Official journal of the Spanish Society of Chemotherapy

Original

Revista Española de Quimioterapia
doi:10.37201/req/008.2021

Diagnostic accuracy of combining C-Reactive protein and Alvarado Score among 2-to-20-year-old patients with acute appendicitis suspected presenting to Emergency Departments

Kinda Altali Alhames[1*]
Francisco Javier Martín-Sánchez[2,3*]
Pedro Ruiz-Artacho[4,5]
Francisco Javier Ayuso[2]
Victoria Trenchs[6]
Mikel Martínez Ortiz de Zarate[7]
Carmen Navarro[8]
Manuel Fuentes Ferrer[9]
Cristina Fernández[9]
Juan González del Castillo[2,3]
Andrés Bodas[1,3]

[1]Pediatric Department, Hospital Clínico San Carlos, Madrid, Spain.
[2]Emergency Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain.
[3]Facultad de Medicina. Universidad Complutense, Madrid, Spain.
[4]Internal Medicine Department, Clínica Universidad de Navara, Madrid. Interdisciplinar Teragnosis and Radiosomics Research Group (INTRA-Madrid), Universidad de Navarra, Madrid, Spain.
[5]CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain.
[6]Emergency Department, Hospital Universitario Sant Joan de Deu, Barcelona, Spain.
[7]Emergency Department, Hospital Universitario de Basurto, Bilbao, Spain.
[8]Emergency Department, Hospital Universitario Virgen de la Macarena, Sevilla, Spain.
[9]Preventive Medicine Department. Hospital Clínico San Carlos, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain.

Article history
Received: 9 January 2021; Revision Requested: 27 January 2021; Revision Received: 30 January 2021; Accepted: 4 February 2021; Published: 30 April 2021

ABSTRACT

Objective. Main objective was whether the combination of C-Reactive Protein (CRP) and Alvarado Score (AS) increase the diagnosis accuracy of AS among 2-to-20-year-old patients with suspected acute appendicitis presenting to Emergency Departments.

Materials and methods. This is a secondary analysis of prospective cohort study consecutively including all patients from 2 to 20 years of age attended for suspected acute appendicitis in 4 Spanish Emergency Departments during 6-month period. We collected demographic, clinical, analytic and radiographic, and surgical data. AS categories were retrospectively calculated as low (0-4 points), intermediate (5-6 points) or high (7-10 points). The cut-off levels were >0.5 mg/dl for CRP. The outcome was diagnosis of acute appendicitis within 14 days of the index visit.

Results. A total of 331 patients with suspected of acute appendicitis (mean age 11.8 (SD 3.8) years; 52.9% males) were recruited. According to AS, 108 (32.6%) were at low risk, 76 at (23.0%) intermediate risk and 147 (44.4%) at high risk of acute appendicitis. One hundred and sixteen (35.0%) cases had confirmed histopathological diagnosis of acute appendicitis. The AUCs of ROC were 0.76 (0.70-0.81) for AS and 0.79 (95% CI 0.75-0.84) for CRP-AS being the difference statistically significant (p=0.003). The CRP for diagnosis acute appendicitis in low risk AS group had negative predictive value of 95.8% (95%CI 87.3-98.9) and likelihood ratio negative of 0.4 (95%CI 0.2-1.0).

Conclusions. CRP-AS has shown to increase the diagnostic accuracy of AS for acute appendicitis. This approach may be useful to rule out the diagnosis of acute appendicitis in paediatric patients attended for abdominal pain suggestive of acute appendicitis.

Key words: c-reactive protein; acute appendicitis; biomarkers; emergency medicine.

Corresponding Author:
Francisco Javier Martín-Sánchez.
Emergency Department. Hospital Clínico San Carlos.
Calle Profesor Martín-Lagos s/n, 28040 Madrid.
Telephone: (34) 91.330.37.50
FAX: (34) 91.330.35.69
Email: fjjms@hotmail.com

*Both authors have equally contributed to this study

Precisión diagnóstica de la combinación de la proteína C reactiva y la puntuación de Alvarado en pacientes de 2 a 20 años con sospecha de apendicitis aguda durante su atención en los servicios de urgencias

RESUMEN

Objetivo. El objetivo principal fue conocer si la combinación de la proteína C reactiva (PCR) y la escala de Alvarado (AS) aumenta la precisión de ésta última en el diagnóstico de apendicitis aguda en pacientes de 2 a 20 años que son evaluados en los servicios de urgencias hospitalarios con esta sospecha clínica.

Materiales y métodos. Se trata de un análisis secundario de un estudio de cohorte prospectivo que incluyó de forma consecutiva a todos los pacientes de 2 a 20 años atendidos por sospecha de apendicitis aguda en 4 servicios de urgencias hospitalarios españoles durante un periodo de 6 meses. Recopilamos datos demográficos, clínicos, analíticos, radiográficos

y quirúrgicos. Las categorías de AS se calcularon retrospectivamente como bajas (0-4 puntos), intermedias (5-6 puntos) o altas (7-10 puntos). Los niveles de corte fueron >0,5 mg/dl para PCR. El resultado fue el diagnóstico de apendicitis aguda dentro de los 14 días posteriores a la visita índice.

Resultados. Se reclutaron 331 pacientes con sospecha de apendicitis aguda (edad media 11,8 (DE 3,8) años; 52,9% varones). Según AS, 108 (32,6%) tenían bajo riesgo, 76 (23,0%) riesgo intermedio y 147 (44,4%) alto riesgo de apendicitis aguda. Ciento dieciséis (35,0%) casos habían confirmado el diagnóstico histopatológico de apendicitis aguda. Las AUC de ROC fueron 0,76 (0,70-0,81) para AS y 0,79 (IC del 95%: 0,75-0,84) para PCR-AS, siendo la diferencia estadísticamente significativa (p=0,003). La PCR para el diagnóstico de apendicitis aguda en el grupo de AS de bajo riesgo tuvo un valor predictivo negativo del 95,8% (IC 95% 87,3-98,9) y una razón de verosimilitud negativa de 0,4 (IC 95% 0,2-1,0).

Conclusiones. Se ha demostrado que la combinación de PCR-AS aumenta la precisión diagnóstica del AS para apendicitis aguda. Este enfoque puede ser útil para descartar el diagnóstico de apendicitis aguda en pacientes pediátricos atendidos por dolor abdominal sugestivo de apendicitis aguda.

Palabras clave: Proteína C-reactiva, apendicitis aguda, biomarcadores, urgencias

INTRODUCCION

Abdominal pain is one of the main reasons for presenting to Emergency Departments (EDs) [1]. Acute appendicitis (AA) is the most common surgical emergency in childhood and one of the main differential diagnoses to consider in paediatric patients and adolescents [2,3].

Despite of advances in the diagnosis and surgical treatment of AA, the diagnosis still remains difficult, especially in paediatric populations [4], being a clinical challenge even for experienced emergency physicians [5]. The clinical history and physical examination may be less useful compared to adults because children are more frequently associated with atypical clinical manifestations [6]. Differential diagnosis of an AA is extensive, and many clinical conditions can mimic AA [5]. The delay in the diagnosis increases morbidity and mortality, whereas false positive diagnosis of AA leads to unnecessary surgery. In this sense, the studies show a frequency of perforation between 17 and 33% and a percentage of negative laparotomy between 3 and 54% [2].

Different clinical scores have been developed to help physicians to improve the accuracy of the diagnosis of AA, reducing the time needed for diagnosis and the number of inappropriate imaging tests and appendectomies [7]. The Alvarado score (AS) is the most frequently score used in clinical practice [8]. The AS considers symptoms, signs, and laboratory, which are leukocytosis and neutrophilia (Table 1). Some studies have shown that diagnostic accuracy of AS is not sufficient to establish the presume diagnosis or rule out, especially in children, and this can lead to delays in the diagnosis increasing the risk of appendicitis perforations [7,8].

The C-reactive protein (CRP) is a protein synthetized from hepatocytes that increases within 4-6 hours after acute tissue injury and peaking at 36-48 hours. One hand, it has been reported that CRP used solely or in combination with white blood cell (WBC) could be effective in the discrimination between acute and complicated appendicitis [9]. On the other hand, there is little evidence and the results are contradictory among paediatric patients and adolescents [10,11]. Despite this, some authors recommend evaluating routinely CRP level, WBC and Neutrophil percentage (NP) among patients with initial diagnosis of appendicitis [12,13].

Considering all previously written, further evidence is necessary to confirm the role of CRP in conjunction with AA in the diagnosis of acute appendicitis among paediatric patients and adolescents. In this sense, the main objective was to determinate whether the combination of CRP and AS increase the diagnosis accuracy of AS among 2-to-20-year-old patients with acute appendicitis suspected presenting to EDs. The secondary objectives were to study the diagnostic accuracy of the CRP level in the different categories of AS in this group of patients and to compare the diagnostic capacity of CRP level with WBC and NP.

MATERIAL AND METHODS

Study design and setting. We performed a secondary analysis of observational prospective cohort study that consecutively included children and adolescents attended for abdominal pain suspected of AA in 4 Spanish ED (Hospital Clínico San Carlos of Madrid, Hospital de Basurto of Bilbao, Hospital Virgen de la Macarena of Sevilla and Hospital Sant Joan de Déu of Barcelona) from June to December 2014. The study was approved by the Ethical Committee of the reference centre and was carried out according to the principles of Good Clinical Practice. Informed consent was obtained from the adolescents and from the parents of the children included in the study.

Population. All patients from 2 to 20 years of age with abdominal pain suspected of AA of less than 72 hours of evolution were consecutively included in the study. The exclusion criteria were: patients with a radiological test of the abdomen prior to attending the ED, pregnancy, history of appendicectomy, inflammatory disease or active cancer, abdominal traumatism, surgery or invasive abdominal procedure within the previous 7 days, use of systemic steroids in the last 14 days, receipt of any other immunosuppressive treatment or chemotherapy within the previous 29 days and participation in an investigation study in the previous 30 days.

Study protocol. The patients were assessed by the attending physician following the standard protocol of usual clinical practice, that is, collecting the clinical history and performing a physical examination and routine laboratory tests and, if necessary, an imaging test, ultrasonography and/or computerized tomography, and evaluation by a surgeon on duty. The laboratory and imaging tests and interconsultation

with an on-duty surgeon were requested as per the criteria of the attending physician, independently of the participation in the study. In patients undergoing appendicectomy, the diagnosis of AA was made from the surgical piece by a specialist in anatomopathology. All the patients discharged directly without surgery were evaluated at 14 days to know whether they had received medical care and had a clinical and/or histopathological report compatible with AA.

Variables. The investigators of each centre collected the following data on a standardized form: demographic (age and gender), clinical (symptoms, signs and time of evolution), analytical (WBC, NP and CRP) and radiological (abdominal ultrasonography and/or computerized tomography) and, if necessary, surgical and histopathological data. The forms were reviewed by the coordinating investigator of each centre. The patients were retrospectively classified according to the AS as low (0-4 points), intermediate (5-6 points) or high (7-10 points) risk of AA. The cut-off levels were > 0,5 mg/dl for CRP, ≥10 x 10^9 /L for WBC and ≥ 75% for NP. The final diagnosis of AA was based on the report of the histopathological study of the resected appendix in patients who had undergone appendicectomy, or via a telephone call at 2 weeks of follow up to know if they had been histologically diagnosed. AA was histologically demonstrated by mucosal neutrophil infiltration of the appendix with or without local peritonitis.

Statistical analysis. Categorical variables are expressed as numbers and percentages and the quantitative variables are expressed as means and standard deviations or medians and interquartile ranges if the distribution was not normal (this was tested using Kolmogorov-Smirnov test). Categorical variables were compared with the Pearson chi-square test or Fisher test and quantitative variables using the Student's-t test (or the Mann-Whitney U test if the distribution was not normal). Logistic regression was used to combine CRP and AS in the diagnosis of acute appendicitis. The values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LHR+) and negative likelihood ratio (LHR-) were calculated for CRP and CRP stratified by AS. To determine the discriminatory capacities of the CRP, leukocytosis, neutrophilia, AS and combination of AS and CRP to diagnose acute appendicitis the areas under the curve (AUC) of receiver-operating characteristic (ROC) curves were calculated. The AUC of ROC were compared by DeLong test. We considered differences to be statistically significant if the p value was less than 0.05 (two-tail), and 95% CI of AUC ROC excluded 0.5. Statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL) STATA 14.0 statistical package (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Patient characteristics. We included 331 patients with suspected of AA. The mean age was 11.8 (SD 3.8) years and 175 (52.9%) were males. Table 2 shows the characteristics of the patients included in the study. The median time of clinical course was 24 (IQR 9–48) hours. According to AS, 108 (32.6%) were at low risk, 76 at (23.0%) intermediate risk and 147 (44.4%) at high risk of AA. At least one imaging test was performed in 189 (57.1%): 172 (52.0%) ultrasonographies, 6 (1.8%) CTs and both in 11 (3.3%) cases. Appendectomy was carried out during the index visit in 118 (35.6%) patients, 109 (94.0) of whom had a histopathological diagnosis of AA. At the end of the 2-week follow-up, 116 (35.0%) had confirmed histopathological diagnosis of AA.

Table 1 Alvarado Score for Appendicitis Diagnosis

Manifestations	Value
Signs	
Right Lower Quadrant Tenderness	2
Elevated Temperature (37.3°C or 99.1°F)	1
Rebound Tenderness	1
Symptoms	
Migration of Pain to the Right Lower Quadrant	1
Anorexia	1
Nausea or Vomiting	1
Laboratory Values	
Leukocytosis > 10,000 mm^3	2
Leukocyte Left Shift	1

Risk of acute appendicitis: low (0-4 points), intermediate (5-6 points) or high (7-10 points)

Table 2 shows the characteristics of the sample and the univariate analysis based on the presence or not of appendicitis. Statistically significant differences were observed in the age, gender, time of evolution, associated symptoms and physical examination, WBC, NP, CRP levels, the risk categories according to the AS, and the performance of exploratory surgery.

Primary data analysis. The figure 1 shows the diagnosis capacity of combination CRP and AS, and AS. The AUCs of ROC were 0.76 (0.70-0.81) for AS and 0.79 (95% CI 0.75-0.84) for CRP-AS being the difference statistically significant (p=0.003).

Secondary data analysis. The table 3 shows the characteristic of CRP test along and stratified between three AS groups. Six (5.2%) out of 116 patients with AA were classified as low risk AS and CRP ≤ 0.5 mg/dl. The CRP for diagnosis AA in low risk AS group had NPV of 95.8% (95% CI 87.3-98.9) and LHR- of 0.4 (95% CI 0.2-1.0). A negative CRP result reduced the probability of AA from 8.8% to 5.2% in this low risk AS group. Regarding the comparation between diagnostic accuracy of CRP level with WBC and NP, no statistically significant differences were found.

DISCUSSION

Table 2 **Characteristics of the patients included in the study based on the diagnosis of appendicitis.**

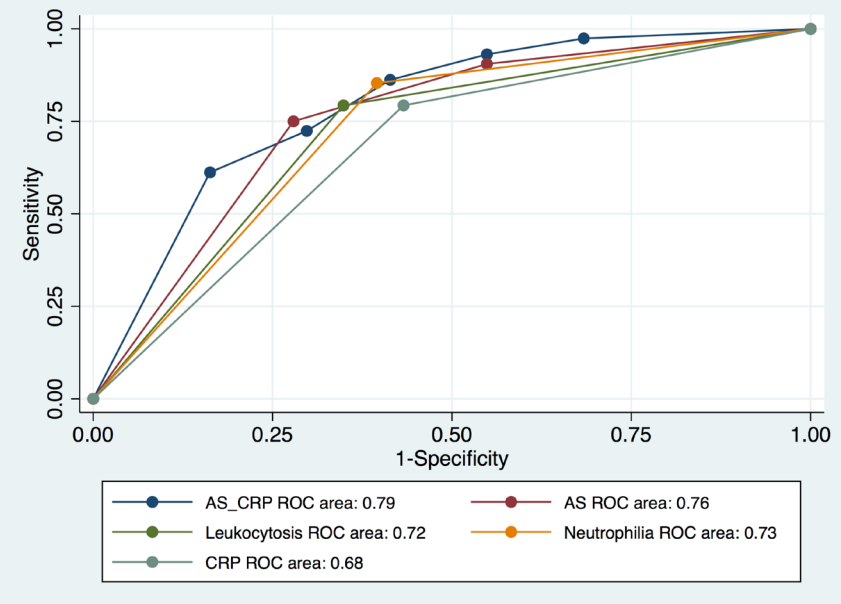
	All Patients (n=331)	Appendicitis (n=116)	No Appendicitis (n=215)	p
Demographic data				
Age (years); [mean (SD)]	11.8 (3.8)	11.1 (3.7)	12.2 (3.8)	0.013
Male; [n (%)]	175 (52.9)	74 (63.8)	101 (47.0)	0.003
Clinical data				
Time since symptom onset (hours); [n (%)]				<0.001
0-12	88 (26.6)	19 (16.4)	69 (32.1)	
12-24	63 (19.0)	30 (25.9)	33 (15.3)	
24-48	92 (27.8)	42 (36.2)	50 (23.3)	
48 o more	88 (26.6)	25 (21.6)	63 (29.3)	
Associated Symptoms; [n (%)]				
Periumbilical pain with migration to LRQ	286 (86.4)	104 (89.7)	182 (84.7)	0.205
Anorexia	110 (33.2)	53 (45.7)	57 (26.5)	<0.001
Nausea	165 (49.8)	69 (59.5)	96 (44.7)	0.100
Vomiting	139 (42.0)	65 (56.0)	74 (34.4)	<0.001
Physical Examination; [n (%)]				
Fever (37.8ºC)	35 (10.6)	15 (12.9)	20 (9.3)	0.306
LRQ Tenderness	290 (87.6)	109 (94.0)	181 (84.2)	0.010
Rebound tenderness	190 (57.4)	84 (72.9)	106 (49.3)	<0.001
Percussion tenderness	200 (60.4)	87 (75.0)	113 (52.6)	<0.001
Rigidity	98 (29.6)	52 (44.8)	46 (21.4)	<0.001
Rovsing sign	53 (16.0)	26 (22.4)	27 (12.6)	0.020
Laboratory data				
White blood cell count (ml/mm3); [mean (SD)]	11.7 (6.0)	14.5 (4.7)	10.2 (6.2)	<0.001
Neutrophile (mil/mm3)	8.5 (4.9)	11.4 (4.7)	6.9 (4.2)	<0.001
C-reactive protein (mg/L); [median (IQR)]	0.83 (0.29-4.08)	3.02 (0.61-6.57)	0.30 (0.19-1.96)	<0.001
Alvarado Score; [n (%)]				
Low-risk	108 (32.6)	11 (9.5)	97 (45.1)	<0.001
Intermediate-risk	76 (23.0)	18 (15.5)	58 (27.0)	
High-risk	147 (44.4)	87 (75.0)	60 (25.9)	
Imaging data				
US; [n (%)]	172 (52.0)	58 (50.0)	114 (53.0)	0.599
CT; [n (%)]	6 (1.8)	3 (2.6)	3 (1.4)	0.438
US and CT; [n (%)]	11 (3.3)	5 (4.3)	6 (2.8)	0.462
No imaging; [n (%)]	189 (57.1)	66 (56.9)	123 (57.2)	0.956
Treatment data				
Surgery; [n (%)]	118 (35.6)	109 (94.0)	9 (4.2)	<0.001

SD: standard deviation; LRQ: lower right quadrant; IQR: interquartile range; US: ultrasound; CT: computerized tomography

Table 3 Diagnosis characteristic of Alvarado Score and C-Reactive Protein test and C-Reactive Protein stratified between three Alvarado Score groups.

	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	LHR+ (95% CI)	LHR- (95% CI)	AUC (95% CI)
Alvarado score threshold ≥5 (low vs intermediate-high)	90.5 (83.3-94.9)	45.1 (38.4-52.0)	47.1 (40.4-53.8)	89.8 (82.1-94.6)	1.7 (1.4-1.9)	0.2 (0.1-0.4)	0.68 (0.62-0.74)
Alvarado score threshold ≥7 (low-intermediate vs high)	75.0 (65.9-82.4)	72.1 (65.5-77.9)	59.2 (50.8-67.1)	84.2 (78.0-89.0)	2.7 (2.1-3.4)	0.35 (0.25-0.48)	0.73 (0.68-0.79)
CRP (Cut-off 0.5 mg/dl)	79.3% (70.6-86.1)	56.7 (49.8-63.4)	49.7 (42.3-57.1)	83.6 (76.3-89.0)	1.8 (1.5-2.2)	0.4 (0.3-0.5)	0.68 (0.62-0.74)
CRP stratified by Alvarado score							
Low risk							
CRP (Cut-off 0.5 mg/dl)	72.7% (39.3-92.7)	70.1% (59.8-78.8)	21.6% (10.4-38.7)	95.8% (87.3-98.9)	2.4 (1.5-3.9)	0.4 (0.2-1.0)	0.71 (0.55-0.87)
Intermediate risk							
CRP (Cut-off 0.5 mg/dl)	72.2% (46.5-89.3)	50.0% (36.7-63.3)	31.0% (18.1-47.2)	85.3% (68.2-94.5)	1.4 (1.0-2.1)	0.6 (0.3-1.2)	0.61 (0.46-0.76)
High risk							
CRP (Cut-off 0.5 mg/dl)	81.6% (71.6-88.8)	41.7% (29.3-55.1)	67.0% (57.1-75.6)	61.0% (44.5-75.4)	1.4 (1.1-1.8)	0.4 (0.3-0.8)	0.62 (0.52-0.71)

Se: Sensibility; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LHR+: Likelihood ratio positive; LHR-: Likelihood ratio negative; AUC: area under curve (ROC). CRP: C-reactive protein.



	AUC	95% CI	p
AS-CRP	0.79	0.75-0.84	<0.001
AS	0.76	0.70-0.81	<0.001
Leukocytosis	0.72	0.67-0.78	<0.001
Neutrophilia	0.73	0.67-0.79	<0.001
CRP	0.68	0.62-0.74	<0.001

*AS: Alvarado score; CRP: C-reactive protein; Area under curve (AUC) ROC. Test De Long: AS-CRP vs. AS p=0.033; CRP vs. Leukocytosis p=0.220; CRP vs. Neutrophilia p=0,138

Figure 1 Comparations between Area under curve (AUC) ROC of leukocytosis, neutrophilia, C-reactive protein (CRP), Alvarado Score (AS) and the combination of CRP and AS for the diagnosis of acute appendicitis.

Table 4 **Estimated probability of acute appendicitis according to the risk categories of Alvarado Score and positive C-reactive protein.**

Alvarado score	Probability of AA (%)	CRP (mg/dl)	Probability of AA (%)
Low risk	8.8	≤ 0.5	5.2
		> 0.5	15.7
Intermediate risk	27.6	≤ 0.5	15.2
		> 0.5	37.7
High risk	58.2	≤ 0.5	36.9
		> 0.5	66.4
TOTAL	35.0	≤ 0.5	16.4
		> 0.5	49.7

AA: acute appendicitis; CRP: C-reactive protein

The present study shows that the combination of AS and CRP is a useful diagnostic tool to rule out the diagnosis of AA in patients from 2 to 20 years of age attended for abdominal pain suggestive of AA. This strategy showed an improvement in the diagnostic accuracy of the AS used alone.

These findings increase the evidence about the limited diagnosis accuracy of AS to be used in clinical practice as a unique strategy for surgery decision making among paediatrics patients with suspected AA [14-17]. Although the utility of inflammatory markers is still controversial in children, the combination of AS and CRP improved the diagnostic capacity compared with the AS alone [17]. This strategy was especially helpful in low risk AS category.

The CRP, WBC and NP have been the serum markers more studies [18]. Our data confirm that these biomarkers have poor test characteristics alone [17,19]. Regarding the CRP, previous studies have been focused on the diagnosis of AA or differential diagnosis between early and advanced AA [17]. In this sense, a higher cut-off (>3mg/dl) of CRP than our study (>0,5mg/dl) was used [20]. Our strategy was opposed, to increase the negative predictive value of the low-risk AS category, adding the CRP. In fact, the estimated probability of AA varied from 15.7% to 5.2% depending on CPR value in low-risk AS category.

The combination of AS, which includes WBC and NP, allowed identifying a low-risk subgroup of paediatric patients in which more conservative management may be applied with imaging examinations (avoiding or delaying) or final destination (hospital observation or close follow-up if discharged). We agree with other authors that the intent of the model is not to establish the diagnosis of AA, if not to reduce the level of uncertainty [21].

A recent study carried on 402 patients with 8.5+/-3 (range 3 to 13,8) years admitted for suspected AA showed a negative predictive value of 79.7% for AS + CRP and 78.3% for AS + CRP + US, using a cut-off point of 0.6 mg/dL for CRP, among low-risk AS category [22]. Other recent study with 200 patients, observed more controversial results regarding to accuracy of these clinical scores [23]. In our research, a lower cut-off point (<=0,5mg/dl) showed a negative predictive value of 95.8% (87.3%-98.9%) in low-risk AS category despite the time since symptom onset was lower in our cohort. Another study conducted in adults with suspected of AA, showed a negative predictive value of 86%for CRP (cut-off 0.5 mg/dl) in low-risk AS category [24].

Other scoring systems have included the CRP such as Appendicitis Inflammatory Response Score (AIR Score) [25] and INFURG-SEMES score [26]. A recent study that compared AIR Score with AS showed an improvement of the diagnostic capacity and a higher NPV (95% vs 90% in low-risk vs intermediate-high risk groups) [25]. Thus, panels of biomarkers, such as APPY 1 Test that also includes CRP, are being researched to rule out the AA in EDs [27].

The present study presents several limitations. First, those inherent in the design of the study. Second, the time of course of AA could have modified the findings of the study. In this sense, the sample size was limited to do stratified analyses based on the time of sample obtainment for the CRP at arrival to ED concerning the onset of the symptomatology. Third, this was an observational study and, thus, we cannot demonstrate that the addition of CRP to AS reduces the number of imaging tests, unnecessary surgical procedures, the times of hospital stay or the associated costs. The fourth limitation is a possible detection bias in the AA on the index visit. To avoid this, we used a 2-week follow-up for patients discharged without surgery to confirm they were correct classification. Finally, we did not evaluate interobserver agreement in the AS calculation because this is a validated model.

In conclusion, the CRP is a biomarker extensively available in EDs. The combination of CRP and AS has shown to increase the diagnostic accuracy of AS for AA. This approach may be useful to rule out the diagnosis of AA in patients from 2 to

20 years of age attended for abdominal pain suggestive of AA.

FUNDING

This study had financial support from Infectious Disease Group of Spanish Emergency Medicine Society (SEMES).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

REFERENCES

1. Hastings RS, Powers RD. Abdominal pain in the ED: a 35 year retrospective. Am J Emerg Med. 2011;29(7):711-6. DOI: 10.1016/j.ajem.2010.01.045
2. Tseng YC, Lee MS, Chang YJ, Wu HP. Acute abdomen in pediatric patients admitted to the pediatric emergency department. Pediatr Neonatol. 2008;49:126-34. DOI: 10.1016/S1875-9572(08)60027-3
3. Martínez Ortiz de Zárate M, González Del Castillo J, Julián Jiménez A, Piñera Salmerón P, Llopis Roca F, Guardiola Tey JM, et al. Epidemiology of infections treated in hospital emergency departments and changes since 12 years earlier: the INFURG study of the Spanish Society of Emergency Medicine (SEMES). Emergencias. 2013;25:368-78.
4. Bliss D, McKee J, Cho D, Krishnaswami S, Zallen G, Harrison M et al. Discordance of the pediatric surgeon's intraoperative assessment of pediatric appendicitis with the pathologists report. J Pediatr Surg 2010; 45: 1398– 1403. DOI: 10.1016/j.jpedsurg.2010.02.048
5. Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000;36:39-51. DOI: 10.1067/mem.2000.105658
6. Becker T, Kharbanda A, Bachur R. Atypical clinical features of pediatric appendicitis. Acad Emerg Med. 2007;14:124-9. DOI: 10.1197/j.aem.2006.08.009
7. Fujii T, Tanaka A, Katami H, Shimono R. Usefulness of the pediatric appendicitis score for assessing the severity of acute appendicitis in children. Pediatr Int. 2020;62(1):70-73. DOI: 10.1111/ped.14032
8. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med. 2011 28;9:139. doi: 10.1186/1741-7015-9-139. DOI: 10.1186/1741-7015-9-139
9. Buyukbese Sarsu S, Sarac F. Diagnostic Value of White Blood Cell and C-Reactive Protein in Pediatric Appendicitis. Biomed Res Int. 2016;2016:6508619. DOI: 10.1155/2016/6508619
10. Zouari M, Jallouli M, Louati H, Kchaou R, Chtourou R, Kotti A, et al. Predictive value of C-reactive protein, ultrasound and Alvarado score in acute appendicitis: a prospective pediatric cohort. Am J Emerg Med. 2016;34:189-92. DOI: 10.1016/j.ajem.2015.10.004
11. Old O. C-Reactive protein estimation does not improve accuracy in the diagnosis of acute appendicitis in pediatric patients. Int J Surg. 2011;9(5):440. DOI: 10.1016/j.ijsu.2008.11.001
12. Xharra S, Gashi-Luci L, Xharra K, Veselaj F, Bicaj B, Sada F, et al. Correlation of serum C-reactive protein, white blood count and neutrophil percentage with histopathology findings in acute appendicitis. World J Emerg Surg. 2012;7(1):27. doi: 10.1186/1749-7922-7-27. DOI: 10.1186/1749-7922-7-27.
13. Shogilev DJ, Duus N, Odom SR, Shapiro NI. Diagnosing appendicitis: evidence-based review of the diagnostic approach in 2014. West J Emerg Med. 2014;15(7):859-71. DOI: 10.5811/westjem.2014.9.21568
14. Heineman J. Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 1: An evaluation of the Alvarado score as a diagnostic tool for appendicitis in children. Emerg Med J. 2012;29:1013-4. DOI: 10.1136/emermed-2012-202054.2
15. Ebell MH, Shinholser J. What are the most clinically useful cutoffs for the Alvarado and Pediatric Appendicitis Scores? A systematic review. Ann Emerg Med. 2014;64:365-372. DOI: 10.1016/j.annemergmed.2014.02.025
16. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Med. 2011;9:139. DOI: 10.1186/1741-7015-9-139
17. Benabbas R, Hanna M, Shah J, Sinert R. Diagnostic Accuracy of History, Physical Examination, Laboratory Tests, and Point-of-care Ultrasound for Pediatric Acute Appendicitis in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2017;24(5):523-551. DOI: 10.1111/acem.13181
18. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg. 2013;100:322-9. DOI: 10.1002/bjs.9008
19. Schellekens DH, Hulsewé KW, van Acker BA, van Bijnen AA, de Jaegere TM, Sastrowijoto SH et al. Evaluation of the diagnostic accuracy of plasma markers for early diagnosis in patients suspected for acute appendicitis. Acad Emerg Med. 2013;20(7):703-10. DOI: 10.1111/acem.12160
20. Kwan KY, Nager AL. Diagnosing pediatric appendicitis: usefulness of laboratory markers. Am. J. Emerg. Med 2010; 28(9): 1009–1015. PMID: 20825931
21. Brito-Brito PR, García-Tesouro E, Fernández-Gutiérrez DA, García-Hernández AM, Fernández-Gutiérrez R, Burillo-Putze G. Validation of an uncertainty of illness scale adapted to use with Spanish emergency department patients and their accompanying relatives or friends. Emergencias. 2018;30:105-14. PMID: 29547233
22. Zouari M, Jallouli M, Louati H, Kchaou R, Chtourou R, Kotti A et al. Predictive value of C-reactive protein, ultrasound and Alvarado score in acute appendicitis: a prospective pediatric cohort. Am J Emerg Med. 2016;34(2):189-92. DOI: 10.1016/j.ajem.2015.10.004
23. Farahbakhsh F, Torabi M, Mirzaee M. A comparative study on the diagnostic validity of three scoring systems in the diagnosis of acute appendicitis in emergency centres. Afr J Emerg Med. 2020;10(3):132-135. DOI: 10.1016/j.afjem.2020.04.009
24. Thirumallai S, Wijesuriya SR, Mitchell A, Delriviere L. Predictive val-

ue of C-reactive protein with Alvarado score in acute appendicitis. ANZ J Surg. 2014;84(5):335-6. DOI: 10.1111/ans.12408

25. Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. World J Surg. 2008;32:1843–1849. DOI: 10.1007/s00268-008-9649-y
26. Altali K, Ruiz-Artacho P, Trenchs V, Martínez Ortiz de Zárate M, Navarro C, Fernández C, et al. Hospital emergency room diagnosis of acute appendicitis in patients aged 2 to 20 years: the INFURG-SEMES score from the emergency infections study of the Spanish Society of Emergency Medicine. Emergencias. 2017;29:231-6. PMID: 28825277
27. González Del Castillo J, Ayuso FJ, Trenchs V, Martinez Ortiz de Zarate M, Navarro C, Altali K, et al. Diagnostic accuracy of the APPY1 Test in patients aged 2-20 years with suspected acute appendicitis presenting to emergency departments. Emerg Med J. 2016;33(12):853-859. DOI: 10.1136/emermed-2015-205259