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Eosinophils, neutrophil-lymphocyte ratio and other biomarkers in complicated acute appendicitis. A case-control study

Eosinófilos, índice neutrófilos-linfocitos y otros biomarcadores en la apendicitis aguda complicada. Estudio de casos y controles

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ABSTRACT. Introduction: the diagnostic approach to acute appendicitis involves patient history, physical examination, imaging studies and laboratory tests, as blood count. **Objectives:** the aim of this study was to investigate the association between complicated (perforated) cases of acute appendicitis in children and blood count biomarkers. **Material and methods:** a case-control study was conducted at a secondary hospital in Mexico City, comparing patients with uncomplicated acute appendicitis (control group) to those with complicated acute appendicitis and varying stages of severity (case group). The study used clinical records of patients under 18 years old who were diagnosed with acute appendicitis and had blood counts before surgery. The study covered the period from 2019 to 2023. **Results:** 278 medical records were included, of which 53.6% were from men. The mean age was 9.9 ± 4 years. 73.7% of the cases presented complicated acute appendicitis. Leukocyte and neutrophil counts, as well as neutrophil/lymphocyte and neutrophil/platelet ratios were higher in the complicated appendicitis group. Lymphopenia was more frequent in younger children. In the multivariate analysis, ≥ 55 eosinophils/mm^3 (OR = 2.2, 95%CI 1.2-4, p = 0.005) and the value of ≥ 3.18 in the neutrophil/lymphocyte ratio (OR = 4.4, 95%CI 2.2-8.5, p < 0.001) were associated with complicated appendicitis. **Conclusion:** complete blood count is a useful tool for identifying cases of complicated acute appendicitis in children. This study proposes a cut-off point for eosinophils and other blood biomarkers to identify complicated cases of acute appendicitis.

Keywords: appendicitis, biomarkers, blood cell count, eosinophils, reference value, lymphopenia.

RESUMEN. Introducción: *el abordaje diagnóstico de la apendicitis aguda incluye el historial del paciente, la exploración física, las pruebas de imagen y los análisis de laboratorio, como el hemograma.* ***Objetivos:*** *investigar la asociación entre los casos complicados (perforados) de apendicitis aguda en niños y los biomarcadores del hemograma.* ***Material y métodos:*** *se realizó un estudio de casos y controles en un hospital de segundo nivel de la Ciudad de México, en el que se comparó a pacientes con apendicitis aguda no complicada (grupo de control) y con apendicitis aguda complicada y distintos grados de gravedad (grupo de casos). El estudio utilizó los registros clínicos de pacientes menores de 18 años a los que se les diagnosticó apendicitis aguda y se les realizó un hemograma antes de la cirugía. El estudio abarcó el periodo comprendido entre 2019 y 2023.* ***Resultados:*** *se incluyeron 278 historias clínicas, de las cuales 53.6% correspondía a varones. La edad media fue de 9.9 ± 4 años; 73.7% de los casos presentaba apendicitis aguda complicada. Los recuentos de leucocitos y neutrófilos, así como las relaciones neutrófilos/linfocitos y neutrófilos/plaquetas, fueron más elevados en el grupo de apendicitis complicada. La linfopenia fue más frecuente en los niños más pequeños. En el análisis multivariante, ≥ 55 eosinófilos/mm^3 (OR = 2.2, IC de 95%: 1.2-4, p = 0.005) y el valor de ≥ 3.18 en la relación neutrófilos/linfocitos (OR = 4.4, IC de 95%: 2.2-8.5; p < 0.001) se asociaron con la apendicitis complicada.* ***Conclusión:*** *el hemograma completo es una herramienta útil para identificar casos de apendicitis aguda complicada en niños. Este estudio propone un punto de corte para los eosinófilos y otros biomarcadores sanguíneos con el fin de identificar casos complicados de apendicitis aguda.*

Palabras clave: *apendicitis, biomarcadores, hemograma, eosinófilos, valor de referencia, linfopenia.*

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Abbreviations:
AA = acute appendicitis
MLR = monocyte/lymphocyte ratio
NLR = neutrophil/lymphocyte ratio
PLR = platelet/lymphocyte ratio

INTRODUCTION

Acute appendicitis (AA) is defined as the inflammation of the vermiform appendix and it represents approximately 1% of pediatric emergency visits for abdominal pain.[1] It typically results from obstruction of the appendiceal lumen, leading to increased mucus production, bacterial overgrowth, and elevated intraluminal pressure, which can cause necrosis and a high risk of perforation.[2] The condition most commonly presents between the ages of 10 and 19 years, while it is relatively rare in infants and preschoolers.[3] Nevertheless, the risk of perforation is higher in patients under 10 years of age, with an estimated incidence ranging from 23 to 73% in those older than 1 year and approaching 100% in younger children.[4]

During the 2015 World Society of Emergency Surgery Congress, a panel of experts convened to evaluate the severity of appendicitis and develop a four-stage classification system:[5]

Stage 1: hyperemic appendix.
Stage 2: appendix with mucosal erosions, suppuration, and fibrinopurulent exudates.
Stage 3: gangrenous appendix with wall necrosis.
Stage 4: perforated appendix.

Another simpler classification is based on perforation data:[6]

Uncomplicated acute appendicitis: no data of perforation (hyperemic and congestive appendix).
Complicated acute appendicitis: perforated, with or without localized abscess, with or without peritonitis (phlegmonous, gangrenous and perforated appendix).

The diagnostic approach to AA involves a combination of patient history, physical examination, laboratory tests, and imaging studies. These data are integrated into various diagnostic scales, though none of them offers definitive diagnostic certainty.[7] Among the most recognized scales are the Alvarado scale, the Pediatric Appendicitis Score, and the Lintula scale, with the latter two specifically designed for the pediatric population. These scales assess factors such as sex, pain characteristics, accompanying symptoms, and fever to guide clinical diagnosis and inform treatment decisions.

A complete blood count is one of the most valuable and commonly requested laboratory tests in emergency settings. This readily accessible, low-cost test provides detailed information on the composition and quantity of blood cells, including erythrocytes, leukocytes, and platelets. This test helps clinicians to identify and evaluate a range of pathologies affecting various organs and systems.[8]

An ideal marker for diagnosing and assessing the severity of AA should be straightforward, provide rapid results, and offer high accuracy, sensitivity, and specificity, all while being cost-effective. Consequently, routinely performed blood tests are highly valuable indicators. Commonly used assessments include absolute leukocyte count; levels of neutrophils, lymphocytes, monocytes, and platelets, as well as, neutrophil/lymphocyte ratio (NLR); monocyte/lymphocyte ratio (MLR) and platelet/lymphocyte ratio (PLR).[4]

The aim of this study was to investigate the association between complicated cases of acute appendicitis in children and blood count biomarkers.

MATERIAL AND METHODS

A case-control study was conducted at a secondary hospital in Mexico City to compare patients with uncomplicated acute appendicitis (control group) to those with complicated acute appendicitis of varying severity (case group). The study used convenience sampling, focusing on clinical records of patients under 18 years old diagnosed with acute appendicitis and who had pre-surgical blood counts from 2019 to 2023. Exclusion criteria included records with underlying pathologies affecting leukocyte levels, incomplete information, prior antibiotic treatment before diagnosis or blood counts, and concurrent infections at the time of diagnosis. Additionally, patients without a blood count or staging report for acute appendicitis were eliminated from the study. The study was conducted without funding. It received approval from the Ethics Committee of the institution (approval number 302-010-02-24) and was conducted in accordance with the declaration of Helsinki.

For the statistical analysis, we employed two classifications AA and examined differences between groups:

1. Complicated and uncomplicated cases.
2. Severity stages based on histopathological findings of the appendix (hyperemic, phlegmonous, gangrenous and perforated).

Sex and age were included in the statistical analysis as both confounding and non-confounding variables. Continuous variables were expressed as median (percentile 25-75th) and dichotomous variables as frequencies and percentages. Kolmogorov-Smirnov test was applied to assess the normality of the variables. To compare quantitative variables, Mann-Whitney U statistical analysis and Kruskal-Wallis for independent samples tests were used, when comparing proportions, the χ^2 or Fisher's exact tests were used. Receiver operating characteristic (ROC) curves were generated and the area under the curve and 95% confidence intervals (CI) were calculated. Cut-off points for the variables were determined using the Youden index (Y = sensitivity + specificity-1), taking the value closest to 1. The variables analyzed were dichotomized according to the evaluated cut-off points. The χ^2 test was applied, and the odds ratio (OR) and 95%CI were calculated. Significant variables identified in the bivariate analysis were subsequently examined using a multivariate analysis. Two methods were used: first, the input method and then the backward stepwise method (WALD). Significance level used was $p < 0.05$. The analyses were performed using the Statistical Package for Social Sciences (SPSS) version 25.0.

RESULTS

Five hundred and six clinical records of patients diagnosed with AA were identified and of these, 225 that did not meet the inclusion criteria were excluded and three were eliminated; the rest (n = 278) were included in the study of which, 53.6% were men and the mean age was 9.9 ± 4 years.

Table 1 summarizes the differences between the complicated and uncomplicated acute appendicitis groups as well as between severity groups according to the pathology report.

It was observed that those cases that presented lymphopenia were younger (9 [5.4-12.3 years]) compared to those that did not present it (11 [8.5-14.1 years]), p = 0.0003 *(Figure 1)*.

Table 2 shows the analysis of the cut-off points found for each variable in the context of complicated AA and the multivariate and retrograde multivariate analysis. In both, the variables eosinophils and NLR were associated with complicated AA.

DISCUSSION

The aim of our study was to describe the relationship between the severity of AA in pediatric population (using the classification by macroscopic findings, based on pathology reports, and the classification based on the presence or absence of perforation), with the levels of leukocytes, neutrophils, lymphocytes, eosinophils, platelets and with the quotients derived from these.

Age and sex were not considered confounding variables because their distributions were similar between the groups with complicated and uncomplicated appendicitis, as well as among the four groups classified by macroscopic findings. These two variables were included in the modeling of the multivariate analysis showing that they were not significant for association with complicated appendicitis.

When comparing age group percentages with the severity strata of appendicitis, we observed that younger patients were generally more affected by the most severe forms. In fact, the only patient in the infant group was classified in the most severe category of acute appendicitis. This case had to be eliminated for statistical analysis purposes because there was only one. It is important to note that the greater severity observed in the younger age groups may be associated with the higher incidence of lymphopenia that we observed in these children. In contrast, the teenager group had a higher percentage of patients in the less severe categories of acute appendicitis. Our results are like those reported in a study that included the Mexican pediatric population, in which it was observed that preschoolers with complicated AA had lower levels of lymphocytes when compared to patients with uncomplicated AA of the same age. However, this difference was not observed in the group of schoolchildren, nor in the group of teenagers.[9]

Prabhudas, et al. reported that younger children experience immunological adaptations after exposure to new antigens, which are essential for developing immunological memory. During this adaptation period, fluctuations in lymphocyte counts are common and can lead to transient lymphopenia. Since the immune system in younger children is still developing, they are more prone to secondary lymphopenia.[10] This increased susceptibility is attributed to a combination of factors, including infection susceptibility, immune system immaturity, prenatal and neonatal influences, postnatal immunological adaptation, and genetic factors, as discussed by Gervassi and Horton.[11] So, lymphopenia has previously been associated with complicated AA in children,[12,13] with the development of intra-abdominal abscesses after appendectomy in children with complicated appendicitis and with AA in adults.[14,15]

The results of our study are consistent with recent reports,[16,17] showing that leukocyte and neutrophil counts were higher in the more severe AA groups, using both four-stage[5] and perforation data[6] classifications.

Table 1: Differences between acute appendicitis groups.

	Acute appendicitis[6]			Appendix[5]				
Variable	Uncomplicated N = 73	Complicated N = 205	p	Hyperemic N = 73	Phlegmonous N = 57	Gangrenous N = 58	Perforated N = 90	p
Sex M:F (n)	45:28	104:101	0.108	45:28	34:23	28:30	42:48	0.162
Age (years)	10	9.83	0.754	10	10.25	10.41	9.29	0.073
Media [rango]	[5.5-13.7]	[6.5-12.5]		[5.58-13.75]	[8-14.91]	[6.89-12.79]	[5.41-12.35]	
Newborns, n (%)	0 (0.0)	0 (0.0)	0.264	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0.009**
Infants, n (%)	0 (0.0)	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	
Preschoolers, n (%)	20 (27.4)	40 (19.5)		20 (27.4)	3 (5.3)	11 (19.0)	26 (28.9)	
School-children, n (%)	33 (45.2)	118 (57.6)		33 (45.2)	36 (63.2)	33 (56.9)	49 (54.4)	
Teenagers, n (%)	20 (27.4)	46 (22.4)		20 (27.4)	18 (31.6)	14 (24.1)	14 (15.6)	
Leukocytes (cells/mm^3)	11,800 [7,695-15,870]	15,010 [10,710-17,765]	**< 0.001**	11,800 [7,695-15,870]	14,440 [10,195-16,190]	15,080 [11,595-18,170]	15,090 [10,265-18,310]	**0.003**
Neutrophils (cells/mm^3)	8,400 [5,155-12,560]	11,590 [8,100-14,901]	**< 0.001**	8,400 [5,155-12,560]	11,340 [7,075-13,945]	11,960 [8,897-15,045]	11,690 [8,187-15,162]	**0.001**
Lymphocytes (cells/mm^3)	1,480 [1,480-1,195]	1,460 [1,060-2,020]	0.165	1,480 [1,195-2,445]	1,620 [1,110-2,094]	1,470 [1,000-1,818]	1,360 [1,040-2,000]	0.410
Eosinophils (cells/mm^3)	50 [40-120]	80 [40-130]	0.157	50 [40-120]	90 [40-160]	70 [47.5-110]	75 [40-130]	0.325
Platelets (cells/ mm^3)	276,000 [224,650-333,700]	276,000 [228,350-384,150]	0.887	276,000 [224,650-333,700]	290,200 [240,500-329,700]	270,000 [227,800-346,275]	268,800 [228,750-367,450]	0.990
NLR	5.6 [2.5-9.54]	7.69 [4.73-12.97]	**< 0.001**	5.63 [2.5-9.54]	6.40 [3.89-11.76]	8.12 [5.18-13.98]	8.54 [4.99-13.16]	**0.001**
PLR	167.66 [115.97-241.17]	196.78 [130.6-305.36]	0.079	167.66 [115.97-241.17]	187.73 [131.65-292.02]	192.3 [131.51-292.71]	209.34 [129.5-326.6]	0.315
NPR	0.03 [0.02-0.05]	0.04 [0.03-0.06]	**0.001**	0.03 [0.01-0.04]	0.03 [0.02-0.05]	0.04 [0.02-0.06]	0.04 [0.03-0.06]	**0.002**

F = female. M = male. NLR = neutrophil/lymphocyte ratio. NPR = neutrophil/platelet ratio. PLR = platelet/lymphocyte ratio.

The systemic inflammatory response can cause neutrophilia and lymphopenia, resulting in increased NLR and PLR. Both are indicators of inflammation in AA. Regarding NLR, Delgado-Miguel, Miguel-Ferrero, et al., reported elevated levels in complicated AA cases,[16,18] as was observed in our study, in which NLR was also higher in the complicated AA group.

Other research has shown the usefulness of NPR in distinguishing between complicated and uncomplicated cases of AA.[19,20] In our study, it was observed that this index was also higher in the complicated AA group, with a difference close to the threshold of statistical significance.

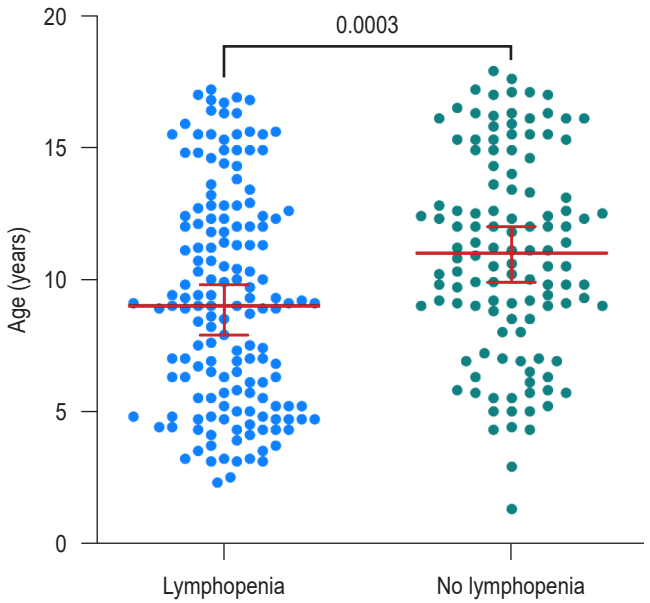

Figure 1: Presence of lymphopenia by age.

Complicated AA was associated with a more intense inflammatory response and elevated NPR, which can lead to complications such as perforation and abscess formation.[17,19]

In our study, NPR was observed to be significantly higher in patients with complicated AA compared to those with uncomplicated appendicitis. This finding is consistent with the available literature, which suggests that an elevated NPR may be an indicator of an intense systemic inflammatory response, reinforcing the notion that NPR is a useful and reliable biomarker to differentiate between complicated and uncomplicated AA cases, since the increase in neutrophil and platelet counts is indicative of a severe acute inflammatory process.

In reference to the cut-off points of the variables studied that turned out to be significant in the association with complicated AA cases, there are several investigations that are shown in *Table 3*, where the cases of our study (*Hospital Pediátrico Coyoacán*) have also been included.

It is possible that patients with pain in the right iliac fossa and without clear histological criteria for AA are in an early phase of the disease. At this stage, the classic neutrophil infiltration necessary for a histological diagnosis of AA has not yet occurred.[45] In contrast, in cases of lymphoid hyperplasia of the

Table 2: Cutoff points, multivariate and backward stepwise multivariate analysis for association with complicated acute appendicitis.

Variable	Cutoff point	Sens (%)	Spec (%)	Crude OR (95%CI)	p	OR* (95%CI)	p	OR** (95%CI)	p
Leukocytes (cells/mm^3)	10,195	77.6	46.6	2.63 [1.5-4.6]	**0.001**	1.04 [0.32-3.34]	0.95		
Neutrophils (cells/mm^3)	7,050	80.5	46.6	3.59 [2.02-6.39]	**< 0.001**	2.35 [0.67-8.29]	0.183		
Eosinophils (cells/mm^3)	55	67.8	53.4	2.41 [1.4-4.16]	**0.001**	2.23 [1.24-4.01]	**0.007**	2.2 [1.2-4]	**0.005**
NLR	3.18	88.8	37	6.64 [2.44-8.83]	**< 0.001**	2.27 [1.03-7.09]	**0.043**	4.4 [2.2-8.5]	**< 0.001**
PLR	187.4	57.1	60.3	2.01 [1.17-3.47]	**0.011**	1.56 [0.83-2.94]	0.171		
NPR	0.03	70.7	54.8	2.52 [1.45-4.38]	**0.001**	0.68 [0.29-2.01]	0.48		
Constant						0.06	**< 0.001**	0.18	**< 0.001**

CI = confidence interval. NLR = neutrophil/lymphocyte ratio. NPR = neutrophil/platelet ratio. OR = odds ratio. PLR = platelet/lymphocyte ratio. Sens = sensitivity. Spec = specificity.
* Multivariate analysis. ** Backward stepwise method (WALD)..

Table 3: Cutoff points, sensibility, specificity, OR and 95%CI in complicated acute appendicitis.

Study	Cutoff value	Sens (%)	Spec (%)	OR (95%CI)	p	Population
			Leukocytes			
HPC	**10,195**	**77.60**	**46.6**	**2.63 [1.5-4.6]**	**0.001**	**C**
Al-Gaithy, (2012)[21]	11,100	76.62	72.41	NR	< 0.001	A
McGowan et al. (2013)[22]	11,000	81.20	36.70	2.61 [1.7-4.01]	NR	A
Shimizu et al. (2016)[23]	11,500	NR	NR	NR	< 0.001	A
Beecher et al. (2016)[24]	12,250	70.03	68.13	NR	NR	A
Aydin et al. (2016)[25]	13,800	53.30	67.00	3.10 [1.71-5.62]	< 0.001	A
Jung et al. (2016)[26]	10,600	71.20	68.20	5.29 [2.27-12.37]	< 0.001	A
Shin et al. (2018)[27]	10,750	81.80	75.00	4.39 [1.36-14.18]	< 0.001	A
Celik et al. (2019)[28]	14,870	86.10	41.60	NR	0.001	C
Prasetya et al. (2019)[29]	13,630	66.10	62.50	3.25 [1.53-6.90]	0.008	C
Vargas-Rodríguez et al. (2022)[30]	11,000	78.22	22.46	1.04 [0.56-1.93]	NR	A
Patmano et al. (2022)[31]	13,610	70.10	53.70	1.21 [1.08-1.36]	< 0.001	A
Mekrugsakit & Tullavardhana, (2023)[32]	15,150	62.00	50.00	NR	NR	A
			Neutrophils			
HPC	**7,050**	**80.50**	**46.60**	**3.59 [2.02-6.39]**	**< 0.001**	**C**
Al-Gaithy, (2012)[21]	7,540	81.82	65.52	NR	< 0.001	A
McGowan et al. (2013)[22]	7,000	88.30	29.60	1.98 [1.28-3.06]	NR	A
Beecher et al. (2016)[24]	9,350	76.19	60.00	NR	NR	A
Jung et al. (2016)[26]	8,100	71.20	65.90	4.77 [2.06-11.07]	< 0.001	A
Celik et al. (2019)[28]	76.00*	97.20	32.20	NR	< 0.001	C
Prasetya et al. (2019)[29]	80.05*	74.50	66.70	5.85 [2.62-13.05]	< 0.0001	C
Vargas-Rodríguez et al. (2022)[30]	85.00*	54.46	65.94	2.17 [1.28-3.66]	NR	A
Mekrugsakit & Tullavardhana, (2023)[32]	80.00*	64.00	52.00	NR	NR	A

Continuous Table 3: Cutoff points, sensibility, specificity, OR and 95%CI in complicated acute appendicitis.

Study	Cutoff value	Sens (%)	Spec (%)	OR (95%CI)	p	Population
			Eosinophils			
HPC	**55.00**	**67.80**	**53.40**	**2.41 [1.40-4.16]**	**0.001**	**C**
			NLR			
HPC	**3.18**	**88.80**	**37.00**	**6.64 [2.44-8.83]**	**< 0.001**	**C**
Ishizuka et al. (2012)[33]	8.00	73.00	39.00	3.02 [1.54-5.94]	0.001	C+A
Kahramanca et al. (2014)[34]	5.74	70.80	48.50	NR	< 0.001	A
Kelly et al. (2015)[35]	7.53	80.00	55.00	NR	< 0.001	C
Shimizu et al. (2016)[23]	5.00	NR	NR	NR	< 0.001	A
Yardımci et al. (2016)[36]	7.95	78.00	67.00	3.04 [2.46-5.22]	0.001	C+A
Beecher et al. (2016)[24]	5.47	78.43	70.33	NR	NR	A
Aydin et al. (2016)[25]	4.87	70.70	56.30	3.03 [1.66-5.49]	< 0.001	A
Sevinc et al. (2016)[37]	4.80	78.40	41.70	2.60 [NR]	NR	C+A
Jung et al. (2016)[26]	5.60	78.00	65.90	6.84 [2.85-16.43]	< 0.001	A
Khan et al. (2018)[38]	6.36	84.00	48.00	NR	< 0.001	C+A
Shin et al. (2018)[27]	6.90	61.80	75.00	5.65 [0.57-55.97]	0.139	A
Celik et al. (2019)[28]	2.87	61.10	73.20	NR	< 0.001	C
Prasetya et al. (2019)[29]	6.59	84.60	56.60	7.15 [2.28-22.40]	< 0.001	C
Hajibandeh et al. (2020)[39‡]	8.80	76.90	100.00	43.33 [3.90-481.82]	< 0.001	C+A
Begic-Kapetanovic et al. (2021)[40]	5.61	79.00	81.0	NR	< 0.001	C
Cruz-Vallejo et al. (2021)[41]	10.40	77.78	67.14	2.53 [1.27-5.05]	< 0.001	C
Rajalingam et al. (2022)[42]	6.96	26.50	91.60	3.95 [2.63-5.99]	< 0.001	A
Ayeni et al. (2022)[43]	8.86	70.30	70.00	NR	< 0.001	C
Prasetya et al. (2019)[29]	5.50	61.39	43.48	1.22 [0.82-1.52]	NR	A
Patmano et al. (2022)[31]	6.69	77.00	76.30	NR	< 0.001	A
Mekrugsakit & Tullavardhana, (2023)[32]	7.40	62.00	58.00	NR	NR	A

Continuous Table 3: Cutoff points, sensibility, specificity, OR and 95%CI in complicated acute appendicitis.

Study	Cutoff value	Sens (%)	Spec (%)	OR (95%CI)	p	Population
Ortiz-Ley et al. (2023)[9]	7.40	NR	NR	2.20 [0.63-7.66]	0.20	C§
	12.43	NR	NR	1.82 [0.76-4.37]	0.17	C¶
	16.80	NR	NR	2.26 [0.72-7.09]	0.15	C‖
Moreno-Alfonso et al. (2023)[19]	7.77	72.00	76.00	8.20 [4.00-16.40]	NR	C
			PLR			
HPC	**187.40**	**57.10**	**60.30**	**2.01 [1.17-3.47]**	**0.011**	**C**
Shin et al. (2018)[27]	180.10	51.50	75.00	1.30 [0.29-5.79]	0.727	A
Celik et al. (2019)[28]	284.00	42.00	86.00	NR	0.004	C
Cruz-Vallejo et al. (2021)[41]	284.00	77.78	63.57	2.11 [1.09-4.08]	< 0.001	C
Rajalingam et al. (2022)[42]	180.50	22.40	89.00	2.35 [1.59-3.47]	< 0.001	A
Ayeni et al. (2022)[43]	193.67	64.00	61.00	NR	< 0.001	C
Mekrugsakit & Tullavardhana, (2023)[32]	144.40	55.00	44.00	NR	NR	A
Ortiz-Ley et al. (2023)[9]	405.70	NR	NR	10.00 [1.10-90.59]	0.049	C§
	687.80	NR	NR	4.75 [0.53-42.54]	0.270	C¶
	504.70	NR	NR	2.78 [0.46-16.49]	0.460	C‖
Yesilalioglu et al. (2023)[44]	133.73	60.00	58.40	NR	0.032	A
Moreno-Alfonso et al. (2023)[19]	213.32	60.00	85.00	8.52 [3.90-18.30]	NR	C

A = adults. C = children. CI = confidence interval. HPC = Hospital Pediátrico Coyoacán. NLR = neutrophil/lymphocyte ratio. NR = not reported. OR = odds ratio. PLR = platelet/lymphocyte ratio. Sens = sensitivity. Spec = specificity.
* Data recorded in percentage. ‡ Systematic review and meta-analysis. § Preschoolers. ¶ School-children. ‖ Teenagers.

appendix, commonly observed in pediatric age and typically associated with inflammatory conditions such as viral gastroenteritis and mesenteric adenitis, an increase in eosinophils has been observed in the wall of the appendix. This increase, although higher in cases of reactive lymphoid hyperplasia, has also been seen in AA.[46] These histological findings suggest that AA may be, at least in part, due to a reaction with type I hypersensitivity characteristics. Other findings supporting this idea include eosinophil infiltration, mast cell degranulation, germinal center edema, perivascular histiocytic proliferation and muscle edema, all of which are common in the appendicular tissue of AA cases.[47]

It has also been observed that in cases of AA with elevated eosinophil levels in the appendix wall, this increase correlates with the severity of inflammation in the organ.[48] Similarly, an elevation of the TH2 cytokine profile (IL-4, IL-5 and IL-9) has been demonstrated in the appendiceal lavage fluid, as well as elevated levels of immunoglobulin E in the appendiceal samples from cases of phlegmonous appendicitis.[49] Among these cytokines, IL-5 acts as a chemotactic factor that guides eosinophils to the target organ, which may be the appendix. Once in the tissue, eosinophils release several proteins such as eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, which have potent inflammatory properties that destroy cells.[50]

Although our study observed higher median blood eosinophil levels in complicated acute appendicitis cases compared to uncomplicated cases, this difference

was not statistically significant. However, eosinophil count emerged as one of the two significant variables in both multivariate analyses with its cut-off point showing a significant association with complicated AA cases. So, we conducted an exhaustive literature review to contrast our results, but we found no evidence that established a cut-off point for blood eosinophil levels to associate with AA and complicated AA cases. Existing evidence only supports a cut-off point for eosinophils in the appendix wall in adults.[51] Therefore, although limited to the pediatric population, our study is the first to propose a cut-off point for blood eosinophil levels to identify complicated AA cases.

Establishing a cut-off point for blood eosinophil levels could enhance our understanding of the pathophysiology of complicated AA in children. In such cases, damage to the appendix epithelium might stimulate the proliferation and release of eosinophils into the bloodstream. These eosinophils could then accumulate in the tissue, where they produce mediators that may exacerbate tissue damage,[50] potentially contributing to the development of complicated AA.

This study has several limitations, including the selection bias inherent to its retrospective design at a single institution. In addition, the irregular availability of reagents and equipment in the laboratory prevented the inclusion of variables such as monocytes, basophils, and other inflammatory biomarkers such as C-reactive protein and procalcitonin. Although the usefulness of these biomarkers in identifying complicated cases of AA has been previously demonstrated[16] many of the records reviewed lacked these reports, so it was decided not to include them in the study so as not to compromise the sample size. We also did not exclude parasitic infections in patients presenting with eosinophilia. But despite its limitations, this study highlights the importance of considering eosinophils as a potentially useful biomarker to differentiate between complicated and uncomplicated appendicitis, suggesting their inclusion in future prospective studies to improve the diagnosis and management of this condition.

CONCLUSIONS

1. A blood count is a useful tool for identifying cases of complicated acute appendicitis in children.
2. Patients with complicated AA showed higher leukocyte and neutrophil values, as well as elevated NLR and NPR.
3. Lymphopenia was more frequent in younger patients with AA.
4. This study proposes cutoff points to identify complicated AA in pediatric patients for the following variables: leukocytes, neutrophils, eosinophils, NLR, PLR, and NPR.
5. The most reliable markers to associate with complicated AA are blood eosinophil levels and NLR.
6. This study is pioneering in that it proposes a cutoff point based on blood eosinophil levels to identify complicated cases of AA in both children and adults.
7. These parameters should be included in prospective studies to take on a predictive character.

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