

Cellular indices and acute phase reactants as predictors of abscess after appendectomy

Índices celulares y reactantes de fase aguda como predictores de absceso tras apendicectomía

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Abstract

Objective: To compare the accuracy of four biomarkers as predictors of post-appendectomy abdominal abscess (PAA). **Methods:** Diagnostic study of patients under 15 years of age operated for appendicitis in a pediatric hospital between 2010 and 2022 was analyzed. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP) and procalcitonin (PCT) were compared between patients with PAA and those without such complication (NPAA). **Results:** 86 patients with PAA (64% men; mean age: 9.4 ± 3.5 years) and 91 patients NPAA (65% men; mean age: 10.2 ± 2.9 years) were included. NLR, PLR, CRP and PCT values were higher in the PAA group than in the NPAA group ($p < 0.0001$). PCT had the highest area under the ROC curve (0.761), a cutoff point of 0.37, sensitivity 74%, specificity 75%, and positive predictive value of 74% for predicting the occurrence of PAA. **Conclusions:** PCT is a good predictor of abdominal abscess after appendectomy. Considering preoperative PCT values to optimize postoperative management and antibiotics could be an additional tool in the prevention of this complication.

Keywords: Appendicitis. Abdominal abscess. Procalcitonin. Neutrophil-lymphocyte ratio. C-reactive protein. Platelet-lymphocyte ratio.

Resumen

Objetivo: Comparar la precisión de cuatro biomarcadores como predictores de absceso abdominal posapendicectomía (APA). **Métodos:** Estudio diagnóstico de los pacientes menores de 15 años intervenidos por apendicitis en un hospital pediátrico entre 2010 y 2022. Se compararon el índice neutrófilo-linfocito (INL), el índice plaqueta-linfocito (IPL), la proteína C reactiva (PCR) y la procalcitonina (PCT) entre los pacientes con APA y los que no presentaron dicha complicación (NAPA). **Resultados:** Se incluyeron 86 pacientes con APA (64% hombres; edad media: 9.4 ± 3.5 años) y 91 pacientes NAPA (65% hombres; edad media: 10.2 ± 2.9 años). Los valores de INL, IPL, PCR y PCT fueron significativamente mayores en el grupo APA que en el grupo NAPA ($p < 0.0001$). La PCT tuvo el mayor área bajo la curva ROC (0.761), un punto de corte de 0.37, sensibilidad del 74%, especificidad del 75% y valor predictivo positivo del 74% para predecir la aparición de APA. **Conclusiones:** La PCT es un buen predictor de absceso abdominal tras una apendicectomía. Tener en cuenta los valores preoperatorios de PCT para optimizar el manejo y la antibioticoterapia en el posoperatorio podría ser una herramienta adicional en la prevención de esta complicación.

Palabras clave: Apendicitis. Absceso abdominal. Procalcitonina. Índice neutrófilo-linfocito. Proteína C reactiva. Índice plaqueta-linfocito.

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Introduction

Acute appendicitis is the most frequent surgical emergency in pediatrics, with a lifetime cumulative risk of 9%¹. Its diagnosis fundamentally depends on clinical abdominal and general evaluation, although in pediatric age, early diagnosis is often difficult due to difficulties in anamnesis and the absence of classic symptoms². Appendicitis requires timely diagnosis and treatment, as its delay can lead to appendicular perforation and the development of complications.

Patients who undergo surgery for advanced appendicitis are at higher risk of developing complications, such as post-appendectomy abdominal abscess (APA). This complication occurs in approximately 4% of non-perforated appendicitis cases and in 6-28% of perforated cases, and is associated with a significant increase in morbidity and mortality^{3,4}. Although the value of different laboratory parameters as possible predictors of APA has been investigated, the results have been diverse⁵.

Recently, the usefulness of various biomarkers, such as the direct bilirubin-lymphocyte ratio, the neutrophil-lymphocyte ratio (NLR), and the platelet-lymphocyte ratio (PLR), has been evaluated as predictors of APA and in other surgical conditions, with disparate results⁶⁻⁸. However, scientific evidence is still limited, and there are no comparative studies on the usefulness of these ratios and other inflammatory parameters as predictors of this complication. The objective of this study is to compare the accuracy of four biomarkers as predictors of APA.

Methods

A retrospective diagnostic study was conducted on a consecutive series of patients under 15 years of age who developed APA, comparing them with a random sample of subjects undergoing surgery for acute appendicitis who did not present this complication (NAPA), in a second-level maternal-child hospital, between January 2010 and December 2022. Patients in the control group (NAPA) were sequentially selected from the same study population and during the same time period as patients with APA, regardless of the type of appendicitis, with the only mandatory characteristic being the absence of APA, in order to control for possible selection biases and make the groups comparable. Different variables were collected from the computerized medical records, including age, sex,

weight in kilograms, histological type of appendicitis, days of hospital stay, C-reactive protein (CRP) and procalcitonin (PCT) values, NLR and PLR at the time of hospital admission (these ratios are presented as continuous numerical values and have no units of measurement). Cell counts were performed with the Beckman Coulter hematological analyzer, and in all cases, the pathologist was unaware of the analytical results of the subjects and the occurrence of APA. Patients undergoing incidental appendectomy, with unorganized free fluid, or with an incomplete clinical record, were excluded from the study.

NLR and PLR were calculated by dividing the absolute number of neutrophils and platelets by the number of lymphocytes, respectively. The clinical diagnosis of acute appendicitis was based on anamnesis, physical examination, and ultrasound and analytical findings; the definitive diagnosis was based on histopathological analysis, classified as congestive, phlegmonous, gangrenous, perforated appendicitis, or peritonitis. The diagnosis of appendicular phlegmon was established during surgical intervention by identifying the cecal appendix with primary inflammatory signs and covered by a mass of intestinal loops with adjacent fibrin or edematous omentum. Localized peritonitis was defined as purulent or fecaloid contamination of one or two quadrants of the abdominal cavity, and generalized if there was contamination in three or more quadrants. Abscess was defined as a delimited collection of echogenic or purulent fluid within the abdominal cavity during the first month after an appendectomy, radiologically confirmed and accompanied by clinical signs of infection. All patients received intravenous antibiotic treatment with cefotaxime (150 mg/kg per day) and metronidazole (30 mg/kg per day) from the time of acute appendicitis diagnosis and during the postoperative period according to the type of appendicitis: three doses for phlegmonous, 3-5 days for gangrenous, and 7 days for the rest of appendicitis types.

Qualitative variables were expressed as relative and absolute frequencies, while quantitative variables were presented as mean and standard deviation or as median and interquartile range (IQR). The distribution of quantitative variables were determined using the Kolmogorov-Smirnov test to define the hypothesis testing method to be used (Mann-Whitney U or Student's t-test), and qualitative variables were analyzed using the χ^2 test or Fisher's exact test. Statistical significance was set as a p-value < 0.05 for an allowed type I error of 5%. CRP, PCT, NLR, and PLR were

evaluated to calculate their sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and *odds ratio* (OR). The optimal cutoff point for predicting the occurrence of APA was obtained using the area under the receiver operating characteristic curve (AUC-ROC). According to the AUC-ROC, the accuracy of the test was considered poor (0.5-0.6), fair (0.61-0.7), acceptable (0.71-0.8), good (0.81-0.9), or excellent (> 0.9). Although reference values for some of these ratios have been described in the pediatric population, in this study, a specific cutoff point was calculated for each of them, as it is a particular pathological situation (APA)⁹.

The collected data were anonymized and tabulated in Microsoft Excel (Version 16.66.1) and analyzed using the SPSS statistical software (IBM Corp., Armonk, NY, USA). This work was approved by the Clinical Research Ethics Committee (Registration No. 3318-0000200) and followed the recommendations of the STARD guidelines (*Standards for Reporting Diagnostic Accuracy Studies*)¹⁰.

Results

During the period from 2010 to 2022, 1766 appendectomies were performed in patients under 15 years of age at the hospital under study. The APA rate was 5% ($n = 89$). This analysis included 86 children with APA who met the inclusion criteria and 91 appendectomized patients without postoperative collection as a comparative sample (Fig. 1). Of the total subjects with APA, 64% were male, similar to 64.8% in the group of appendectomized patients without complications ($p = 0.903$). The mean age of patients with APA was 9.4 ± 3.5 years, while in the NAPA group it was 10.2 ± 2.9 years ($p = 0.166$). Participants with APA had a weight of 35.8 ± 14.9 kg, while in the NAPA group, the average weight was 41.4 ± 17.1 kg ($p = 0.021$). No patient had a surgical history or relevant comorbidity, and all were operated on within the first 24 hours of admission (Table 1).

The main type of appendicitis in patients with APA versus the NAPA group was generalized peritonitis, at 32.6% ($n = 28/86$) vs. 2.2% ($n = 2/91$), followed by localized peritonitis at 31.4% ($n = 27/86$) vs. 8.8% ($n = 8/91$), perforation at 18.6% ($n = 16/86$) vs. 6.6% ($n = 6/91$), appendicular phlegmon at 10.5% ($n = 9/86$) vs. 2.2% ($n = 2/91$), gangrene at 3.5% ($n = 3/86$) vs. 13.2% ($n = 12/91$), and phlegmonous inflammation of the appendix at 3.5% ($n = 3/86$) vs. 61.5% ($n = 56/91$); only in the NAPA group were there congestive

appendicitis cases (5.5%, $n = 5/91$). These differences were statistically significant ($p < 0.0001$).

The most used surgical approach was trans umbilical video-assisted in 72% of NAPA patients and 73% of APA patients, followed by laparotomy access (9% vs. 8%) and laparoscopic (5% vs. 2%), with a similar rate of conversion to laparotomy from the laparoscopic or video-assisted approach (14% in NAPA patients vs. 17% in APA patients; $p > 0.05$). In no case was surgical drainage placed. The hospital stay for APA patients was 14 days (IQR: 5 days), while in the NAPA group it was 2 days (IQR: 4 days) ($p < 0.0001$).

The NLR value in the APA group versus the NAPA cohort was 12.2 vs. 6.4, the PLR was 260.8 vs. 153.1, CRP was 74.1 vs. 11.4 mg/l, and PCT was 0.90 vs. 0.10 ng/ml, respectively. All inflammatory markers were significantly higher in patients with APA compared to those without postoperative collection ($p < 0.0001$) (Table 1).

PCT was the inflammatory marker with the best performance and highest AUC-ROC for predicting the occurrence of APA (Fig. 2), with a cutoff point of 0.37 ng/ml, sensitivity of 74%, specificity of 75%, PPV of 74%, and NPV of 76%. The predictive capacity of each of the analyzed biomarkers is shown in detail in table 2.

Discussion

Abdominal abscesses occur in up to 20% of patients after appendectomy, especially in those with complicated appendicitis^{11,12}. Although different clinical and analytical prognostic variables have been evaluated in the pediatric population, including weight, the presence of appendicolith, or intolerance to oral intake in the postoperative period, among others, there are still gaps in the current literature regarding the usefulness of some parameters inflammatory^{13,14}. This study aimed to determine and compare the accuracy of CRP, PCT, NLR, and PLR as predictors of APA in pediatrics. This is the first study to determine and compare these parameters with the objective of analyzing their prognostic value in the occurrence of APA. It was found that CRP, PCT, NLR, and PLR values at admission were significantly higher in patients with APA compared to those without this complication, all showing acceptable accuracy. However, PCT was the biomarker that demonstrated the best performance.

The incidence of APA in our cohort was 5%, lower than reported in similar series where it reaches up to 18%¹⁵. Regarding prognostic clinical variables,

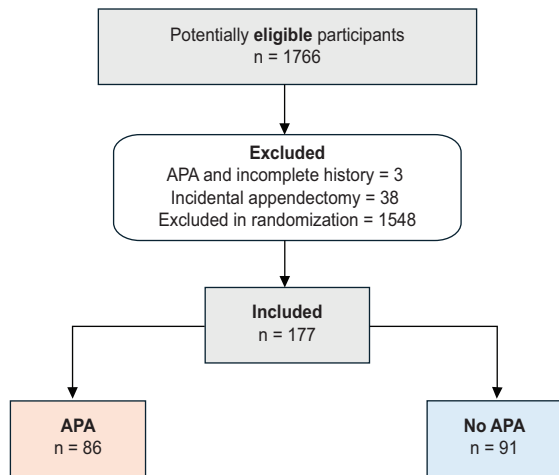


Figure 1. Flow diagram showing the potentially eligible, excluded, and included population in each of the two analyzed groups. APA: post-appendectomy abdominal abscess.

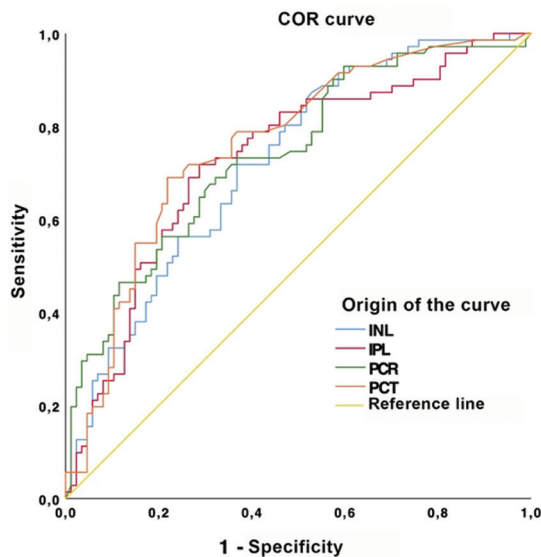


Figure 2. Area under the receiver operating characteristic curve of the analyzed parameters. NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin.

although overweight has been described as a risk factor for the development of APA because intraperitoneal adipose tissue can inhibit the inflammatory response to contamination of the abdominal cavity¹⁵, in our population, patients with APA had a lower weight than those without postoperative collection (35.8 ± 14.9 kg vs. 41.4 ± 17.1 kg; $p = 0.021$). However, this finding could have biases because the height of all patients was not recorded, and therefore, we do not know the body mass index. Likewise, perforation

Table 1. Demographic characteristics and biomarker values in the studied population

Variable	APA (n = 86)	NAPA (n = 91)	p
Woman	36%	35%	0.903
Man	64%	65%	
Age (years)	9.4 ± 3.5	10.2 ± 2.9	0.166
Weight (kg)	35.8 ± 14.9	41.4 ± 17.1	0.021
Hours from admission to surgery	7.2 ± 3.6	8.1 ± 3.1	0.178
CRP (mg/l)	74.1 ± 170.3	11.4 ± 42.5	< 0.0001
PCT (ng/ml)	0.9 ± 4.8	0.1 ± 0.26	< 0.0001
NLR	12.2 ± 12.7	6.4 ± 6.2	< 0.0001
PLR	260.8 ± 150.7	153.1 ± 260.8	< 0.0001

APA: post-appendectomy abdominal abscess; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; NAPA: no APA; CRP: C-reactive protein; PCT: procalcitonin. Values are presented as median and interquartile range.

Table 2. Area under the ROC curve and accuracy of each inflammatory marker studied as predictors of abdominal abscess after appendectomy

Biomarker	AUC-ROC	Cutoff point	S	AND	PPV	NPV	OR	p
CRP (mg/l)	0.741	21.9	72%	67%	67%	72%	5.25	< 0.0001
PCT (ng/ml)	0.761	0.37	74%	75%	74%	76%	8.6	< 0.0001
NLR	0.724	7.77	73%	63%	65%	71%	4.5	< 0.0001
PLR	0.731	191.8	73%	73%	72%	74%	7.2	< 0.0001

ROC: area under the receiver operating characteristic curve; E: specificity; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; OR: odds ratio; CRP: C-reactive protein; PCT: procalcitonin; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

of the cecal appendix has been shown to be a risk factor for the development of APA¹⁶, and although this association was not directly studied in this work, our results suggest the same, as there were more patients with appendicular perforation (18.6% vs. 6.6%) and peritonitis (64% vs. 11%) among patients with APA compared to the NAPA group. On the other hand, in this study, no statistically significant differences were found between the different surgical approaches and their association with the occurrence of APA, nor in the antibiotherapy used, since, according to the service protocol, all patients received the same antibiotic regimen before and after the surgical intervention.

Delgado et al.¹⁷ reported significantly higher CRP values in patients with APA compared to those without

complications (81.8 vs. 33.1 mg/l, respectively), with an AUC-ROC of 0.73, although with low sensitivity for the diagnosis of abscess (65%) and a discretely higher specificity of 72%. These results are similar to those found in our study, where CRP demonstrated a PPV of 67% for the occurrence of postoperative collection. However, in the experience of other authors, CRP showed no differences between patients with and without APA (8.20 vs. 5.36 mg/l; $p = 0.06$), and it was concluded that postoperative laboratory analyses have limited clinical utility for evaluating the development of peritoneal abscess¹⁸. These differences could be explained because the researchers in the mentioned study evaluated the value of CRP during the postoperative period, while in our study, inflammatory parameters were analyzed at the time of admission to the emergency department. Regarding PCT, Gavela et al.¹⁹ evaluated its use as a predictor of appendicitis severity and showed that it was significantly higher in patients with perforated appendicitis and peritonitis (4.95 ng/ml) than in those with simple appendicitis (0.15 ng/ml), with a specificity and PPV similar to ours, but with much higher sensitivity and NPV, 97% and 89%, respectively, compared to the present study, where sensitivity was 74% and NPV was 76%¹⁹. It is possible that these differences are due to discrepancies in the sociodemographic characteristics of each population and the primary objective of each study, which makes the results not entirely comparable.

Lodwick et al.²⁰ described lymphocytopenia as an effective predictor of post-appendectomy collection, which indirectly suggests that NLR could be a useful inflammatory parameter. Other authors have confirmed this hypothesis, reporting that NLR has an AUC-ROC of 0.85 and a cutoff point of 10.5 with a sensitivity of 85% and a specificity of 75% for predicting the occurrence of APA¹⁷. This predictive power of NLR is superior to that documented in our study (AUC-ROC 0.724, sensitivity 73%, and specificity 63%) when establishing the cutoff point at 7.7; this disparity in results is probably explained because a higher cutoff point was used in that study than in ours, which increases the sensitivity of the test but may increase the number of false negatives. In the same work, NLR demonstrated the best performance as a predictor of APA, compared to the absolute number of leukocytes, neutrophils, fibrinogen, and CRP¹⁷; however, a possible bias is that the population under 5 years of age was excluded. Considering the age group of patients is of great clinical importance; in fact, Aydoğdu et al.²¹ evaluated different cellular

indices in the diagnosis of pediatric appendicitis and concluded that, in childhood, the reference values of NLR, PLR, and lymphocyte-monocyte ratio vary according to age and sex, which should be taken into account when evaluating blood test results.

During the inflammatory process of acute appendicitis, an immune reaction that also involves platelets is triggered. Therefore, platelet changes have been studied to determine the usefulness of PLR in the diagnosis and prognosis of appendicitis²². Our analysis documented a significantly higher PLR value in patients with APA (260.8) than in those without this complication (153.1), which was associated with an increase of up to 7.2 times in the probability of developing APA (OR: 7.2; 95% confidence interval: 3.7-14). These findings are consistent with what has been described in the literature, documenting that patients with higher PLR values were more likely to present complicated appendicitis and postoperative complications⁸.

This study describes the usefulness of PCT as a predictor of APA in pediatric patients undergoing acute appendicitis surgery, with better diagnostic performance than CRP, NLR, and PLR. Due to its wide availability, healthcare personnel should be aware of its potential role in the prevention, diagnosis, and timely treatment of APA, with the aim of reducing the morbidity and mortality associated with this complication. In patients with a reasonable clinical suspicion of APA, with symptoms such as fever and intolerance to oral intake during the postoperative period, elevated preoperative PCT values support the urgent performance of an imaging test. This study presents the limitations inherent to a retrospective study in a single hospital center, in addition to the physiological heterogeneity in blood cell counts in the pediatric population. To our knowledge, this is the first study to compare these four inflammatory markers as predictors of APA, therefore, prospective studies with a larger number of patients are required to corroborate our results and seek prevention strategies for the development of APA, such as adjusting the perioperative fluid therapy and antibiotic protocol in patients at high risk of peritoneal collection.

Conclusions

PCT is a good biomarker as a predictor of APA in the pediatric population. The evaluation of PCT values before surgical intervention would allow optimizing perioperative management and postoperative antibiotic therapy, becoming a valuable tool to prevent this complication.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of people and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols. The authors obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not required. This work was approved by the Clinical Research Ethics Committee (Registration No. 3318-0000200) and has followed the recommendations of the STARD guidelines (*Standards for Reporting Diagnostic Accuracy Studies*).

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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