

## Predictive Value of Neutrophil Count for Postoperative Complications in Children after Surgery of Perforated Appendicitis

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### Abstract

**Introduction:** Perforated appendicitis (PA) in children is associated with a considerable risk for postoperative complications (POCs) such as wound infection and intra-abdominal abscess. The **aim** of this study was to determine the diagnostic accuracy of hematological parameters in the early POC detection in children after PA surgery.

**Materials and Methods:** The study enrolled 71 patients with PA divided into two groups: 14 patients with POC (POC+ group) and 57 patients without POC (POC- group). Clinical and hematological parameters were followed preoperatively, prior to the surgery (PRO) and postoperatively on day 2 (POD2) and day 4 (POD4). **Results:** The POC+ group had longer duration of higher axillar temperature as well as extended intensive and inpatient care. This group also had a significantly lower absolute neutrophil count ratio between POD2 and POD4. According to the receiver operating characteristic curve analysis, relative neutrophil count on POD4 higher than 71.8% and the ratio of absolute neutrophil count between POD2 and POD4 lower than 44.5% were found to be useful for predicting POC. **Conclusion:** Absolute neutrophil count ratio between POD2 and POD4 and relative neutrophil count at POD4 could be efficient in identifying children at higher risk of developing POC after PA surgery.

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## Introduction

Perforation complicates 32.5% of appendicitises in children (1). Perforated appendicitis (PA) represents a surgical emergency requiring immediate appendectomy. In this setting, postoperative complications (POCs) occur in 6.4-13.2% of cases (2). Post appendectomy complications in children including abdominal abscess, wound infection, ileus and mechanical intestinal obstruction, result in prolonged hospital stay, increased morbidity and higher treatment cost (2,3). Thus, predicting complications after PA surgery are important both for the patient and the healthcare service.

The most frequently used laboratory parameters in POC identification after pediatric appendectomy are white blood cell count (WBC), C-reactive protein (CRP) level (4) and lymphocyte count (5). Until now, these laboratory parameters were considered auxiliary alongside positive ultrasonographic POC signs, considering that no single hematological parameter or their ratio appears to be reliable in identifying patients at higher risk for POC development. We hypothesized that during the postoperative period, the degree of inflammatory process as a consequence of an emerging infection due to POCs, would correlate with hematological parameters alone and/or with their ratio.

Therefore, the aim of this study was to determine the postoperative diagnostic accuracy of various hematological parameters in the identification of children prone to develop POCs after PA surgery.

## Materials and Methods

This retrospective study included 71 pediatric patients (46 males, 25 female), aged between 3-17 years, who underwent emergency appendi-

cetomy for PA from January 2015 until January 2019 at the Department of Pediatric Surgery, Clinical Centre Nis. The study was approved by the Ethics Committee of the Clinical Centre Nis (No.7202/2019). This body waived the need for written informed consent of the patients as the study was considered an audit of routine practice.

Appendicitis diagnosis was based on clinical presentation, laboratory and imaging results (abdominal radiography and sonography). Emergency appendicectomies were all performed as open surgical procedures. Patients with gangrenous, non-perforated, appendicitis were not included in the study. The diagnosis of PA was confirmed intraoperatively (6) and by pathohistological examination. Systemic antibiotic prophylaxis was performed with ceftriaxone and metronidazole in accordance with the local hospital guidelines.

All study participants were classified into two groups: with (POC+) and without (POC-) postoperative complications. Postoperative complications were defined as a wound infection and intra-abdominal abscess developing within the 30 days after surgery. Centers for Disease Control and Prevention criteria were used to define wound infection. Any liquid collection, detected by abdominal radiography and ultrasound imaging during the postoperative period was considered to be intra-abdominal abscess (7). Other POCs were not considered for this study.

The patients' data including demographic characteristics, duration of pre-hospital symptoms, hospital observations (from admission until the time of operation), operation time, POC presence, duration and the degree of axillary temperature in preoperative and postoperative peri-

od, duration of Intensive Care Unit (ICU) stay and overall hospital stay were retrieved from the medical records.

Hematological parameters, including WBC, relative lymphocyte (Ly%) and neutrophil (Ne%) count, absolute count of lymphocytes (ACL) and neutrophils (ACN) were measured prior to surgery (PRO) and on postoperative day 2 (POD2) and 4 (POD4). The ratio of WBC, ACL and ACN was calculated between PRO/POD2, POD2/POD4 and PRO/POD4 time points. The higher axillary temperature was defined as a temperature higher than 37°C.

The cohort and the investigated parameters were characterized using descriptive statistics. Frequency of attributive variables between groups was compared using the Pearson  $\chi^2$  test and Fisher's exact test. The comparison of means between groups and non-parametric POC variables was done using the t-test and Mann-Whitney test, respectively. The receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut off values for investigated hematological parameters. The performance of each parameter in POC prediction was compared

by calculating the area under the curve (AUC). Statistical analysis was done using Microsoft Office Excel and R-software. The value of  $p < 0.05$  was considered statistically significant.

## Results

Of 71 enrolled patients, 14 (19.72%) developed POCs: 3 (4.23%) had wound infection and 11 (15.49%) had a postoperative abscess. The median time of POC emergence was 7 days after surgery (ranging 5-12 days).

There were no significant differences in the age, gender, body weight, duration of pre-hospital symptoms, hospital observation time and operation time between the POC+ and POC- group. Patients with POCs had longer periods of pyrexia as well as higher degree of axillary temperature on POD2 and POD4. Also, the POC+ group had a longer ICU and overall hospital stay (Table 1). Among investigated hematological parameters, WBC, Ne% and ACN were found to be higher, whereas Ly% and ACL lower in POC+ patients, however, the observed differences did not reach statistical significance. On the other hand, the ratio between ACN measured on POD2 and

**Table 1. Demographic and clinical characteristics of study participants**

	POC- group	POC+ group	p value
Number of patients (%)	57 (80.28)	14 (19.72)	
Age (years)	9.77 $\pm$ 4.05	8.71 $\pm$ 4.38	0.399
Male sex (%)	37 (64.9)	9 (64.3)	0.590
Body weight (kg)	38.66 $\pm$ 18.75	33.86 $\pm$ 19.61	0.293
Duration of pre-hospital sym. (h)	37.53 $\pm$ 29.70	54.07 $\pm$ 33.73	0.092
Hospital observation (h)	7.81 $\pm$ 7.53	10.75 $\pm$ 9.19	0.373
Operation time (h)	1.20 $\pm$ 0.44	1.30 $\pm$ 0.38	0.196
Duration of higher axil. temp. at hospital (days)	2.26 $\pm$ 1.34	5.93 $\pm$ 4.36	<0.001*
Axil. Temp (°C) at:			
PRO	37.94 $\pm$ 0.86	37.92 $\pm$ 0.88	0.932
POD2	37.21 $\pm$ 0.52	37.54 $\pm$ 0.50	<0.05*
POD4	36.87 $\pm$ 0.41	37.33 $\pm$ 0.40	<0.001*
ICU stay (days)	3.62 $\pm$ 1.66	6.77 $\pm$ 5.57	<0.005*
Hospital stay (days)	6.33 $\pm$ 2.36	14.21 $\pm$ 3.51	<0.001*

POC- group- patients without postoperative complications; POC+ group- patients with postoperative complications; PRO- pre-operatively, prior to surgery; POD2- postoperative day 2; POD4-postoperative day 4; ICU- Intensive Care Unit.

POD4 was significantly lower in POC+ group, (Table 2).

According to the ROC curve analysis, relative neutrophil count on POD4 and POD2/POD4 ACN ratio were the most accurate hematological

markers in distinguishing the POC+ and POC- group (Table 3).

Utilizing the value of Ne% on POD4 higher than 71.8% as a predictor of POC+ group, the cut off point had a sensitivity of 55.6% and specificity

**Table 2. Hematological profile of patients with perforated appendicitis**

	POC- group	POC+ group	p value
WBC ( $\times 10^9/L$ ) at			
PRO	19.04 $\pm$ 6.57	17.74 $\pm$ 5.38	0.613
POD2	12.17 $\pm$ 5.46	13.12 $\pm$ 5.93	0.746
POD4	9.90 $\pm$ 3.90	11.56 $\pm$ 7.83	0.719
Ly% at			
PRO	11.24 $\pm$ 5.97	14.08 $\pm$ 8.36	0.269
POD2	15.73 $\pm$ 7.59	14.76 $\pm$ 6.19	0.800
POD4	25.00 $\pm$ 7.55	23.49 $\pm$ 7.94	0.415
Ne% at			
PRO	80.75 $\pm$ 7.18	80.86 $\pm$ 8.50	0.960
POD2	75.38 $\pm$ 8.19	79.11 $\pm$ 7.59	0.169
POD4	63.66 $\pm$ 8.00	68.56 $\pm$ 7.43	0.075
ACL ( $\times 10^9/L$ ) at			
PRO	1.90 $\pm$ 0.78	2.29 $\pm$ 1.18	0.263
POD2	1.74 $\pm$ 0.78	1.78 $\pm$ 0.75	0.753
POD4	2.39 $\pm$ 1.05	2.60 $\pm$ 1.77	0.783
ACN ( $\times 10^9/L$ ) at			
PRO	15.42 $\pm$ 5.98	14.01 $\pm$ 4.50	0.414
POD2	9.31 $\pm$ 4.60	10.58 $\pm$ 5.49	0.570
POD4	6.33 $\pm$ 2.67	8.16 $\pm$ 6.12	0.443
WBC ratio at			
PRO/POD2	1.71 $\pm$ 0.70	1.45 $\pm$ 0.53	0.358
POD2/POD4	1.26 $\pm$ 0.43	1.03 $\pm$ 0.32	0.131
PRO/POD4	2.02 $\pm$ 0.79	1.70 $\pm$ 0.71	0.274
ACL ratio at			
PRO/POD2	1.21 $\pm$ 0.55	1.32 $\pm$ 0.38	0.263
POD2/POD4	0.70 $\pm$ 0.25	0.77 $\pm$ 0.32	0.603
PRO/POD4	0.85 $\pm$ 0.39	0.99 $\pm$ 0.57	0.645
ACN ratio at			
PRO/POD2	1.90 $\pm$ 1.02	1.51 $\pm$ 0.65	0.369
POD2/POD4	1.55 $\pm$ 0.55	1.15 $\pm$ 0.39	0.043*
PRO/POD4	2.62 $\pm$ 1.27	2.01 $\pm$ 0.98	0.173

POC- group- patients without postoperative complications; POC+ group- patients with postoperative complications; PRO- preoperatively, prior to surgery; POD2- postoperative day 2; POD4- postoperative day 4; WBC- white blood cell count; Ly%- relative count of lymphocytes; Ne%- relative count of neutrophils; ACL- absolute count of lymphocytes, ACN- absolute count of neutrophils; PRO/POD2- between preoperative and postoperative day 2; POD2/POD4- between postoperative day 2 and 4; PRO/POD4- between preoperative and postoperative day 4.

**Table 3. Receiver operating characteristics (ROC) curve analysis: ability of certain hematological parameters to differentiate patients at higher risk for postoperative complication**

	AUC	p	Cut off	Sensitivity (%)	Specificity (%)	95% CI
Ne% on POD4	0.756	0.02	71.8 (%)	55.6%	91.7%	0.572-0.940
ACN ratio at POD2/POD4	0.264	0.03	44.5 (%)	100%	2.8%	0.074-0.454

Ne%- relative count of neutrophils; ACN ratio at POD2/POD4 - absolute neutrophil count ratio between postoperative day 2 and 4; AUC- Area under the curve; CI- confidence interval.

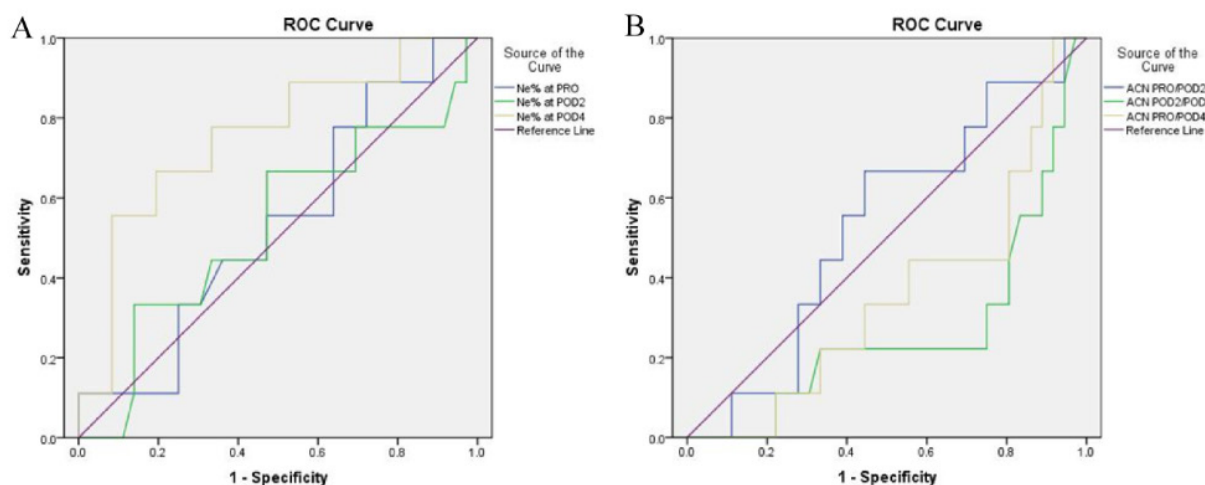
ty of 91.7%. The POD2/POD4 ACN ratio lower than 44.5% had a sensitivity of 100% and specificity of 2.8% for determining patients with POC (Figure 1).

## Discussion

The postoperative complications are still a major cause of morbidity, prolonged ICU staying and hospital treatment after appendectomy in children. The early identification of patients with POCs is crucial for timely and optimal treatment. Our data suggest that during postoperative period, ACN ratio and Ne% could be useful diagnostic parameters.

Severe complications after PA surgery result in considerable morbidity and prolonged hospital stay, despite advances in diagnosis and the use

of new, more potent antibiotics (3). The percentage of POCs differs between studies, ranging from 3 to 21%, depending on defining criteria (8,9). They are more frequent in patients with complicated appendicitis (10,11), and in those managed by open appendicectomy (11). These adverse prognostic criteria were the basis for enrolment in our study. Our POC rate of 19.72% is in agreement with the results of other studies (11,12). Some studies also reported that axillary temperature higher than 38°C on POD3 is associated with POC development, particularly postoperative abscesses (13,14). Our results reiterate these findings, albeit the increase of axillary temperature may be lower than 38°C on POD2 and POD4. As previously reported, POC+ patients also had prolonged ICU and overall hospital stay (3,15).



**Fig. 1. Receiver operating characteristics (ROC) curves for relative count of neutrophils (A) and absolute neutrophil count ratio at different time intervals (B)**

The identification of patients at risk for POCs would be of clinical importance, especially in the view of an early diagnosis. Some authors reported that preoperative increase of WBC and CRP (4,16,17) and the decrease of lymphocytes (5), could point towards POC development. However, other studies report that a preoperative increase of these parameters is the consequence of developed peritonitis in the context of complicated appendicitis and could not be used as reliable POC predictors (18). Several laboratory parameters were used to identify inflammatory activity during the postoperative period. Namely, postoperative increase of WBC on postoperative day 5 (19) and decrease of lymphocytes (5), might be signs of a postoperative abscess after appendectomy, however, only decrease of lymphocytes had predictive value, at the time of ultrasound confirmation. The question arises as to whether haematological parameters alone or their ratio in the postoperative period can be useful in POC detection before ultrasound confirmation. We found that lower ACN ratio between POD2 and POD4 (<44.5%) and higher Ne% on POD4 (>71.8%), were useful parameters in discriminating pediatric patients with POCs after PA surgery. These results could be explained as a consequence of an emerging infection. Bratton et al. (20) reported that neutrophil count normalization occurs between 48-72 hours after resolution of infection, which is in agreement with our results. Until recently ACN was used only for the diagnosis and differentiation between simple appendicitis and PA (21). We found that ACN determined for each postoperative day is a worse POC predictor than POD2/POD4 ACN ratio, which provides a better insight into inflammatory events during the postoperative course. This parameter would greatly help in POC diagnosis before ultrasound confirmation, which is also suggested by others (22).

There are limitations to this study. The retrospective design of medical records and small number

of patients with POCs may be a limiting factor and a weak point of our study.

## Conclusion

Children with POC after PA surgery have lower POD2/POD4 ACN ratio and higher Ne% at POD4 in comparison to uncomplicated cases, indicating that close monitoring of these parameters could facilitate the early identification of cases likely to develop POCs. These findings are of practical importance, considering that investigated parameters do not require any additional time or cost and are routinely performed in clinical practice. Taking into consideration that CRP and procalcitonin are important inflammatory parameters in everyday clinical practice of pediatric patients after PA surgery, comparison of these parameters with ACN ratio may be useful in future studies.

## Abbreviations

ACL: absolute count of lymphocytes  
ACN: absolute count of neutrophils  
AUC: area under the curve  
CRP: C reactive protein  
CI: confidence interval  
ICU: Intensive Care Unit  
Ly%: relative lymphocyte count  
Ne%: relative neutrophil count  
PA: perforated appendicitis  
POC: postoperative complication  
PRO: preoperatively  
POD2: postoperative day 2  
POD4: postoperative day 4  
ROC: receiver operating characteristic  
WBC: white blood cell count

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## Authors' Contributions

MV: conceptualization, methodology, investigation, formal analysis, writing of original draft;  
 BI: investigation, writing review, editing,  
 J-V Lj: formal analysis, writing review, editing;  
 SM: writing review, editing;  
 KM: formal analysis, writing review, editing;  
 DS: writing review, editing.

## Conflicts of Interest

The authors declare no conflict of interest.

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