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Original Article / Оригинални рад

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

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

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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 contain of patients with uncomplicated appendicitis (UA) whereas the second group including 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 UA group. In the CA group, 41.93% had postoperative complications; and these patients had longer length of fever ($p<0.05$), higher level of CRP ($p<0.05$) and prolonged hospitalization ($p<0.01$) than CA group without complication. Preoperative *cut off* values of CRP and PCT (75.8 mg/l and 0.36 ng/ml) pointed towards higher probability for development of postoperative complications. Rectal temperature and duration of fever had predictive influence in determination of postoperative complications in 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 to 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

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.

Методе Анализирано је 54 болесника који су подељени у групу са некомпликованим (НА) и компликованим апендицитисом (КА). Клинички и лабораторијски параметри у преоперативном периоду су коришћени за предикцију компликација након отворене апендектомије.

Резултати Пацијенти са КА су показали значајно више вредности ректалне температуре ($p<0,05$), дужу фебрилност ($p<0.001$), виши ниво ЦРП ($p<0,001$) и ПЦТ ($p<0,001$), дужи боравак у Јединици интензивне неге (ЈИН) ($p< 0,001$) и дужу хоспитализацију ($p< 0,001$) у односу на пацијенте 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 пацијенте КА групе без постоперативних компликација. Преоперативне *cut-off* вредности ЦРП и ПЦТ (75,8 мг/л и 0,36 нг/мл) 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 пацијенте 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: аппендицитис; деца; Ц-реактивни протеин; прокалцитонин; постоперативне компликације

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 remained unidentified [3]. Routine laboratory test 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 folds higher in patients with 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 delay the diagnosis of appendicitis or perforated appendicitis were wound infections, intra-abdominal abscesses, small intestine obstruction during the postoperative period and may increase 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.

METHODS

This retrospective clinical study had encompassed 54 young patients with diagnosis of acute appendicitis with age ranging from 3 to 15 years, at the Clinic of Child Surgery and Orthopaedics, Clinical Centre Niš. Written informed consent was obtained from parents of all patients. Patients were divided into two groups: first group consisted of 23 patients with uncomplicated appendicitis (UA) (phlegmonous appendicitis), while the second group was made of 31 patients with complicated appendicitis (CA). In this settings, appendicitis was considered complicated when localised or widespread peritonitis, abscess or appendix perforation were registered intraoperatively. Diagnosis of acute appendicitis was made, based on clinical, laboratory and radiographic findings during the preoperative period. Postoperative patohistological 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 analysed in both groups of patients. Patients appendectomised due to other reasons as well as those that had haematological disease or proved immune disturbances, were excluded from the analysis. All patients had undergone standard preoperative preparation and antibiotic prophylaxis.

Following parameters were analysed: age, body weight, sex, length of preoperative observation, body temperature (axilar and rectal temperature) and duration of fever. Number of white blood cells (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 haematology parameters were analysed on the ACT diff haematology analyzer Beckman Coulter. Levels of CRP were determined on Ilab 300 clinical chemistry analyser with the reference values ranging from 1-5 mg/l. The level of PCT was performed by immunoluminometric method (LUMItest^{TM}, B·R·A·H·M·S Diagnostica, Berlin, Germany) using Modular analytics E170 analyser. Values of PCT below 0,05 ng/ml were considered normal.

Statistical analysis

Descriptive statistics consisted of number (N), percentage (%), arithmetic mean, standard deviation. For parametric testing Student t-test or nonparametric Mann Whitney test as well as χ^2 test or Fisher 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 predictive influence on appearance of postoperative complications after open appendectomy, we performed multivariate logistic regression model. Values that were considered statistically significant had $p < 0.05$. Statistical analysis was performed using R- program.

RESULTS

All 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 axilar body temperature values as shown in the Table1. Group with complicated appendicitis had higher values of rectal temperature comparing to UA (38.37±0.79 ^{o}C vs. 37.79±0.82 ^{o}C, $p<0.05$). Period of fever lasted longer in group with CA than in UA group (4.33±3.44 days v.s. 1.56±1.19 days, $p<0.001$) (Table 1). There was no difference

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

	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	$p > 0.05$
Axilar temperature (ºC)	37.35 ± 0.72	37.75 ± 0.72	$p > 0.05$
Rectal temperature (ºC)	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 (x10^9/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 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	$p < 0.001$

concerning the number of leukocytes or neutrophilia between groups, although the higher number of leukocytes (17.94±6.81x10^9/l vs. 14.42 ± 5.26 x10^9/l), and more prominent neutrophila (79.74±8.36 % vs. 76.65±11.18 %) were recorded in CA comparing to UA group (Table1). Level of CRP in CA group were significantly higher than in a UA group of patients (69.49±46.56 mg/l vs. 18.49±24.15 mg/l, p<0.001). Higher preoperative level of PCT were also registered in CA group comparing to UA patients (5.61±9.68 ng/ml vs. 0.13 ± 0.11ng/ml, p<0.001) (Table 1).

Inflammatory postoperative complications were found only in CA group, while in UA group no complications developed after removal of inflamed appendix (p<0.001). Duration of stay in ICU was significantly prolonged in CA (5.59 ± 4.08 days) comparing to UA subgroup (0.48±0.73 days) (p<0.001). Overall hospital treatment was longer in patients with CA (12.16±5.77 days) comparing to UA group (7.21±1.56 days), p<0.001 (Table 1).

ROC analysis has determined the cut off values for CRP (75.8 mg/l) and PCT (0.36 ng/ml), (Graphs 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 appendectomised children (p=0.001) (Figure 1). Area under the ROC curve is 0.823 with standard error 0.076 and 95% confidence interval (0.674–0.973) pointed toward predictive impact of CRP levels for development of postoperative complications.

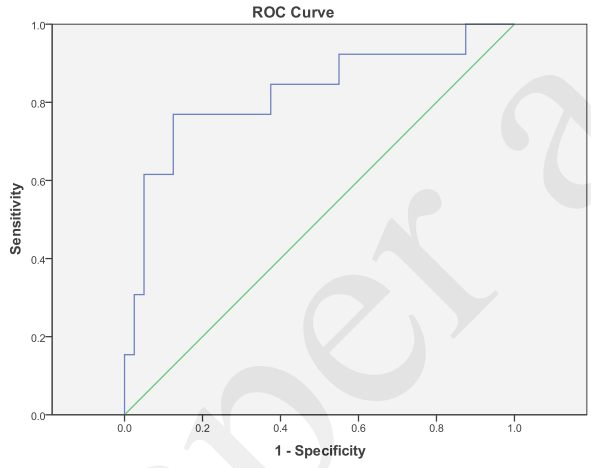

Figure 1. ROC curve for prediction of inflammatory postoperative complications based on average CRP levels.

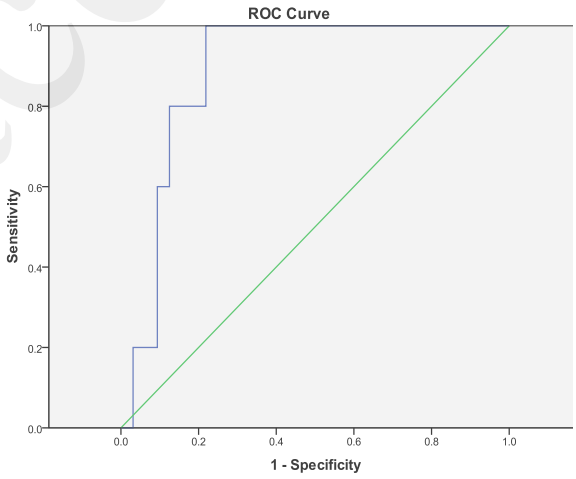

Figure 2. ROC curve for prediction of inflammatory postoperative complications based on average PCT levels.

The shape of ROC curve pointed that PCT values above 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 is 0.888 with standard error 0.055 and 95% confidence interval (0.780–0.995) pointing 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 development of postoperative complications, detected that 18 (58.07 %) patients have no postoperative complications,

however in 13 patients (41.93%) complications were detected. Length of fever ($p<0.05$), CRP level ($p<0.05$) and duration of hospitalisation ($p<0.01$) have significant influence for development of postoperative complications in CA group, i.e CA patients without postoperative complications have lower duration of fever, lower CRP level and shorter hospitalisation, 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 to predict occurrence of postoperative complications (Table 3). Other parameters, including of CRP and PCT, had no such predictive ability regarding to appearance of postoperative complications in CA group (Table 4).

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

	No (n=18)	Yes (n=13)	*p* value
Axilar temperature (ºC)	37.74±0.77	37.76±0.67	$p > 0.05$
Rectal temperature (ºC)	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 (x10^9/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	$p < 0.01$

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

Omnibus Tests of Model Coefficients[a]	Chi-square	Sig.	Model Summary[b]	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
	16.414	.006		23.477[a]	.432	.578
	B	S.E.	Wald	df	Sig.	Exp(B)
Axil Temp	6.344	3.519	3.250	1	.071	569.192
Rectal Temp	-6.405	3.264	3.850	1	.050	.002
Length of fever	.935	.411	5.167	1	.023	2.546
WBC	.122	.120	1.029	1	.310	1.130
Ne	.032	.097	.107	1	.744	1.032
Constant	-2.370	33.992	.005	1	.944	.093

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

Omnibus Tests of Model Coefficients[a]	Chi-square	Sig.	Model Summary[b]	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
	.577	.749		18.519[a]	.038	.052
	B	S.E.	Wald	df	Sig.	Exp(B)
CRP	.013	.019	.445	1	.505	1.013
PCT	.003	.061	.003	1	.958	1.003
Constant	-1.457	1.224	1.418	1	.234	.233

DISCUSSION

This study has shown that the rise of rectal temperature and prolonged fever during the hospital treatment as well as the high preoperative values of CRP and PCT might be seen in children with complicated appendicitis. If the average preoperative values of CRP are above the 75.8 mg/l and PCT values are higher than 0.36 ng/ml (high sensitivity for CRP 76.9% and for PCT 100%) post

appendectomy inflammatory complications are expected. In CA group of patients with postoperative complications, longer duration of fever and higher level of CRP could be expected and consequently lead to prolongation of hospital staying.

Laboratory parameters for diagnosis of acute appendicitis traditionally relies on number of leukocytes, CRP levels, rectal temperature rise, that all had low sensitivity and specificity for approximate confirmation of acute appendicitis [7]. In the study of Towo and associates [8], the rise of leukocytes and neutrophil percentage as well as the elevation of CRP and fibrinogen was detected in complicated forms of appendicitis. In contrast to previous authors, Eldar and associates [9] have shown that laboratory parameters have no significance in defining the severity of appendicitis. Our study suggested that elevation of 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 CA and UA groups. The role of a CRP in diagnosis of appendicitis is problematic even nowa days [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 and associates [13] the CRP level was found to be a good predictor of complicated form of appendicitis. Other study has found that CRP has a sensitivity of 83 to 90% for determining the complicated forms of appendicitis in children (perforation and abscess formation) [12]. Some authors, on the contrary, claim that specificity and sensitivity of biochemical markers might be improved with the clinical picture of patients [14]. Our study has found that CRP levels above 69.49 mg/l strongly point towards existence of complicated appendicitis in contrast to uncomplicated form, where the level of CRP tend to be lower than 18.49 mg/l. In that manner this study has shown that preoperative values of CRP could be a reliable predictor of complicated appendicitis in children. Kafetzis and associates have 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 [15]. Anielski and associates [10] have found evidence that elevated PCT represents a biomarker of appendicitis, but has not managed to define the cut off values for various forms of appendicitis. Our study has shown 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), that might be useful in defining the severity of acute appendicitis in children. Our study found that CRP and PCT are more useful than number of leukocytes and neutrophil percentage for identifying of complicated form 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 had leukocytosis above 14 x 10^9/l [16]. 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 complications post appendectomy [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 (sensititivity 76.9% and specifity 87.5%) and 0.36 ng/ml for PCT (sensititivity 100% and specifity 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 an 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 increased risk of developing an intra-abominal abscess [16] and prolonged hospitalization in the perforated appendicitis [22]. In study of Fike et al. [22] recently 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 of CA group with postoperative complications had longer duration of fever, higher level of CRP and prolonged hospitalization than patients of CA group without postoperative complications. 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 CA group. Also, Obinwa et al. detected that preoperative pyrexia was the most discriminatory factor among other preoperative systematic inflammatory parameters in prediction of postoperative complications [23]. 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 small number of patients with postoperative complications in CA group (only in 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 higher risk for postoperative complications and these inflammatory parameters should be monitored more closely after surgical treatment of CA. The early diagnosis of surgical complications in patient 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 higher risk for development of postoperative complications. Patients with postoperative complications in CA group are associated with longer duration of fever, higher level of CRP and prolonged hospitalisation; however only rectal temperature and duration of fever had predictive

influence to occurrence of postoperative complications. Further studies with more patients are needed to detect influence of inflammatory parameters in prediction of complications after open appendectomy in children.

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