are present (*i.e.*, normal WBC count and elevated CRP), if clinical findings are doubtful, it is necessary to consider perforated appendicitis. Nevertheless, larger mul-

ticenter studies are needed to allow for further conclusions.

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