

## ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# C-reactive protein and procalcitonin as a predictive factors on appearance of postoperative complications after open appendectomy in children

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## SUMMARY

**Introduction/Objective** Acute appendicitis is one of the most common surgical conditions in children that may be followed by inflammatory postoperative complications.

The aim of this study was to determine the association of the preoperative levels of C-reactive protein (CRP) and procalcitonin (PCT) and occurrence of inflammatory postoperative complications in children with appendicitis.

**Methods** Fifty-four patients were separated into two groups. The first group contained patients with uncomplicated appendicitis (UA) whereas the second group comprised patients with complicated appendicitis (CA). Clinical and laboratory parameters in preoperative period were used for prediction of complications after open appendectomy in children.

**Results** Patients with CA had significantly higher values of rectal temperature ( $p < 0.05$ ), longer length of fever ( $p < 0.001$ ), CRP ( $p < 0.001$ ), PCT ( $p < 0.001$ ), longer duration of stay at the intensive care unit (ICU) ( $p < 0.001$ ), and prolonged hospitalization ( $p < 0.001$ ) than the UA group. In the CA group, 41.93% had postoperative complications; these patients also had longer duration of fever ( $p < 0.05$ ), higher level of CRP ( $p < 0.05$ ), and prolonged hospitalization ( $p < 0.01$ ) compared to patients in the CA group without complications. Preoperative cut-off values of CRP and PCT (75.8 mg/l and 0.36 ng/ml, respectively) pointed towards higher probability for development of postoperative complications. Rectal temperature and duration of fever had predictive influence in determination of postoperative complications in the CA group.

**Conclusion** The cut-off values of preoperative levels of CRP and PCT were able to discriminate the subset of patients with higher risk for postoperative complications. Rectal temperature and duration of fever had predictive influence on the occurrence of postoperative complications, while other clinical and laboratory parameters were not able to predict appearance of the complications after open appendectomy in children.

**Keywords:** appendicitis; children; C-reactive protein; procalcitonin; postoperative complications

## INTRODUCTION

Acute appendicitis is among the most common urgent surgical conditions in children [1]. Preoperative diagnostics of acute appendicitis and estimation of severity of clinical picture still represent the clinical challenge in paediatric population due to similarities in laboratory analysis and clinical picture with other diseases [2]. Ideal laboratory parameter with the ability to estimate the severity and the course of appendicitis still remain unidentified [3]. Routine laboratory tests such as C-reactive protein (CRP) could not reliably discriminate the existence of appendicitis from the other conditions characterised with abdominal pain [4]. Recent studies have shown that procalcitonin (PCT) correlates significantly with the severity of inflammation in patients with appendicitis, being more accurate than parameters such as fever, number of leukocytes, or elevated sedimentation rate [5]. Levels of PCT could be several-

fold higher in patients with an advanced form of appendicitis accompanied with bacterial infection [6]. For this reason, PCT is considered to be able to identify both more severe clinical forms of appendicitis and the existence inflammatory postoperative complications after appendectomy in children. The most common consequences of delaying the diagnosis of appendicitis or perforated appendicitis were wound to be infections, intra-abdominal abscesses, and small intestine obstruction during the postoperative period, which may increase the morbidity and mortality of hospitalized children.

The aim of the study is to estimate the significance of preoperative levels of CRP and PCT and to identify the cut-off values that could precisely predict the severity of clinical picture of acute appendicitis and the appearance of inflammatory postoperative complications in children.

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## METHODS

This retrospective clinical study encompassed 54 young patients with a diagnosis of acute appendicitis, with age ranging from three to 15 years, at the Clinic for Child Surgery and Orthopaedics, Clinical Centre of Niš. Written informed consent was obtained from parents of all the patients. The patients were divided into two groups: the first group consisted of 23 patients with uncomplicated appendicitis (UA) (phlegmonous appendicitis), while the second group comprised 31 patients with complicated appendicitis (CA). In this setting, appendicitis was considered complicated when localised or widespread peritonitis, abscess or appendix perforation were registered intraoperatively. A diagnosis of acute appendicitis was made, based on clinical, laboratory, and radiographic findings during the preoperative period. Postoperative pathohistological examination of appendix was used to determine the severity and the extent of appendix inflammation. The appearance of other inflammatory complications with special emphasis on wound infection, occurrence of postoperative abscess or intestinal obstruction, within 30 days after open appendectomy, was also analyzed in both groups of patients. Patients appendectomized due to other reasons as well as those that had a hematological disease or proved immune disturbances were excluded from the analysis. All the patients had undergone standard preoperative preparation and antibiotic prophylaxis.

The following parameters were analyzed: age, body weight, sex, length of preoperative observation, body temperature (axillar and rectal temperature), and duration of fever. White blood cell count (WBC) and percentage of neutrophils (Ne), levels of CRP and PCT were determined before the surgical intervention. After open appendectomy, the overall duration of hospital treatment as well as the duration of stay at the intensive care unit (ICU) was also followed.

Blood samples were taken from peripheral vein and hematology parameters were analyzed on the Ac-T diff<sup>TM</sup> hematology analyzer (Beckman Coulter, Brea, CA, USA). The levels of CRP were determined on Ilab 300 clinical chemistry analyser (Werfen, Barcelona, Spain) with the reference values range of 1–5 mg/l. The level of PCT was performed by the immunoluminometric method (LUMItest<sup>TM</sup>, B-R-A-H-M-S Diagnostica, Berlin, Germany) using the Modular Analytics E170 analyser (Roche Diagnostics, Indianapolis, IN, USA). Values of PCT below 0.05 ng/ml were considered normal.

## Statistical analysis

Descriptive statistics consisted of the number (n), percentage (%), arithmetic mean, and standard deviation. For parametric testing, Student's t-test or nonparametric Mann–Whitney test, as well as the  $\chi^2$  test or Fisher's exact test were used. The receiver operating characteristic curve (ROC) analysis was used to define sensitivity and specificity of laboratory parameters for measurement of their influence on the appearance of complications. In order to test whether clinical or laboratory parameters have predic-

tive influence on appearance of postoperative complications after open appendectomy, we performed multivariate logistic regression. Values considered statistically significant had  $p < 0.05$ . Statistical analysis was performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

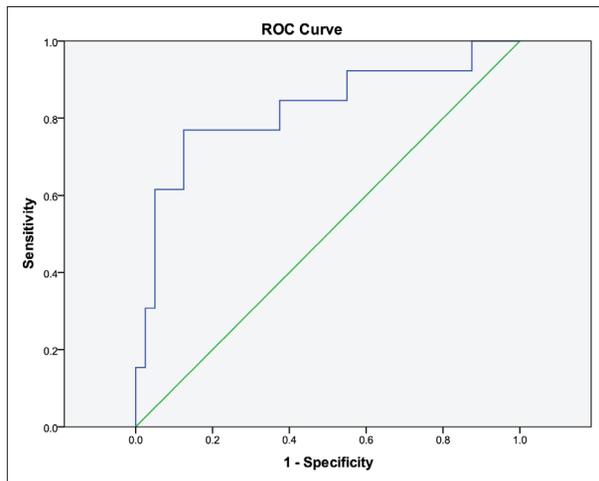
All the data were successfully collected according to the study protocol for the complete group of 54 patients. There was no difference between UA and CA groups, concerning the age of patients, their body weight, length of preoperative observation, and axillar body temperature values, as shown in Table 1. The CA group had higher values of rectal temperature compared to the UA group ( $38.37 \pm 0.79^\circ\text{C}$  vs.  $37.79 \pm 0.82^\circ\text{C}$ ,  $p < 0.05$ ). The fever lasted longer in the CA group than in the UA group ( $4.33 \pm 3.44$  days vs.  $1.56 \pm 1.19$  days,  $p < 0.001$ ) (Table 1). There was no difference concerning the number of leukocytes or neutrophilia between the groups, although the higher number of leukocytes ( $17.94 \pm 6.81 \times 10^9/\text{l}$  vs.  $14.42 \pm 5.26 \times 10^9/\text{l}$ ), and more prominent neutrophilia ( $79.74\% \pm 8.36\%$  vs.  $76.65\% \pm 11.18\%$ ) were recorded in the CA group than in the UA group (Table 1). The levels of CRP in the CA group were significantly higher than in the UA group of patients ( $69.49 \pm 46.56$  mg/l vs.  $18.49 \pm 24.15$  mg/l,  $p < 0.001$ ). Higher preoperative levels of PCT were also registered in the CA group than in the UA group patients ( $5.61 \pm 9.68$  ng/ml vs.  $0.13 \pm 0.11$  ng/ml,  $p < 0.001$ ) (Table 1).

Inflammatory postoperative complications were found only in the CA group, while in the UA group no complications developed after the removal of the inflamed appendix

**Table 1.** Characteristics of clinical and laboratory parameters in patients with uncomplicated (UA) and complicated appendicitis (CA) groups

Parameters	UA (n = 23)	CA (n = 31)	p-value
Age (years)	10.26 ± 3.49	8.81 ± 3.69	$p > 0.05$
Body weight (kg)	37.52 ± 17.54	33.71 ± 14.6	$p > 0.05$
Boys – n (%)	15/23 (65.20%)	23/31 (74.20%)	$p > 0.05$
Girls – n (%)	8/23 (34.80%)	8/31 (25.8%)	$p > 0.05$
Length of preoperative observation (hours)	10.05 ± 10.75	8.10 ± 7.40	$p > 0.05$
Axillar temperature ( $^\circ\text{C}$ )	37.35 ± 0.72	37.75 ± 0.72	$p > 0.05$
Rectal temperature ( $^\circ\text{C}$ )	37.80 ± 0.82	38.37 ± 0.80	$p < 0.05$
Length of fever (days)	1.57 ± 1.20	4.33 ± 3.44	$p < 0.001$
WBC ( $\times 10^9/\text{l}$ )	14.42 ± 5.26	17.94 ± 6.81	$p > 0.05$
Ne (%)	76.65 ± 11.18	79.74 ± 8.36	$p > 0.05$
CRP (mg/l)	18.49 ± 24.15	69.49 ± 46.56	$p < 0.001$
PCT (ng/ml)	0.13 ± 0.12	5.61 ± 9.68	$p < 0.001$
Postoperative complications (%)	0 (0%)	13/31 (41.90%)	$p < 0.001$
Duration of stay in the ICU (days)	0.48 ± 0.73	5.59 ± 4.08	$p < 0.001$
Overall hospital treatment (days)	7.21 ± 1.56	12.16 ± 5.77	$p < 0.001$

Ne – neutrophils; WBC – white blood cell count; CRP – C-reactive protein; PRC – procalcitonin; ICU – intensive care unit



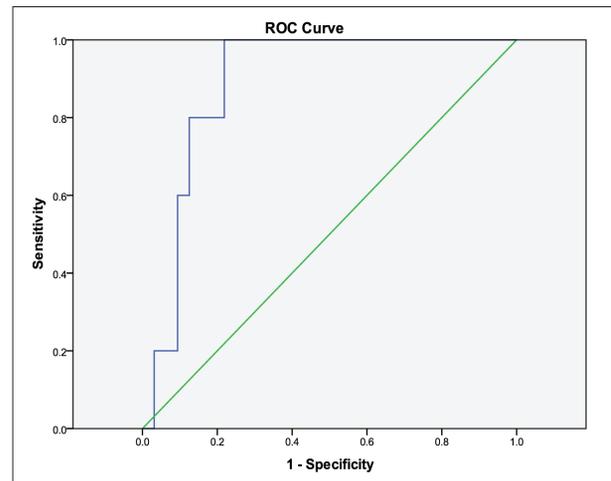
**Figure 1.** Receiver operating characteristic (ROC) curve for predicting inflammatory postoperative complications based on average CRP levels

( $p < 0.001$ ). Duration of stay in the ICU was significantly prolonged in the CA group ( $5.59 \pm 4.08$  days) compared to the UA subgroup ( $0.48 \pm 0.73$  days) ( $p < 0.001$ ). Overall hospital treatment was longer in patients with CA ( $12.16 \pm 5.77$  days) compared to the UA group ( $7.21 \pm 1.56$  days),  $p < 0.001$  (Table 1).

The ROC analysis determined the cut-off values for CRP (75.8 mg/l) and PCT (0.36 ng/ml) (Figures 1 and 2). The ROC curve shape pointed out that CRP levels above the established cut-off values, with high sensitivity (76.9%) and specificity (87.5%), could predict occurrence of inflammatory postoperative complications in appendectomized children ( $p = 0.001$ ) (Figure 1). Area under the ROC curve value of 0.823 with standard error of 0.076 and 95% confidence interval (0.674–0.973) points toward predictive impact of CRP levels for the development of postoperative complications.

The shape of ROC curve pointed that PCT values above the determined cut-off values are highly sensitive and specific predictors of appearance of inflammatory postoperative complications ( $p = 0.006$ ) (Figure 2). Area under the curve of 0.888 with standard error of 0.055 and 95% confidence interval (0.780–0.995) points toward the positive predictive impact of PCT values, with sensitivity of 100% and specificity of 78.1%, on the postoperative complications occurrence.

Analysis of clinical and laboratorial parameters in patients with CA in regard to the development of postoperative complications detected that 18 (58.07%) patients have



**Figure 2.** ROC curve for predicting inflammatory postoperative complications based on average PCT levels

**Table 2.** Clinical and laboratory parameters of patients in complicated appendicitis group with postoperative complications

Parameters	No (n = 18)	Yes (n = 13)	p-value
Axillar temperature (°C)	37.74 ± 0.77	37.76 ± 0.67	$p > 0.05$
Rectal temperature (°C)	38.44 ± 0.88	38.28 ± 0.70	$p > 0.05$
Length of fever (days)	3 ± 1.37	6.08 ± 4.50	$p < 0.05$
WBC ( $\times 10^9/l$ )	17.79 ± 7.84	18.13 ± 5.38	$p > 0.05$
Ne (%)	79.17 ± 8.28	80.50 ± 8.73	$p > 0.05$
CRP (mg/l)	55.60 ± 30.51	87.65 ± 58.03	$p < 0.05$
PCT (ng/ml)	5.03 ± 10.32	6.76 ± 9.28	$p > 0.05$
Duration of stay in ICU (days)	04.60 ± 1.97	7.00 ± 5.75	$p > 0.05$
Overall hospital treatment (days)	9.67 ± 3.53	15.62 ± 6.59	$p < 0.01$

no postoperative complications; however, complications were detected in 13 patients (41.93%). Fever duration ( $p < 0.05$ ), CRP level ( $p < 0.05$ ), and the duration of hospitalization ( $p < 0.01$ ) have significant influence for the development of postoperative complications in the CA group, i.e. CA patients without postoperative complications have shorter duration of fever, lower CRP levels, and shorter hospitalization time than patients with postoperative complications (Table 2). Multivariate analysis of clinical and laboratory parameters in patients with CA detected that preoperative rectal temperature ( $p = 0.05$ ) and duration of fever ( $p = 0.02$ ) had significant influence on the prediction of occurrence of postoperative complications (Table 3).

**Table 3.** Multivariate analysis of clinical and laboratory parameters in prediction of postoperative complications in patients with complicated appendicitis

Omnibus tests of model coefficients	$\chi^2$	Sig.	Model summary	-2 Log likelihood	Cox & Snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
	B	S.E.	Wald	df	Sig.	Exp (B)
	16.414	0.006		23.477	0.432	0.578
Axillar temperature	6.344	3.519	3.250	1	0.071	569.192
Rectal temperature	-6.405	3.264	3.850	1	0.050	0.002
Length of fever	0.935	.411	5.167	1	0.023	2.546
WBC	0.122	0.120	1.029	1	0.310	1.130
Ne	0.032	0.097	0.107	1	0.744	1.032
Constant	-2.370	33.992	0.005	1	0.944	0.093

**Table 4.** Multivariate analysis of CRP and PCT in prediction of postoperative complications in patients with complicated appendicitis

Omnibus tests of model coefficients	$\chi^2$	Sig.	Model summary	-2 Log likelihood	Cox & Snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
	0.577	0.749		18.519	0.038	0.052
	B	S.E.	Wald	df	Sig.	Exp (B)
CRP	0.013	0.019	0.445	1	0.505	1.013
PCT	0.003	0.061	0.003	1	0.958	1.003
Constant	-1.457	1.224	1.418	1	0.234	0.233

Other parameters, including CRP and PCT, had no such predictive ability regarding the appearance of postoperative complications in the CA group (Table 4).

## DISCUSSION

This study has shown that the rise of rectal temperature and prolonged fever during the hospital treatment, as well as high preoperative values of CRP and PCT, might be seen in children with complicated appendicitis. If the average preoperative values of CRP are above 75.8 mg/l and PCT values are higher than 0.36 ng/ml (high sensitivity for CRP amounts to 76.9%, and 100% for PCT), post-appendectomy inflammatory complications are expected. In the CA group of patients with postoperative complications, longer duration of fever and higher levels of CRP could be expected and consequently lead to the prolongation of hospital stay.

Laboratory parameters for the diagnosis of acute appendicitis traditionally rely on the number of leukocytes, CRP levels, and rectal temperature rise – all of which demonstrate low sensitivity and specificity for approximate confirmation of acute appendicitis [7]. In a study by Youatou Towo et al. [8], the rise of leukocytes and neutrophil percentage as well as the elevation of CRP and fibrinogen were detected in complicated forms of appendicitis. In contrast to previous authors, Eldar et al. [9] have shown that laboratory parameters have no significance in defining the severity of appendicitis. Our study suggests that elevation in the number of leukocytes and the rise of neutrophil percentage could not define the severity of acute appendicitis in children, based on the absence of difference between the CA and UA groups. The role of CRP in diagnosing appendicitis is problematic even nowadays [10, 11]. CRP is a plasma protein, whose level is raised in response to cytokines induced by tissue injury, infection, or inflammation [12]. In a study by Kim et al. [13], the CRP level was found to be a good predictor of complicated form of appendicitis. Another study found that CRP has a sensitivity of 83–90% for determining complicated forms of appendicitis in children (perforation and abscess formation) [12]. Contrary to this, some authors claim that specificity and sensitivity of biochemical markers might be improved with the clinical picture of patients [14]. Our study finds that CRP levels above 69.49 mg/l strongly point towards existence of complicated appendicitis in contrast to the uncomplicated form, where the levels of CRP tend to be lower than 18.49 mg/l. In this way this study shows that preoperative values of CRP could be a reliable predictor

of complicated appendicitis in children. Kafetzis et al. [15] found that elevation of PCT above 0.5 ng/ml has sensitivity of 73% and specificity of 92.3% for defining the perforated appendicitis in children. Anielski et al. [10] found evidence that elevated PCT represents a biomarker of appendicitis, did not manage to define the cut-off values for various forms of appendicitis. Our study shows the existence of higher PCT values in children with complicated appendicitis (5.61 ng/ml), while PCT levels were considerably lower in uncomplicated forms (0.13 ng/ml), which might be useful in defining the severity of acute appendicitis in children. Our study finds that CRP and PCT are more useful than number of leukocytes and neutrophil percentage for identifying complicated forms of acute appendicitis in children.

In case of postoperative complications after appendectomy, elevated number of leukocytes could not reliably predict postoperative abscesses after appendectomy, since only 50% of cases have leukocytosis above  $14 \times 10^9/l$  [16]. A study that identifies CRP as a marker of postoperative complications after appendectomy found that CRP values above 100mg/l reliably predict appearance of postoperative complications [17]. Besides its diagnostic value, PCT was found to have prognostic impact able to identify post-appendectomy complications [18]. In case of preoperative levels of CRP higher than 3 mg/l and PCT values above 0.18 ng/ml, a higher percentage of complications might be expected. Therefore, the surgical intervention should be done sooner [19]. Preoperative values of CRP and PCT in our study have shown excellent predictive abilities for appearance of inflammatory postoperative complications in children after appendectomy. If the CRP and PCT are higher than their cut off values, 75.8 mg/l for CRP (sensitivity of 76.9% and specificity of 87.5%) and 0.36 ng/ml for PCT (sensitivity of 100% and specificity of 78.1%), respectively, the postoperative complications could be expected in 95% of patients after appendectomy.

The outcome of advanced appendicitis is difficult to determine. Ideally, a pathway for the treatment of advanced appendicitis would identify those at risk for developing a postoperative complication, having in mind that complications such as intra-abdominal abscess have the incidence of 5–28% [20, 21]. Other studies showed that the use of laboratory evaluation as discharge criteria in advanced appendicitis can help to identify a small subset of patients who are at an increased risk of developing an intra-abdominal abscess and prolonged hospitalization in the perforated appendicitis [16, 22]. In a recent study by Fike et al. [22] it was shown that the occurrence of an intra-abdominal abscess doubles the hospital stay and cost of perforated

appendicitis [22]. In our study, 41.93% of patients with postoperative complications in the CA group had longer duration of fever, higher level of CRP, and prolonged hospitalization compared to patients without postoperative complications in the CA group. In multivariate analysis, we detected that prolonged duration of fever and higher level of rectal temperature were significant predictors of occurrence of postoperative complications in the CA group. Also, Obinwa et al. [23] detected that preoperative pyrexia was the most discriminatory factor among other preoperative systematic inflammatory parameters in predicting postoperative complications. In our study, other clinical and laboratory parameters have no ability to predict postoperative complications. Determination of predictive abilities of preoperative risk factors, including PCT and CRP, was limited by the small number of patients with postoperative complications in the CA group (only 13 patients) in our pilot study. Therefore, further studies including more patients are needed to confirm certain risk factors for postoperative complications in pediatric patients with CA. Cut-off value of preoperative level of CRP and PCT discriminates the subset of patients at a higher risk for postoperative complications, and these

inflammatory parameters should be monitored more closely after surgical treatment of CA. Early diagnosis of surgical complications in patients with complicated appendicitis is an ongoing challenge and there is a continuing quest for a more reliable prognostic biomarker or clinical scoring system.

## CONCLUSION

This study has shown that higher values of CRP and PCT might be expected in children with complicated appendicitis. Cut-off values of CRP and PCT could discriminate the subset of patients with a higher risk for the development of postoperative complications. Patients with postoperative complications in the CA group are associated with longer duration of fever, higher level of CRP, and prolonged hospitalization; however, only rectal temperature and duration of fever had predictive significance regarding the occurrence of postoperative complications. Further studies with more patients are needed to detect influence of inflammatory parameters in predicting complications after open appendectomy in children.

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## Ц-реактивни протеин и прокалцитонин као предиктивни фактори појаве постоперативних компликација након отворене апендектомије код деце

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### САЖЕТАК

**Увод/Циљ** Акутни апендицитис је једно од најчешћих хируршких стања код деце, које може бити праћено појавом инфламаторних постоперативних компликација.

Циљ рада је одредити повезаност преоперативних вредности Ц-реактивног протеина (ЦРП) и прокалцитонина (ПКТ) на појаву инфламаторних постоперативних компликација код деце са апендицитисом.

**Методe** Анализирана су 54 болесника, који су подељени у групу са некомпикованим (НА) и компикованим апендицитисом (КА). Клинички и лабораторијски параметри у преоперативном периоду су коришћени за предикцију компликација након отворене апендектомије.

**Резултати** Болесници са КА су показали значајно више вредности ректалне температуре ( $p < 0,05$ ), дужу фебрилност ( $p < 0,001$ ), виши ниво ЦРП ( $p < 0,001$ ) и ПКТ ( $p < 0,001$ ), дужи боравак у Јединици интензивне неге ( $p < 0,001$ ) и дужу хоспитализацију ( $p < 0,001$ ) у односу на болеснике са НА. У групи

деце са КА, 41,93% је развило постоперативне компликације и код њих је уочена дужа фебрилност ( $p < 0,05$ ), виши ниво ЦРП ( $p < 0,05$ ) и дужа хоспитализација ( $p < 0,01$ ) у односу на болеснике КА групе без постоперативних компликација. Преоперативне *cut off* вредности ЦРП и ПКТ (75,8 mg/l и 0,36 ng/ml) показују ризичну групу за развој постоперативних компликација, док предиктивни утицај на појаву постоперативних компликација код КА групе имају само ректална температура и трајање фебрилности.

**Закључак** Преоперативне *cut off* вредности ЦРП и ПКТ дефинишу болеснике високог ризика за настанак постоперативних компликација. Ректална температура и трајање фебрилности имају предиктиван утицај на појаву компликација, док остали клинички и лабораторијски параметри нису у стању да предвиде појаву постоперативних компликација након отворене апендектомије код деце.

**Кључне речи:** апендицитис; деца; Ц-реактивни протеин; прокалцитонин; постоперативне компликације