Comparison of inflammatory markers in the differentiation of uncomplicated appendicitis and complicated appendicitis

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ABSTRACT

Aim: Appendicitis is the common emergency surgery performed in the pediatric age group. In our study, it was aimed to compare the pre-operative inflammatory markers with the pathology results of the patients who were operated for appendicitis in our clinic and to reveal their success in the distinction between uncomplicated appendicitis and complicated appendicitis.

Material and Method: The data of 98 patients who were operated with a pre-diagnosis of appendicitis in the pediatric surgery clinic of our hospital between 2019 and 2021 were retrospectively analyzed. Uncomplicated appendicitis and complicated appendicitis grouping was made according to pathological diagnoses. The inflammatory markers were evaluated.

Results: According to the pathological grouping, 51 (56.7%) patients are in the uncomplicated appendicitis group. It was observed that only the change in the C-reactive protein (CRP) value in the binary regression evaluation created for the parameters whose difference was significant evaluation increased the complicated appendicitis probability 1.028 times. It was seen that the CRP value of 34.65 was a parameter that could distinguish between uncomplicated appendicitis and complicated append with 79.5% sensitivity and 78.4% specificity.

Conclusion: The treatment of appendicitis in children is a subject that is still being studied and has many points that have not been clarified. Among the markers that can be used in treatment planning, CRP gives usable results.

Keywords: Appendicitis, C-reactive protein, immature granulocyte, inflammatory markers, neutrophil lymphocyte ratio, pediatrics

INTRODUCTION

Appendicitis is the most common emergency surgery performed in the pediatric age group (1). However, it has been reported in recent studies that some appendicitis cases will benefit from antibiotic treatment and that they can be followed up without surgery, or it will be more appropriate to operate already complicated cases after antibiotic treatment for a while (2, 3). Ultrasonography and tomography images are often supported to identify patients who can be followed up without surgery or who will not be urgently operated but will be suitable for a period of antibiotic treatment (1).

Ultrasonography or tomography imaging is not available in all clinics in cases of appendicitis admitted to the hospital outside of routine working hours. For this reason, clinical scoring, biochemical and hematological parameters are used to distinguish between uncomplicated appendicitis (UA) and complicated appendicitis (CA) in addition to radiological evaluation (4).

Among these parameters, white blood cell count (WBC), neutrophil count (NEUT) and C-reactive protein (CRP) are now included in clinical evaluation scoring (5,6). It has been accepted that CRP, an inflammatory marker, is valuable in distinguishing between UA and CA (7). In addition to CRP, neutrophil lymphocyte ratio (NEU/LN) is found as a parameter that can be used in the differentiation of UA and CA in many studies (7,8).

In addition to these parameters described in the literature, there are studies showing that the number of immature granulocytes (IG) and the percentage of immature granulocytes (IG%), which have been shown to play a role in many inflammatory processes and which are automatically measured in new generation hemogram analyzers, are parameters that can be used to differentiate UA from CA (9,10).

In our study, it was aimed to compare the pre-operative WBC, CRP, NEUT, NEUT%, NEU/LN, IG and IG% with the pathology results of the patients who were operated for

appendicitis in our clinic and to reveal their success in the distinction between UA and CA.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 28.01.2021, Decision No: 2020-KAEK-143-33). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of 98 patients who were operated with a pre-diagnosis of appendicitis in the pediatric surgery clinic of our hospital between 01 October 2019 and 31 January 2021 were retrospectively analyzed. Age, gender, CRP and hemogram values of the patients and pathology results were recorded. Eight of the patients were excluded from the study due to the lack of data because their preoperative analyzes were performed outside our hospital.

According to the pathological diagnosis, patients with lymphoid hyperplasia of the appendix, simple uncomplicated appendicitis, flagmenous appendicitis and suppurative appendicitis were grouped as UA, patients with gangrenous appendicitis, necrotizing appendicitis and perforated appendicitis were grouped as CA.

SPSS-22 program was used to analyze the data. Continuous variables were analyzed using Student's t-test if they fit the normal distribution and Wilcoxon-Mann-Whitney test if they did not fit the normal distribution. Categorical variables were analyzed using the chi-square test. Statistical significance level was accepted as <0.05. Statistically significant variables were included in the binary logistic regression. The multivariate model was evaluated for compliance using Hosmere Lemeshow test statistics and Receiver Operating Characteristic (ROC) area under the curve.

RESULTS

Of the 90 patients included in the study, 52 (57.8%) were male and 38 (42.2%) were female patients. The mean age of the patients was 11.15±4.05 (3-17) years, the mean WBC 14908±5305, hemoglobin values 12.8±1.3 g/dl and platelet values were calculated as 299670±69 150 1 /µl. There was no significant difference between uncomplicated and complicated appendicitis according to gender (p=0.504). The mean age of uncomplicated appendicitis was 12.56±3.52 years, and the mean age of complicated appendicitis was 9.3±4.00 years, and there was a statistically significant difference (p<0.001). According to the pathological grouping, 51 (56.7%) patients are in the UA group (**Table 1**).

Table 1. Distribution of patients according to pathological diagnoses	
Pathological Diagnosis	**n**
Uncomplicated Appendicitis	
Lymphoid Hyperplasia	6
Acute Appendicitis	24
Flagmenous/Suppurative Appendicitis	21
Complicated Appendicitis	
Gangrenous/Necrotizing Appendicitis	27
Perforated Appendicitis	12

In the results, it was seen that CRP, NEUT%, NEU/LN, IG and IG% were statistically significantly higher in the CA group (**Table 2**).

Table 2. Average values of inflammatory markers and their ratios comparison of uncomplicated appendicitis and complicated appendicitis			
	Uncomplicated appendicitis (n=51)	**Complicated appendicitis (n=39)**	**P**
WBC	14239±5447	15782±5049	0.173
CRP	27.66±33.74	103.03±83.86	<0.001
NEUT	11153±5360	13075±4681	0.74
NEUT%	74.97±13.46	82.10±7.17	0.004
IG	50±32	69±50	0.034
IG%	0.33±0.12	0.40±0.23	0.040
NEU/LN	7.58±6.53	12.18±9.21	0.007

WBC: White Blood Cell, CRP: C-reactive Protein, NEUT: Neutrophil, IG: Immature Granulocytes, NEU/LN: Neutrophil Lymphocyte Ratio

It was observed that only the change in the CRP value in the binary regression evaluation created for the parameters whose difference was significant in the statistical analysis evaluation increased the CA probability 1.028 times, and the other parameters did not have a statistically significant effect (**Table 3**).

Table 3. Clinical predictors of complicated appendisitis						
	B	**Wald**	**OR**	**95% C.I.**		**p**
				Lower	**Upper**	
CRP	0.028	15.868	1.028	1.014	1.043	<0.001
NEUT%	0.029	0.382	1.029	0.940	1.127	0.536
NEU/LN	0.023	0.163	1.024	0.914	1.147	0.687
IG	0.009	0.347	1.009	0.979	1.040	0.556
IG%	-1.622	0.230	0.197	0.000	148.546	0.631
Overall Percentege=74.4%						

CRP: C-reactive Protein, NEUT: Neutrophil, NEU/LN: Neutrophil Lymphocyte Ratio, IG: Immature Granulocytes

In the ROC curve given in **Figure 1** for the UA and CA distinction among the evaluated parameters, the largest area under the curve occurred in the CRP (0.841, p <0.001, 0.759-0.923). While it was seen that NEU/L and NEUT% had significance in ROC curve with values of p=0.004 and p=0.018, respectively, WBC, NEUT, IG and IG% were not significant (**Table 4**). According to the evaluation made, it was seen that the CRP value of 34.65 was a parameter that could distinguish between UA and CA with 79.5% sensitivity and 78.4% specificity. It was observed that the age of the patient, evaluated separately from inflammatory markers, differed between UA and CA with a cutoff value of 11.5 and sensitivity of 68.6% with a sensitivity of 69.2% (0.734, p <0.001, 0.630-0.838).
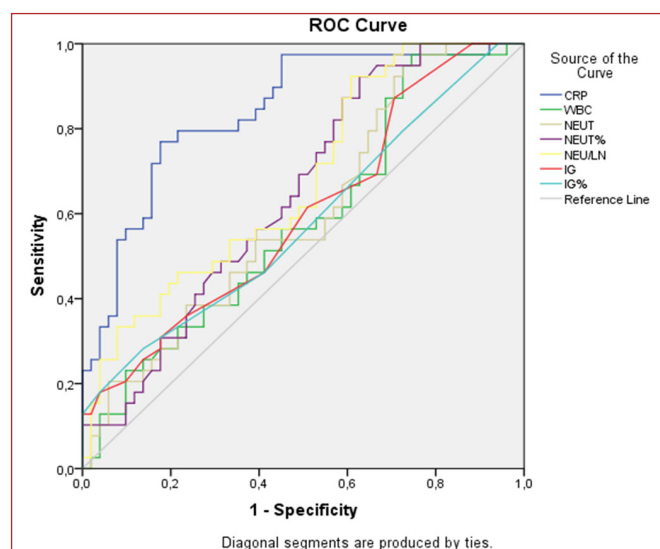

Figure 1. ROC curve analysis of inflammatory markers

Table 4. Performance of inflammatory markers					
Inflammatory markers	AUC (95% C.I.)	p	Cutoff	Sensitivity	Specificity
CRP	0.841 (0.759-0.923)	<0.001	34.65	79.5	78.4
WBC	0.581 (0.463-0.701)	0.184	15165	53.8	54.9
NEUT	0.599 (0.482-0.716)	0.109	11275	53.8	52.9
NEUT%	0.647 (0.534-0.759)	0.018	80.75	56.4	58.8
NEU/LN	0.676 (0.566-0.787)	0.004	7.2	56.4	56.9
IG	0.597 (0.479-0.715)	0.115	45.0	61.5	49.0
IG%	0.580 (0.460-0.700)	0.194	0.35	46.2	58.8
CRP: C-reactive Protein, WBC: White Blood Cell, NEUT: Neutrophil, NEU/LN: Neutrophil Lymphocyte Ratio, IG: Immature Granulocytes,					

DISCUSSION

Appendicitis, the traditional treatment of which is open or closed appendectomy, is increasingly being mentioned in the 21st century (11). Although it is now accepted that some cases of appendicitis can be treated with antibiotics, the characteristics of these patients are still not clear (12,13). As seen in our study, pediatric patients with CA were younger in age. Similarly, in the studies of Miyauchi et al. and Pham et al., young age was seen as a risk factor for CA (12,14). It is true that younger age is a risk factor, but there is no clarity or limitation on which age is younger. In our study, the cut-off for age was 11.5 years. The cut-off value for age was calculated as 5 in Pham's study and 9 in the Miyauch's study (12,14). Appendicitis is more likely to be complicated at an early age, but there is no clear limit for the younger age.

In many studies, it is seen that the distinction between UA and CA is also based on surgical findings (12-14). However, in our study, the grouping method was preferred according to pathology diagnoses, which we thought would be useful in terms of obtaining more standard results. Although no intestinal content was seen in the abdomen during the operation, it would not be correct to evaluate necrotizing appendicitis as UA. Likewise, evaluating the reactive inflammatory fluid that can benefit from the antibiotics formed around the cecum as complicated appendicitis will also cause wrong grouping. With the pathological grouping in our study, the distinction between gangrenous/necrotizing appendicitis in which microperorations and necrosis is seen, and flagmenous/supurative appendicitis in which inflammation due to reactive response occurs is made more clearly. For this reason, we think that the pathological grouping method will be useful in terms of obtaining more standard results for future studies.

It was observed that the WBC and NEUT values, which we attach importance to in our clinical practice, did not differ between the UA and CA groups in our study. It is stated in the publications that these values can be used in the distinction between UA and CA (12-15). It is possible that the results of these markers, which are known to be affected by many conditions and differ in standard ranges, did not differ in our study due to the age distribution of our patient group (16,17).

In the meta-analysis conducted by Yu et al., It was revealed that low CRP levels are exclusive with a specificity value of up to 100% for CA (15). However, the sensitivity of high CRP values ranges between 26.0-73.9% (15). Although our study gave a higher sensitivity with a sensitivity value of 79.5% for the CRP value, our specificity value remained low at 78.4%. CRP seems that the most valuable parameter in the meta-analysis and in our study is CRP.

Although WBC and NEUT values did not differ significantly between UA and CA, it was observed that there were differences between the two groups in our NEUT% and NEU/LN study. It is understood from our study that NEUT% and NEU/LN are markers that can be used and evaluated to differentiate UA and CA in children. Similar to other studies, it was seen from our study that NEUT% and NEU/LN are markers that can be used and evaluated to differentiate UA and CA in children (18,19). It is seen that the platelet-lymphocyte ratio can be used as another marker in the literature, but this ratio was not used in our study (18,19). However, it is true that more standardized comprehensive studies are required to strengthen the inferences to be made for these markers.

As a new inflammatory marker, it is seen that IG and IG%, which are significant in neonatal sepsis and severe bacterial infections in childhood, are distinctive for adult appendicitis cases in Ünal's study (10,20,21). In our study, UA and CA It was observed that the IG and IG% of the cases were statistically significantly higher. As stated in the conclusion of the study conducted by Mathews et al., UA and CA also differ in IG and IG% children, but they were not superior to other markers (9). It is possible to deduce from our results that supports Mathews' study for IG and IG%. According to the publication of Roehlr et al., values under 10 years old (30-40, 0.3%) and between 10-20 years old (69.5, 0.7%) and IG and IG% differ significantly in the population accepted as normal (22). In the light of this information, it would be more appropriate to evaluate these age groups separately in studies on IG in terms of accuracy and reliability of the results.

The important limitations of our study are that it is retrospective and single center. Apart from the parameters we evaluate, it can be used in other clinical, laboratory and radiological examinations to distinguish between UA and CA, and the absence of these examinations in our study reduces the rates in multiple evaluations. In particular, the absence of radiological examination results is sometimes due to the fact that patients were operated without radiological examination, and this situation increases the importance of our results for us. One of the deficiencies of our study is that the distribution by age groups that were not formed when planning the study most likely affected our results.

CONCLUSION

The treatment of appendicitis in children is a subject that is still being studied and has many points that have not been clarified. Among the markers that can be used in treatment planning, CRP gives usable results. More detailed and larger series are needed for IG and other markers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 28.01.2021, Decision No: 2020-KAEK-143-33).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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