American Journal of Emergency Medicine 37 (2019) 1289–1294

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Assessment of proadrenomedullin as diagnostic or prognostic biomarker of acute appendicitis in children with acute abdominal pain

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ARTICLE INFO

Article history:
Received 27 May 2018
Received in revised form 25 September 2018
Accepted 25 September 2018

Keywords:
Appendicitis
Abdominal pain
Biomarkers
Proadrenomedullin
Prognosis

ABSTRACT

Background: Acute appendicitis (AA) is one of the most frequent surgical pathologies in pediatrics.
Objectives: To investigate the utility of proadrenomedullin (pro-ADM) for the diagnosis of AA.
Methods: Prospective, analytical, observational, and multicenter study conducted in 6 pediatric emergency departments. Children up to 18 years of age with suspected AA were included. Clinical, epidemiological, and analytical data were collected.
Results: We studied 285 children with an average age of 9.5 years (95% confidence interval [CI], 9.1–9.9). AA was diagnosed in 103 children (36.1%), with complications in 10 of them (9.7%). The mean concentration of pro-ADM (nmol/L) was higher in children with AA (0.51 nmol/L, SD 0.16) than in children with acute abdominal pain (AAP) of another etiology (0.44 nmol/L, SD 0.14; $p < 0.001$). This difference was greater in complicated cases compared with uncomplicated AA (0.64 nmol/L, SD 0.17 and 0.50 nmol/L, SD 0.15, respectively; $p = 0.005$). The areas under the receiver-operating characteristic curves were 0.66 (95% CI, 0.59–0.72) for pro-ADM, 0.70 (95% CI, 0.63–0.76) for C-reactive protein (CRP), 0.84 (95% CI, 0.79–0.89) for neutrophils, and 0.84 (95% CI, 0.79–0.89) for total leukocytes. The most reliable combination to rule out AA was CRP ≤1.25 mg/dL and pro-ADM ≤0.35 nmol/L with a sensitivity of 96% and a negative predictive value of 93%.
Conclusion: Children with AA presented higher pro-ADM values than children with AAP of other etiologies, especially in cases of complicated AA. The combination of low values of pro-ADM and CRP can help to select children with low risk of AA.

1. Introduction

Acute appendicitis (AA) is among the main causes of acute abdominal pain (AAP), and it is one of the most frequent surgical pathologies in pediatrics, accounting for up to 80% of pediatric abdominal surgical emergencies [1]. In at least one-third of AA cases, the clinical course is atypical, showing symptoms that differ from the usual clinical picture and thus making a rapid diagnosis difficult [2]. The delay in diagnosis leads to an increase in the percentage of perforation, postoperative morbidity, mortality, and hospital stay. Therefore, the clinical challenge is to be able to diagnose AA with enough time to prevent progression to perforation while minimizing the number of negative appendectomies performed. To solve that, several diagnostic modalities have been developed such as laboratory tests, clinical assessment scales, and

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https://doi.org/10.1016/j.ajem.2018.09.038
0735-6757/

imaging tests [3,4]. Leukocyte and neutrophil counts and C-reactive protein (CRP) are the most used laboratory tests. However, none of them has, by itself, enough predictive value to rule out AA early in the pediatric population [5].

Proadrenomedullin (pro-ADM) is a precursor of the adrenomedullin peptide produced under stress conditions by several tissues. It can be routinely measured in peripheral blood because it has a long half-life, lack of activity, and lack of ability to bind other proteins [6]. It also has vasodilator, anti-inflammatory, and microbicidal functions [7]. Several studies performed in adults associate high levels of pro-ADM (nmol/L) with community-acquired pneumonia, septic shock, and cardiovascular disease, making pro-ADM a useful marker of severity or morbidity [8,9].

The number of studies assessing the role of pro-ADM in children is very limited. One of them associates increased levels of pro-ADM with a high risk of mortality and multiorgan failure in critical patients [10]. Another suggests that high levels of pro-ADM in children with pneumonia predict a higher risk of pleural effusion [11]. However, there is only one study linking pro-ADM with AA [12]. In this work, Míguez et al. propose using the combination of low values of both CRP and pro-ADM to rule out AA in children with AAP.

Given the preliminary results described by Míguez et al. [12], we designed a multicenter study to confirm the usefulness of pro-ADM to diagnose AA in children with AAP. The main objectives were (a) to assess the accuracy of pro-ADM as predictor of the degree of histopathological affectation of the appendix, (b) to compare the diagnostic performance of pro-ADM against other traditionally used analytical markers (CRP, leukocyte count, and neutrophil count) and the Pediatric Appendicitis Score (PAS), and (c) to confirm the suitability of pro-ADM alone or in combination with other biomarkers to eliminate AA.

2. Methods

2.1. Study design

This is a prospective analytical-observational, multicenter study approved by the ethics committees of all participant hospitals according to the Helsinki Declaration. Principles of good clinical practice were followed during the study. A written informed consent was signed by the parents or legal guardians of all patients enrolled.

The study was carried out in 6 pediatric emergency departments (PEDs) of the Spanish Pediatric Emergency Research Group RiSEUP-SPERG (Supplementary digital content 1). Patients were children aged 0 to 18 years presenting at the PED with AAP with clinical suspicion of AA after initial medical assessment. The sample was composed of all children who consecutively came to the PED of the participant hospitals during the 6 months of the study. AAP with suspected AA was defined according to the subjective assessment of the ED physician after history and clinical examination.

Inclusion criteria were belonging to the study population and having the informed consent signed by either the parents or legal guardians and also by the patient himself in the case of being over 12 years old. Exclusion criteria were AP of >72 h, lack of blood sample for pro-ADM quantification, or if the child met any of the following conditions: recent surgery (3 previous months); personal history of immunological pathology, inflammatory bowel disease, cardiovascular or chronic respiratory disease; or treatment with antibiotics or steroids in the past month.

This study did not modify the usual clinical practice since in the intervention protocols of the participating centers, the practice of performing analytical studies with leukocyte and neutrophil counts as well as CRP in all patients with suspected AA was already established. Imaging tests or consultation with the pediatric surgeon was required at the discretion of the doctor in charge of the patient.

An electronic case report form was filled in for each patient. Data were sent monthly to the main investigator, who was responsible for keeping the general database in the strictest confidentiality. Emergency records were reviewed weekly to identify possible lost patients and errors in transcription or submission. The data recorded were sex, age, clinical history (time of progression of abdominal pain, pain characteristics, fever, anorexia, nausea, or vomiting), leukocyte count, neutrophil count, CRP, and the PAS. If imaging tests were performed, data from those tests were also recorded.

Histopathology of the appendix and surgeon's report were registered in the days after the intervention for those children undergoing surgery. The degree of appendix affectation was defined as in Míguez et al. [12]. The histological confirmation of the appendix and the surgeon's report set out the final diagnosis of AA. Children discharged after the first emergency visit received a telephone call between the fifth and seventh day to determine if they had a new consultation for the same reason at a health center, and if they had done so, what the diagnosis was and if they had required admission or surgery. When contact by telephone was not possible, the centralized clinical records of each Autonomous Community were checked.

2.2. Blood sample and pro-ADM measures

Leukocyte and neutrophil counts and CRP analyses were measured using the standard procedures of each hospital, while pro-ADM was measured for all samples in a single reference laboratory. Pro-ADM was determined using the same EDTA tubes previously used for the hemogram of each child once the blood had already been processed. Tubes were prepared and stored in the laboratory of each hospital until their transport to the reference laboratory. Conditions of storing and transport were established by the reference laboratory and strictly preserved in all samples until the completion of the pro-ADM measurement. Pro-ADM values were not considered either in the evolution or in the management of the patient.

MR-proADM was measured with a BRAHMS MR-proADM KRYPTOR analyzer (BRAHMS GmbH; Hennigsdorf, Brandenburg, Germany) through an immunofluorescence assay with polyclonal antibodies. MR-proADM values (nmol/L) of 0.39 (median) to 0.55 (97.5th percentile) were considered normal according to the manufacturer's technical information.

2.3. Statistical analyses

Parametric quantitative variables were indicated through mean and standard deviation and nonparametric variables through median and interquartile range. Confidence intervals were of 95%. Qualitative variables were summarized with absolute frequencies and percentages. Association between qualitative variables was determined by means of chi-square test. Means were compared through Student's *t*-test and medians through the Mann-Whitney test. Diagnostic tests were compared by means of performance tests and receiver-operating characteristic (ROC) curves. Cutoff points for each diagnostic test were assessed with the Youden Index. Statistical analyses were performed with SPSS 20.0 (SPSS, Chicago, IL) and MedCalc 11.2.1 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Sample characteristics

During the 6 months of the study, a total of 104,047 children were registered in the ED of all participant hospitals, and 4315 (4%) consulted for AAP. AA was suspected in 519 children (0.5% of the total emergencies). Finally, 285 met inclusion criteria (Fig. 1).

Patients' main characteristics are shown in Table 1. A total of 110 children underwent surgery (100 after their first consult to the ED and 5 more after a second one). Of them, 103 had AA (35.1%) according to histopathological evidence (100 of the operated children after their first consult and 3 of the 5 operated children after their second consult). Ten AA (10%) were perforated.

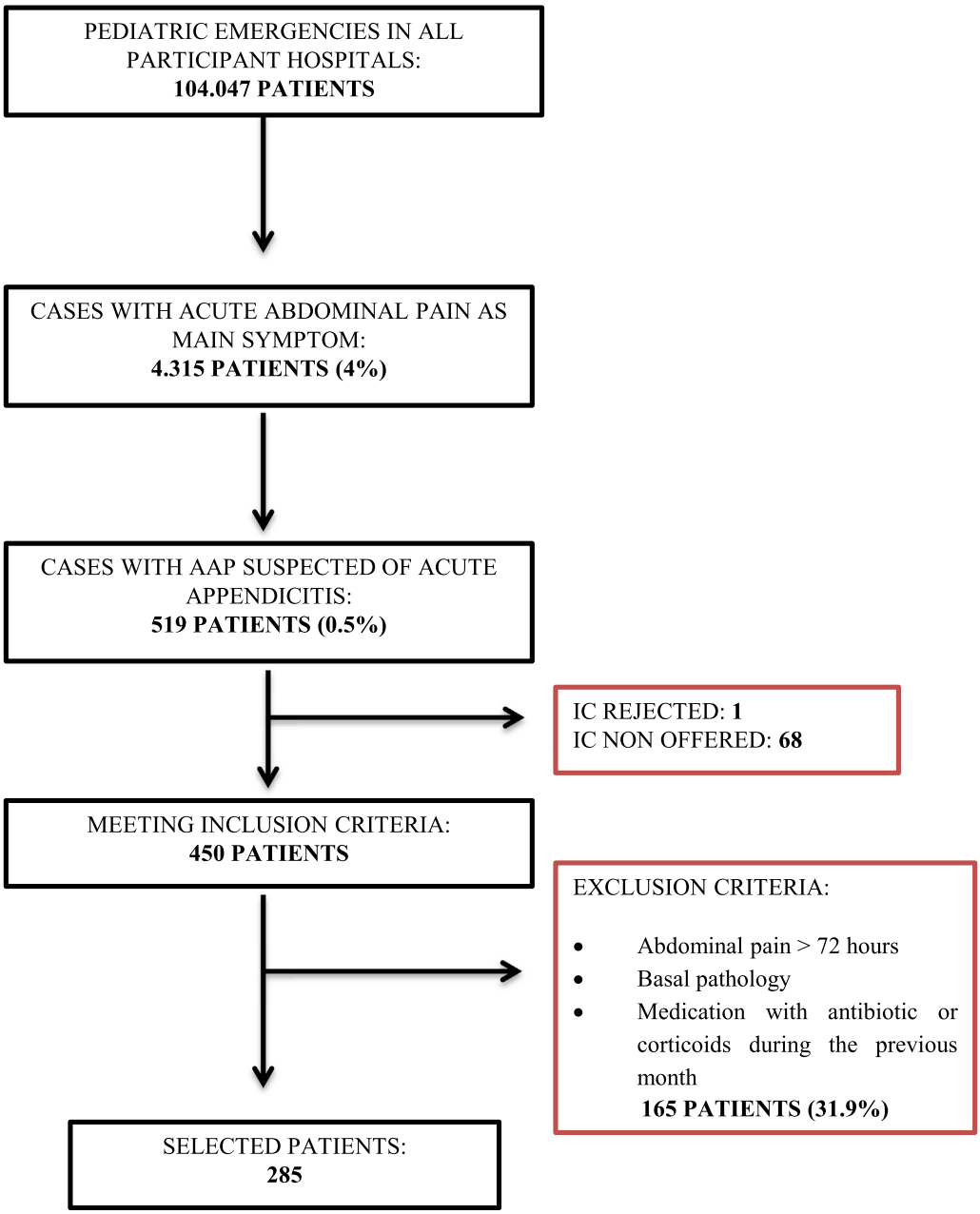

Fig. 1. Patient's flow diagram.

Unspecified abdominal pain was the most frequent (151 children, 53%), followed by mesenteric adenitis (16 children, 5.6%), ileocolitis (4 children), acute gastroenteritis [5], pneumonia [2], streptococcal pharyngitis [1], flu type B [1], constipation [1], and intussusception [1]. A follow-up phone call was performed between the 5th and 7th days to all children discharged after the first visit to the ED (152). Of them, 46 (30.3%) had consulted hours or days later to the same center. Five (3.3%) subsequently underwent surgery, with three (2%) diagnosed with AA.

3.2. Main objective and secondary outcomes

Pro-ADM values according to the presence/absence of AA are reported in Table 1 and Fig. 2. Mean pro-ADM concentration was significantly higher ($p < 0.001$) in children with AA (0.51 nmol/L; SD 0.16) than in children with other diagnoses (0.44 nmol/L; SD 0.14).

In children with AA, pro-ADM levels were stratified according to the degree of appendix evolution. Pro-ADM values were significantly higher ($p = 0.005$) in patients with complicated AA (0.64 nmol/L; SD 0.17) in comparison with noncomplicated cases (0.50 nmol/L; SD 0.15).

Regarding the diagnostic accuracy evaluated by means of ROC curves (Table 2, Fig. 3), leukocyte and neutrophil counts showed the best diagnostic performance in patients with or without appendicitis. The optimal cutoff points were 13,300 u/μL for leukocytes, 10,800 u/μL for neutrophils, 1.25 mg/dL for CRP, 0.35 nmol/L for pro-ADM, and a score of 6 for the PAS.

The optimal cutoff points for not having AA consisted of the combination of CRP 1.25 mg/dL and pro-ADM ≤0.35 nmol/L with sensitivity (96%) and negative predictive value (93%; Table 2).

Table 1
General and stratified characteristics of the patients according to the final diagnosis of acute appendicitis. Data are expressed in absolute numbers (N), percentage (%) and 95% confidence intervals (CI 95%).

Patients' characteristics	Total		Acute appendicitis		No acute appendicitis		*p* value
	N = 285		N = 100		N = 185		
	N (%)	CI 95%	N (%)	CI 95%	N (%)	CI 95%	
Epidemiology							
Age (years)[a]	9.5 (3.4)	9.1–9.9	8.90 (3.5)	8.21–9.59	9.85 (3.4)	9.36–10.34	0.025
Sex (male)	167 (58.6)	52.9–64.3	70 (68)	58.9–77.0	97 (53.3)	46.0–60.5	0.025
Symptoms							
Nausea (yes)	154 (54)	48.2–59.8	59 (57.3)	47.7–66.8	95 (52.2)	44.9–59.5	0.408
Vomiting (yes)	152 (53.3)	47.5–59.1	69 (67.0)	57.9–76.1	83 (45.6)	38.4–52.8	0.001
Pain in RIF (yes)	187 (65.6)	60.1–71.1	65 (63.1)	53.8–72.4	122 (67.0)	60.2–73.9	0.503
Diffuse/periumbilical pain (yes)	115 (40.4)	34.7–46.0	44 (42.7)	33.2–52.3	71 (39.0)	31.9–46.1	0.540
Pain migration (yes)	70 (24.6)	19.6–29.6	27 (26.2)	17.7–34.7	43 (23.6)	17.5–29.8	0.626
Physical exploration							
Voluntary defense (yes)	71 (24.9)	19.9–29.9	18 (17.5)	10.1–24.8	53 (29.1)	22.5–35.7	0.029
Involuntary defense (yes)	68 (23.9)	18.9–28.8	47 (45.6)	36.0–55.3	21 (11.5)	6.9–16.2	<0.001
Mc Burney (yes)	60 (21.1)	16.3–25.8	27 (26.2)	17.7–34.7	33 (18.1)	12.5–23.7	0.108
Signs of peritoneal irritation (yes)	153 (53.7)	47.9–59.5	72 (69.9)	61.0–78.8	81 (44.5)	37.3–51.7	<0.001
Markers							
Pro-ADM (nmol/l)[a]	0.47 (0.15)	0.45–0.48	0.51 (0.16)	0.48–0.55	0.44 (0.14)	0.42–0.46	<0.001
CRP (mg/dl)[b]	0.7 (0.20–2.95)	0.38–1	1.6 (0.3–6.3)	1.3–3.2	0.3 (0.1–1.7)	0.2–0.4	<0.001
Leukocytes (u/μl)[b]	11.700 (8.450–15.550)	10.500–12.410	16.000 (12.600–19.600)	14.560–16.800	9.700 (7.500–12.275)	9.000–10.100	<0.001
Neutrophils (u/μl)[b]	8.700 (4.650–12.865)	7.480–9.220	12.950 (9.590–15.800)	12.250–14.000	6.000 (3.700–9.205)	5.400–6.900	<0.001
PAS[b]	5 (4–7)	5–6	7 (5–8)	6–7	5 (3–6)	4–5	<0.001
Destination on discharge							
Admittance at first visit (yes)	133 (46.7)	40.9–52.5	100 (97.1)	93.8–100	33 (18.1)	12.5–23.7	<0.001

RIF: right iliac fossa; Pro-ADM: proadrenomedullin; CRP: C-reactive protein; PAS: Pediatric Appendicitis Score.
[a] Values expressed as mean and standard deviation in parentheses.
[b] Values expressed as median and interquartiles in parentheses.

4. Discussion

AA is one of the most frequent abdominal surgical emergencies among children [13]. In our study, 36.1% of patients had appendicitis, similar to other studies [14], and 9.7% perforated, similar to other studies, with perforation occurring between 3.7% and 28.6% [3].

As evidenced by our results, in many cases history and physical exploration by themselves are not enough to rule out AA since >40% of patients who did not have appendicitis were assessed as having some sign of peritoneal irritation. The laboratory tests most commonly used for the diagnosis of AA are leukocyte count, neutrophil count, and CRP. Recently, other markers such as procalcitonin (PCT), D-dimer, calprotectin, and serum amyloid protein have been studied, but they failed to show they were more useful than the classical markers, alone or in combination [3,15]. One of the limitations of biomarkers is their dependency on clinical evolution [14,16]. To account for this, we included patients with AAP with <72 h of signs and symptoms because after this time, the possibility of perforation increases.

Pro-ADM has gained special interest in recent years. The only study published for the evaluation of proadrenomedullin in the diagnosis of

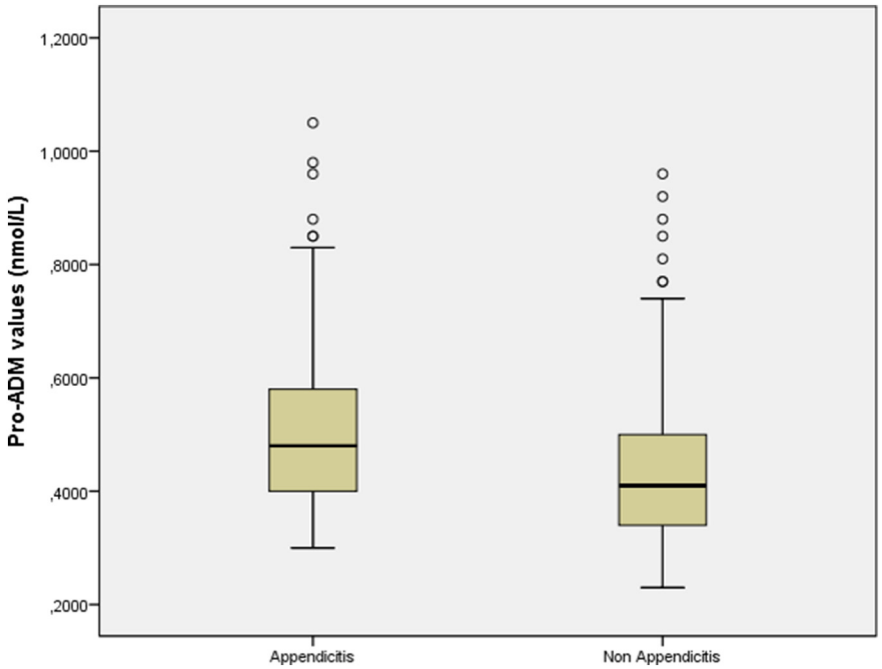

Fig. 2. Distribution of proadrenomedullin values in patients diagnosed with acute appendicitis and patients diagnosed with other pathologies.

Table 2
Diagnostic accuracy of analytical markers and PAS separate and in combinations, in patients with acute abdominal pain suggestive of acute appendicitis of <72 h of evolution.

	Optimal cutoff points	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Area under ROC curve (CI 95%)	LR+ (CI 95%)	LR− (CI 95%)
Separate parameters								
Leukocytes (no./μL)	13.300	74	82	70	85	0.84 (0.79–0.89)	4.20 (3.00–5.87)	0.32 (0.23–0.44)
Neutrophils (no./μL)	10.800	71	86	74	84	0.84 (0.79–0.89)	4.96 (3.40–7.23)	0.34 (0.25–0.46)
CRP (mg/dL)	1.25	60	72	55	76	0.70 (0.63–0.76)	2.15 (1.62–2.85)	0.55 (0.43–0.71)
Pro-ADM (nmol/L)	0.35	92	32	43	88	0.66 (0.59–0.72)	1.35 (1.21–1.52)	0.24 (0.12–0.49)
PAS score	≥6	73	69	57	82	0.76 (0.70–0.82)	2.32 (1.82–2.97)	0.40 (0.28–0.55)
Combined parameters[a]								
Pro-ADM (>0.35 nmol/L) + CRP (>1.25 mg/dL)		96	28	43	93	0.62 (0.56–0.69)	1.34 (1.21–1.47)	0.16 (0.05–0.37)
Pro-ADM (>0.35 nmol/L) + leukocytes (>13.300)		95	30	43	92	0.62 (0.56–0.69)	1.35 (1.22–1.50)	0.16 (0.07–0.40)
CRP (>1.25 mg/dL) + leukocytes (>13.300)		90	61	57	92	0.76 (0.70–0.81)	2.31 (1.91–2.81)	0.16 (0.09–0.29)
CRP (>1.25 mg/dL) + neutrophils (>10.800)		89	64	58	91	0.77 (0.71–0.82)	2.46 (2.01–3.02)	0.17 (0.10–0.30)
Pro-ADM (>0.35 nmol/L) + neutrophils (>10.800)		94	31	43	90	0.63 (0.56–0.69)	1.36 (1.22–1.52)	0.19 (0.09–0.42)
Pro-ADM (>0.35 nmol/L) + PAS (≥6)		94	27	42	89	0.61 (0.54–0.67)	1.29 (1.17–1.43)	0.22 (0.10–1.49)
Leukocytes (>13.300) + neutrophils (>10.800)		76	82	71	86	0.79 (0.73–0.85)	4.31 (3.09–6.10)	0.29 (0.21–0.41)

PPV: predictive positive value; NPV: negative positive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio; CRP: C-reactive protein; Pro-ADM: proadrenomedullin; PAS: Pediatric Appendicitis Score.
[a] The combination of two parameters is considered positive when any or both parameters are positive.

AA in pediatric age is the one carried out in 2015 by Míguez et al. [12]. In this study, mean values of pro-ADM were significantly higher in children with AA compared with other diagnoses of AAP, a fact that we can confirm with our results. The study also showed higher pro-ADM values in complicated AA cases with regard to the uncomplicated ones, although the difference was not statistically significant. This also holds true for some of the classical biomarkers of AA, such as leukocyte count and CRP. Beltran et al. [5] had already concluded in their study that leukocyte and CRP levels can be used reliably to discriminate between simple and complicated AA. PCT has also been proposed as useful for diagnosing specifically complicated AAs [17].

However, according to the results of our study, which agree with those of the single-center study [12], pro-ADM alone is not enough to diagnose AA early. In the analysis of the ROC curves, pro-ADM values showed a lower AUC than other more sensitive and specific markers such as leukocytes and neutrophils. Previous studies show similar results in the AUCs for CRP, although somewhat inferior results for the leukocyte count [17].

Different scores have also been developed to approach the diagnosis of AA. In our study, we included the PAS since it is the most used in Spanish PEDs [18]. PAS has been proposed as a useful score for ruling out AA, and in previous studies, the optimal value for this objective was 5. A score <5 allowed a patient to be discharged with a low suspicion of having AA [12]. In our study, the optimal cutoff point was 6, obtaining the best sensitivity, specificity, and negative predictive values (73%, 69%, and 82% respectively). However, these values show an insufficient performance to be taken into account alone.

Individual biomarkers may not have enough power to diagnose or rule out AA, but the combination of some of them may be sufficient to justify their use in clinical practice, as it has been proposed in the literature. Kwan and Nager [19] reported that the combination of a leukocyte count >12,000 u/μL with a CRP value >3 mg/dL increases the probability of a correct diagnostic of appendicitis (odds ratio: 7.75). Benito et al. [20] used the APPY1 test (the combination of the leukocyte count, CRP, and calprotectin) with the neutrophil count. When the APPY1 test is negative in combination with a neutrophil count <7500 u/μL, the diagnosis of AA can be practically ruled out, since this combination offers a sensitivity of 100% (95% confidence interval [CI], 95.9–100), a negative predictive value of 100% (95% CI, 83.2–100), and a specificity of 35.4% (95% CI, 26.6–45.4). However, the work of Benito

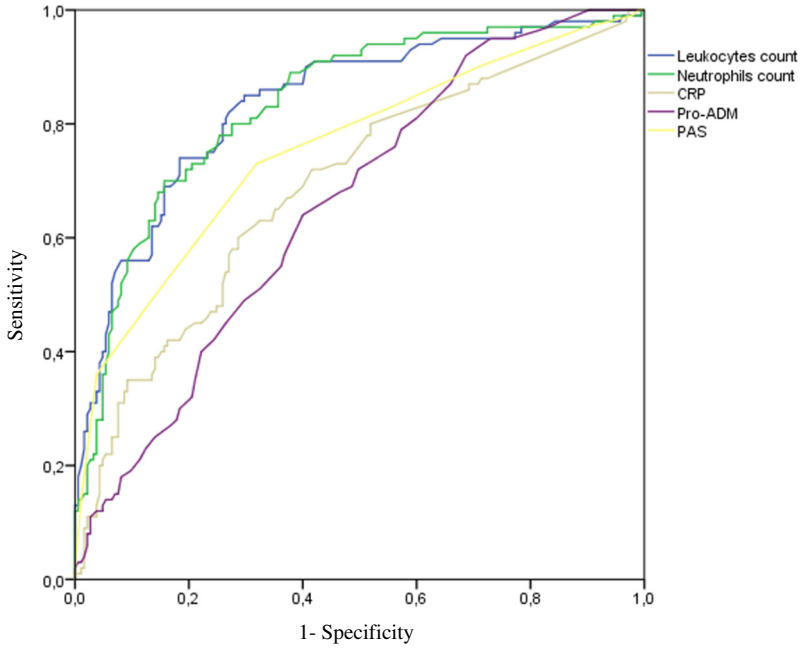

Fig. 3. ROC curves of the different markers used in the diagnosis of acute appendicitis. Area under the curve values are shown in Table 2.

et al. [20] is a single-center study, and it has not been validated subsequently.

According to the study previously published by Míguez et al. [12], the combination of low CRP and pro-ADM values could be useful to rule out AA with a negative predictive value of 100%. In this multicenter study, the CRP and pro-ADM combination had superior performance in ruling out AA, with a sensitivity of 96% and a negative predictive value of 93%. Our results are consistent with the study by Míguez et al.

4.1. Limitations

In our study, there is certain variability in the way AA is suspected, because a clinical criterion is used and depends on the physician in charge of each patient. In addition, we did not obtain interobserver assessments on PAS score assignments. We are unsure how this might have affected our data. In addition, as we have previously exposed, our study includes patients with an AAP of <72 h of evolution, and the results cannot be extrapolated to patients with longer clinical symptoms. Finally, the frequency of appendicitis in subjects lost to follow-up was not studied. We assumed those would be similar to our study population, but if that assumption was incorrect, this could have potentially altered the predictive values of the tests.

5. Conclusions

Children with AA showed higher pro-ADM values than children with AAP of other etiology. This difference is even more important when it comes from complicated AA. However, despite these differences, pro-ADM has not been sufficient by itself to establish or rule out an early diagnosis of AA.

Low values of pro-ADM (≤0.35 nmol/L) in combination with low CRP values (≤1.25 mg/dL) may help clinicians to identify those children with abdominal pain at a low risk of appendicitis, although with a predictive value of 93%, for which it would be necessary to establish additional measures to control those patients incorrectly discharged with this combination.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.09.038.

Conflict of interest

Thermofisher Scientific has covered the inscription fees of one of the authors (NO) to the XXII Meeting of the SEUP.

Source of funding

This study has received a RiSEUP-SPERG grant of the Spanish Pediatric Emergency Research Group.

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