The APpendicitis PEdiatric (APPE) score: a new diagnostic tool in suspected pediatric acute appendicitis

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Abstract

Our aim was to develop an APpendictis-PEdiatric score (APPE score) in quantifying risk of acute appendicitis based on combination of clinical and laboratory markers.

1025 patients were classified in: acute appendicitis (AA) and non-appendicitis. Demographic/clinical features, and laboratory were collected. They were compared for quantitative-variables and categorical-variables. Significant predictors (P=<0,05) were included in logistic regression model. Based on regression-coefficients, a diagnostic score was tested by calculating the area under the ROC curve. Two cut-offs were established to define classes of risk of AA.

9 variables were identified as potentially predictors for AA. Those underwent logistic regression and a score was assigned, for maximum 21-points. The score showed an area under the curve: 0.831 and a linear proportion with the state of appendicular inflammation (R20.85). Patients with a score ≤8 were at low risk of AA (sensitivity 94%); those with a score ≥15 were at high risk for AA (specificity 93%). Those between 8 and 15 were defined at intermediate risk class.

APPE-score guides clinicians in classifying patients with suspected-AA according to clinical and laboratory findings in order to improve their management.

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Introduction

Acute appendicitis (AA) is the most frequent abdominal surgical emergency in the paediatric age and it is diagnosed in 1 to 8 percent of children evaluated urgently for abdominal pain.[1,2] It is estimated that the risk of developing an acute appendicular inflammation is 7% in the course of a lifetime.[3] Despite knowledge and experience acquired over the years on this pathology, at present diagnostic certainty is only guaranteed after surgical exploration and histopathological examination. The workup of patient with the suspicion of acute appendicitis starts with clinical history, physical examination and orienting laboratory tests. Management of patients with abdominal pain secondary to suspected appendicular inflammation is not univocal and remains complex to such an extent that the rate of negative appendectomies can reach up to 40%.[4]

Clinical studies have shown that imaging is a key strategy in optimizing outcomes in appendicitis, not only as an aid in early diagnosis, but also reducing negative appendectomy rates.[5,6] Recently, Douglas *et al.* have shown that graded compression ultrasonography has an accuracy of 93% equivalent to contrast computed tomography.[7] However, this diagnostic difficulty has led researchers to develop several clinical score-systems to help determine the probability of a patient being affected with AA. Score systems commonly used are: the Alvarado score (also called the MANTRELS score),[8] the Pediatric Appendicitis Score (PAS), Refined Low-Risk Appendicitis Score,[9,10] Appendicitis Inflammatory Response (AIR),[11] Children's Appendicitis Score (CAS)[12] and Pediatric appendicitis risk calculator (pARC).[10] It was demonstrated that AIR score has the greatest discriminating power and statistically outperforms the Alvarado score and PAS in predicting AA in children.[13] A recent randomized clinical trial showed that an AIR score-based risk classification can safely reduce the use of diagnostic imaging and hospital admissions in patients with suspicion of appendicitis.[14] More recently pARC has been described as more accurate than PAS in quantifying the risk of appendicitis in patients with acute abdominal pain. However none of these score-systems are based on a logistic regression model.

Our aim in this investigation was to develop and validate a new APpendictis PEdiatric score (APPE score) in quantifying risk of AA based on a combination of clinical history and features, and laboratory inflammatory markers, suitable as an objective instrument in selecting patients for further examination with imaging techniques or next-day re-evaluation. This score should help the clinician in managing paediatric patients with abdominal pain secondary to suspected appendicular inflammation in order to improve diagnostic accuracy and better manage available hospital resources, without increasing costs.

Materials and Methods

This was a retrospective observational cohort study aimed at collecting data to develop a new clinical scoring system for children with suspected appendicitis. The study was conducted at the Department of Paediatric Surgery of Sant'Orsola University-Hospital in Bologna from January 2013 to December 2016.

All patients, younger than 18 years of age, who underwent appendectomy at our institution were reviewed. Exclusion criteria were patients with previous appendectomy and abdominal surgery, chronic medical or malignant conditions (*e.g.* inflammatory bowel disease), patients with recurrent abdominal pain, and patients with appendicular mass or periappendiceal abscesses.

Only patients operated upon the suspicion of AA were included in the study, and their clinical charts were retrospectively reviewed. Eligible patients were identified and enrolled by the on-duty surgical registrars.

Study population

Based on the listed criteria all identified patients were classified into 2 groups based on histological examination: patients with AA and patients with non-appendicitis (NA). A uniform retrospective data form was completed, which included: i) demographic data: age (years), sex (male/female); ii) duration of symptoms – 4 sub-groups: a) patients with pain lasting less than 12 hours, b) between 13 and 24 hours, c) between 25 and 48 hours, and d) more than 48 hours) – vomiting (present/absent), body temperature (°C); iii) physical examination: tenderness in right iliac fossa on palpation, and Blumberg sign (both variables were considered as dichotomous data (present/absence); iv) laboratory tests: white blood cell (WBC) count ($\times 10^3$/uL), differential count (% of neutrophilia) and C-reactive protein (CRP) (mg/dL); v) type of surgical approach (transumbilical video-assisted appendectomy (TULAA), three-trocars laparoscopic appendectomy, open appendectomy) and operative time; vi) stage of inflammation on histopathological examination: absence of inflammation, catarrhal inflammation, phlegmonous inflammation, gangrenous inflammation, peritonitis (presence/absence).

Statistic analysis

All data were collected in an Excel worksheet by Microsoft Inc. and analysed using SPSS software (version 25, SPSS Inc., Chicago, IL, USA). For comparison between the two groups, AA and NA, we used the T student test for quantitative variables whereas the Chi-square test and Fisher's exact test for categorical variables were used as needed. Before proceeding with further analysis, the statistically significant continuous variables were grouped into classes. The newly identified possible predictors of the final endpoint were included in the logistic regression model ($P <$ or $= 0.05$). Based on the resulting regression coefficients, a new score system was obtained. The score was retrospectively applied to our general population (1025 patients); the diagnostic accuracy of the latter was tested by using the ROC curve. Two cut-offs were then established in order to classify patients into three classes of risk of appendiceal inflammation. For each cut off we tested sensitivity, specificity and predictive value. As a further analysis in testing the associative link between the proposed score and the appendicular inflammation state, a simple linear regression was applied.

Results

Study population

Based on the listed criteria we identified 1462 clinical cases in the specified time period; among them 437 were excluded because clinical data were incomplete. The final population was composed of 1025 patients that were classified into 2 groups based on histological examination: 829 (81%) patients with AA and 196 (19%) patients with NA.

Statistic analysis of the parameters and the comparison of the diagnostic weight for each of the clinical features (diagnostic indicants) between the 2 groups are reported in Table 1.

Age and sex

Mean age of patients belonging to AA group was 9.5 years (range 1-17) versus 10 years (range 3-17) in those of NA group, P=0.04. Regarding sex difference between the two groups, we found that 62.6% (n=519) of patients in AA group were male with a male/female ratio of 1.7, while only 48% (n=94) were male in NA group with a male/female ratio of 0.9 ($P<0.05$).

Duration of symptoms

Overall mean duration of symptoms in AA group was 24 hours before surgical evaluation, 70% of them were included in sub-group B and C (symptoms within 13 and 48 hours). Otherwise, mean duration of symptoms in all cases of NA group was 30 hours with uniform distribution among the different timepoints considered (Figure 1) ($P<0.05$).

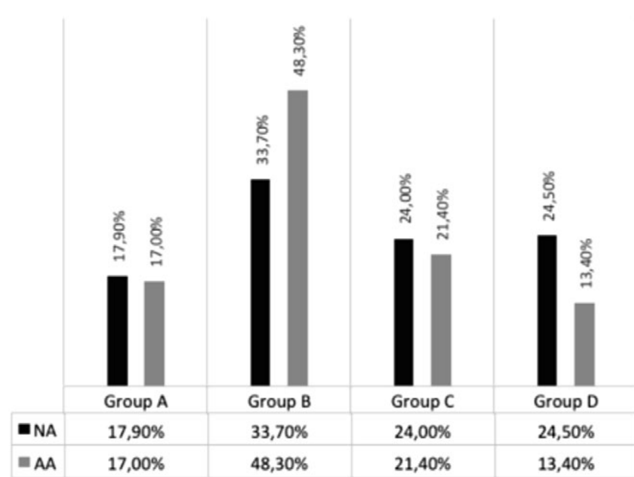

Figure 1. Distribution of patients based on the duration of the symptomatology: Group A, less than 12 hours (h); Group B, within 13-24 h; Group C, within 25-48 h; Group D, more than 49 h. AA, acute appendicitis; NA, non-appendicitis.

Vomiting

66.6% (n=552) of patients with AA had at least one episode of vomiting compared to 32.7% (n=64) of patients with NA (P<0.05). Considering age distribution we observed that more than 80% of patients with AA and vomiting were older than 6 years of age.

Body temperature

An increase in body temperature (≥37 °C) was not statistically significant between the two groups.

Tenderness in right iliac fossa and Blumberg sign

Tenderness in right iliac fossa and positive Blumberg sign were more prevalent in patients of AA group compared to those of NA group, respectively 56.8% *vs* 34.7%, P<0.05, and 81% *vs* 50.5%, P<0.05.

Laboratory findings

WBC count: The median WBC count was higher in AA group (15.04×10^3/uL) compared to the NA group (11.11×10^3/uL), (P<0.005). We therefore analysed the WBC count at different cut-off values and we noticed that 50% of patients with AA had WBC count equal or higher than 15×10^3/uL.

Percentage of neutrophils

This variable was significantly higher in AA group (81.7%) compared to NA group (73.35%), (P<0.05). After establishing cut-off of % of neutrophils at 75% of the total WBC count we observed that 65% of patients of AA group were above the established threshold, otherwise in the NA patient cohort, only 24.7% exceeded it (P<0.05)..

CRP: Median CRP value in AA group was 2.24 mg/dL *versus* 1.08 mg/dL in NA group (P<0.05). Fifty-two percent of patients of NA group had a CRP value lower or equal to 1 mg/dl, while the majority of patients with AA were characterized by a CRP value between 1-6 m/dL.

Analysis of diagnostic indicants

Table 2 summarizes sensitivity, specificity, positive predictive value and negative predictive value of each of the clinical features in both groups.

Surgical procedure

All patients (n=829) with suspected AA were approached by TULAA. In group AA, TULAA was successfully performed in 683 cases (82.4%) while 146 (17.6%) required conversion to laparoscopic 3-trocars appendectomy (13.6%) or to open appendectomy (4%). In the NA cohort, the TULAA technique was successfully performed in 98% of cases, with a conversion rate of 2% all to laparoscopic 3-trocars appendectomy. AA was confirmed by histopathological examination in 829 cases. Data regarding surgical procedures according to different degree of AA (catarrahl, phlegmonous or gangrenous appendicitis) were reported in Table 3.

Table 1. Analysis statistic of the single variables within the two cohorts.

	Acute Appendicitisn=829	Non-Appendicitisn=196	P value
Age (years)*	9.5 (1-17)	10 (3-17)	0,04
Sex			0,00
Male	519 (62,6%)	94 (48%)	
Female	310 (37,4%)	102 (52%)	
Duration of symptoms*	24 (2-240)	30 (2-192)	0,00
Vomiting			0,00
Present	552 (66,6%)	64 (32,7%)	
Absent	277 (33,4%)	132 (67,3%)	
Body temperature (°C)*	37,4 (36,5-41)	37,3 (36,5-40,1)	n.s.d.
Tenderness in right iliac fossa			0,00
Present	471 (56,8%)	68 (34,7%)	
Absent	358 (43,2%)	128 (65,3%)	
Blumberg sing			0,00
Present	671 (80,9%)	99 (50,5%)	
Absent	158 (19,1%)	97 (49,5%)	
WBC ($\times10^3$/uL)*	15,04 (3,31-41,5)	11,11 (3,09-35,10)	0,00
Neutrophils (%)*	81,7 (34,6-94,5)	73,35 (35,1-93,5)	0,00
CRP (mg/dL)*	2,34 (0,1-34,4)	1,08 (0,01-19,44)	0,00
Surgery			
TULAA	82,4%	98%	
VLS	13,6%	2%	
Open	4%	-	
Operative time (min)*	70 (20-360)	60 (22-180)	
Histological examination			-
Catarrhal	14,1%		
Phlegmonous	66,7%		
Gangrenous	19,2%		
Peritonitis	20,2%	-	

*median. TULAA, Transumbilical Laparoscopic Assisted Appendicectomy; VLS, videolaparoscopy; WBC, white blood cells; CRP, C-reactive protein; n.s.d, non significant difference.

Construction of the APPE score

The variables described so far have been subjected to a dedicated statistical analysis. Predictors that have been shown to be statistically significant (P<0.05) between AA and NA groups were: age, sex, duration of symptoms, vomiting, tenderness in right iliac fossa, Blumberg sign, WBC, Percentage of Neutrophils and CRP value.

All indicated variables with discriminating power towards appendicular inflammation were inserted into a logistic regression model in order to test the diagnostic power of each one. The results that emerged in terms of regression coefficient and odds ratio are shown in (Table 4). On the basis of these data the weight of each variable was established within the scoring system.

The discriminating ability of the score was tested by analysing the area under a ROC curve (AUC 0,831 IC 95% 0,8-0,86). The association between the presented score and the acute appendicular inflammation was also analysed with a simple linear regression. The trend of scattering points suggests the existence of a linear relationship between the two variables. The increase in score corresponds to a parallel increase in the percentage of patients affected by appendiceal inflammation, with a regression coefficient (b) equal to 5.37. The coefficient of determination R2 of the straight line was equal to 0.85 which indicates a good adaptation of the model (Figure 2).

Our score is structured on 9 variables for a maximum score of 21. Three diagnostic groups have been defined through the recognition of two cut offs. The final purpose was to obtain three classes of risk: patients with high, medium or low risk of acute appendicitis. For the two selected cut offs, specificity, sensitivity and predictive value were calculated. The lower limit chosen was 8. Patients with scores equal to or less than this value were classified as low risk. This cut off has shown to have a high sensitivity (94.3%). If the patient is placed in this risk group, he or she can be discharged without further diagnostic testing. The upper limit chosen was 15; patients with a score equal to or greater than this value were classified as high risk. This cut off showed a high specificity and positive predictive value respectively 93%, and 97%. For patients in this risk group, we advise further diagnostic testing and surgical intervention as a first therapeutic option. The risk range between the two cut-offs (8.5-14.5) defines patients with intermediate risk of acute appendicitis. In these cases it is advisable to keep the patient under observation and better investigate with diagnostic imaging.

Table 2. Comparative evaluation of clinical features in appendicitis and non-appendicitis patients.

	Acute Appendicitis group/Non-appendicitis group			
Diagnostic Indicators	Sensitivity	Specificity	Positive Value	Negative Predictive Value
Symptoms within 13 and 24 hrs	47.89%	32.65%	75.05%	12.90%
Vomiting	66.59%	67.35%	89.61%	32.27%
Tenderness in right iliac fossa	56.82%	65.31%	87.38%	26.34%
Blumberg sign	80.94%	49.49%	87.14%	38.04%
Fever	84.92%	68.37%	91.91%	51.74%
WBC count >15000/mmc	84.92%	58.16%	89.57%	47.70%
% neutrophils (equal or more 75%)	65.02%	75.51%	91.82%	33.79%
CRP >1mg/dL	77.93%	47.45%	86.25%	33.70%

WBC, white blood cell; CRP, C-reactive protein.

Table 3. Analysis of statistically significant variables in the acute appendicitis cohort according to the degrees of appendicular inflammation.

	Catarrhal n=116	Phlegmosous n=553	Gangrenous n=160
Age (year)*	10	10	9
Sex (M/F %)	56/44	69/31	53,8/46,2
Duration of symptoms (h)*	24	24	28
Body temperature (°C)*	37,2	37,1	38
Vomiting present (%)	42,7	64,8	89,3
Tenderness in RIF (%)	39,3	52,8	79,7
Blumberg sing (%)	61,5	80,6	85,5
WBC ($\times 10^3$/uL)*	12,37	14,87	17,68
Neutrophilis (%)*	77,4	80,6	85,7
CRP (mg/dl)*	1,39	1,85	7,51
Surgery (%)			
TULAA	98,3	87,5	53,2
VLS	1,7	10	35,4
Open	-	2,5	11,4
Operative time (mn)*	60	70	105

*median; TULAA, Transumbilical Laparoscopic Assisted Appendicectomy; VLS, videolaparoscopy; WBC, white blood cells; CRP, C-reactive protein.

Retrospective application of the score

Retrospectively applying the score to the sample population of 1025 patients, we obtained that 38.1% of patients achieved a score equal to or greater than 15, placing themselves in the high risk class. Among these patients, 96.2% were affected with acute appendicitis with a rate of negative appendectomy equal to 3.8%.

The low risk class (patients obtained a score of less than or equal to 8) had a sensitivity of 95% with a predictive value of 97.5% for appendicitis.

Forty-eight percent were classified into the intermediate risk group (patients obtained a score within 8 and 15), among them AA was confirmed in 80%. As such, the discriminatory ability of the score was not distinct enough in this group. Additional imaging study of ultrasound examination of the abdomen was required.

Table 4. Multivariate analysis (logistic regression) with the construction of the score in relation to the regression coefficients and odds ratios.

Variables		Regression Coefficient	Odds ratio	Score
Age (years)	≤6			0
	7-11	0,279	1,322	1
	≥12	0,132	1,141	0,5
Sex	F			0
	M	0,475	1,609	2
Duration of symptoms (h)	≤12	0,273	1,313	1
	13-24	0,426	1,531	1,5
	25-48	0,135	1,145	0,5
	≥49			0
Vomiting	No			0
	Yes	0,861	2,365	3,5
Tenderness in right iliac fossa	No			0
	Yes	0,390	1,477	1,5
Blumberg sing	No			0
	Yes	1,028	2,796	4
WBC($\times 10^3$/uL)	≤10			0
	10-15	0,193	1,213	1
	>15	0,784	2,190	3
Neutrophilis (%)	≤75			0
	>75	0,519	1,681	2
CRP(mg/dL)	≤1			0
	1-6	0,488	1,629	2
	> 6	0,347	1,415	1,5
Total				21

Score ≤8: discharge; Score between 8,5-14,5: diagnostic for images; Score ≥15 surgery
WBC, white blood cells; CRP, C-reactive protein.

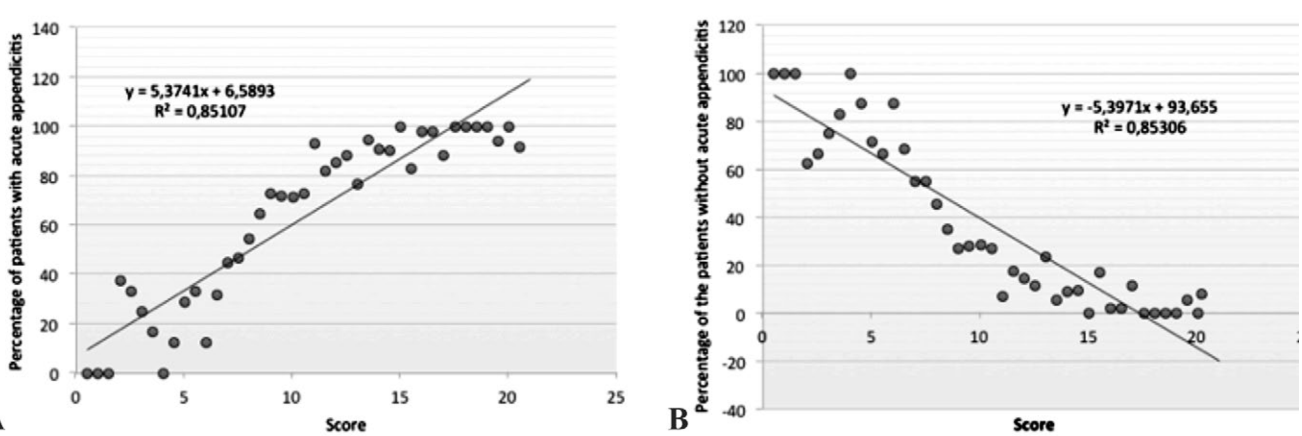

Figure 2. (A) Linear regression in the acute appendicitis group; (B) linear regression in the non-appendicitis group.

Discussion

AA is the most frequent abdominal surgical emergency in the paediatric age; although it is a widespread and widely studied pathology, diagnostic certainty is still guaranteed only after surgical exploration and histopathological examination.[3,4] Thus, diagnosing appendicitis among children is frequently challenging because typical symptoms and signs are often not present, specific findings of appendicitis are difficult to elicit in this patient population, and clinical findings frequently overlap with other conditions.

The aim of this study was to develop a diagnostic tool that can guide the clinician in managing paediatric patients with acute abdominal pain secondary to suspected appendicular inflammation, so as to improve the diagnostic accuracy of available resources.

Numerous studies aimed at developing scoring systems in the diagnosis of acute appendicitis have been reported in literature. Some have been addressed towards the general population as the score of Alvarado,[8] Lintula score,[15] and the AIR;[16] others have been developed specifically for the paediatric population as PAS, CAS and pARC.[5,10,12] The main advantage of these scores is the possibility of categorizing patients into groups that are at low, moderate, and high risk of appendicitis. However, they have limited ability in identifying patients who necessitate an appendectomy. Nevertheless, these scores may have utility in identifying children who may benefit from diagnostic imaging and/or surgical consultation by providing a standard approach. More recently new different scores have been proposed such as Tzanakis score or the Heidelberg Appendicitis score, but in both abdominal ultrasonography is mandatory to build up the score value and it should be considered as a limit to the widespread of these scores because ultrasonography is user dependent and trained pediatric radiologists are needed to diagnose appendicitis.[17,18]

The most widespread and used score was published in 1986 by Alvarado. This is a scoring system (also called MANTRELS) built retrospectively by evaluating each variable using a contingency table with an estimate of sensitivity, specificity and predictive capacity.[8] This score presents several limits. The diagnostic weight of the variables selected for the diagnosis of appendicular inflammation is not established by a statistical regression model and all variables are only expressed in a dichotomic fashion (presence/absence).[16] In the Alvarado score important variables such as age, sex and duration of symptoms are missing. All of these three elements showed significant statistics in the diagnosis of acute appendicitis, as also supported by literature.[19,20] In 2008, Anderson and Anderson published the AIR score, structured on a logistic regression model composed of non-dichotomous variables but expressed at intervals.[16] This scoring system is not designed for the paediatric population; furthermore it does not consider age and duration of symptoms as variables. In this score the Blumberg sign is classified as mild/moderate/strong. This subdivision can be difficult to assess by the clinician, is not very manageable and leads to errors in the scoring system, especially in the paediatric age where interpretation of clinical signs is often difficult, especially under 10 years.[15] Compared to the first score developed by Alvarado, AIR introduced the CPR level among the variables. The relationship between CPR level and appendicular inflammation is well known in literature and is also supported by our analysis.[21,22] We therefore believe it is important that within a score, whose purpose is to recognize patients with appendicular inflammation, this variable needs to be included.

The first and most well-known paediatric score is the PAS which was developed in 2002. It is a tool that utilizes history, physical examination, and laboratory results to categorize the risk of appendicitis in children with abdominal pain on a 10 point scale.[5,23] An algorithm that incorporates the PAS for clinical decision-making is provided. However age, sex, duration of symptoms and CRP are absent among the predictors.[5] The major limit of this score remains its dichotomous clinical response. It does not stratify patients into risk classes but simply establishes whether the patient has a high or low probability of suffering from acute appendicitis. Given the clinical overlap between AA and non-surgical cases of abdominal pain, scores should promote the stratification of patients based on the risk of disease and not their simple binary division, so as to identify cases of doubtful diagnosis and direct them towards further diagnostic investigation.[24] Limited evidence is available to determine which score is best. In a systematic review of 11 prospective studies that evaluated use of the PAS in 2170 children and the Alvarado score in 1589 children, the Alvarado score appeared to be better than the PAS for identifying children at low risk for appendicitis.[25] However, the analysis showed marked heterogeneity among the reviewed studies including significant variation in the percent of patients with appendicitis (15 to 71 percent).[26] pARC has been derived and validated prospectively using a risk score based upon patient's characteristics, clinical story, objective examination, the pARC predicted risk for appendicitis with high discrimination (AUC 0.85). However use of the pARC requires sophisticated calculations that must be programmed and integrated into an electronic health record, which may be a barrier for implementation in some settings.

In 2017, Yap *et al*. have developed a new score called CAS that utilizes a combination of 3 laboratory inflammatory markers (WBC, CRP and neut%) with a second component of 6 predictors. The authors report a score's performance of 98% of sensitivity and a negative likelihood ratio of 0.02.[12] However the main limitation of CAS is that the *low probability* group has a very small cut-off (any scores below 1.5) that could be easily reached up, including most of the patients in both intermediate or high-risk group for what further radiological investigations are indicated.

The APPE score proposed in the current study is based on a model of logistic regression. Thanks to this statistical model we have identified the weight that each variable has in the diagnostic process of acute appendicitis. According to literature, variables such as age, sex and duration of symptoms were statistically significant and therefore introduced in our score.[19,20] Acute appendicitis revealed a clear prevalence in males and in the age group between 7 and 11 years of age. On the contrary, diagnostic error, cases of unnecessary intervention, were concentrated in patients aged 12 years or older and showed a prevalence in the female sex. The quality of our score was tested by means of a ROC curve (AUC 0.831 IC 95% 0.8-0.86) and a linear regression. The latter has allowed us to highlight how the increase in the score increases the percentage of AA and decreases its percentage of NA. It was decided to place two cut-offs instead of a single one as in PAS, with the aim of stratifying patients into risk classes of appendicular inflammation. Retrospectively applying our score, the percentage of unnecessary procedures (diagnostic error) was only 3.8%. A score equal to or greater than 15 immediately sends the patient to surgical intervention without further diagnostic investigation; in this case the positive predictive capacity of the score (VPP) is decisive, which in our study was 96.4%. In a prospective study of a PAS and Alvarado paediatric cohort, they showed insufficient VPP of 45% and 58%, respectively.[24]

Patients with a score of 8 or less are classified as low risk, for these our indication is the discharge procedure. From the retrospective application of our score, 47.5% of patients in the NA group fell into this group. These patients would have been discharged home at the first clinical evaluation without further diagnostic investigation, allowing an optimization of resources. The only patients for whom it is useful to carry out a diagnostic investigation are those in the intermediate risk class (8.5-14.5). The application of this score could therefore allow a reduction of the professional's commitment (surgeon and radiologist) and an improvement of organization in relation to cost/time.

Conclusions

The diagnosis of acute appendicitis still represents a challenge today. Thanks to the study of a population of 1025 patients operated for the clinical suspicion of appendiceal inflammation in our Department, we have built a new score, designed for the paediatric population. APPE score is a simple, relatively accurate diagnostic tool, which is applicable in all clinical situations and has been proposed as an assistance guide when deciding whether to operate or observe a child with abdominal pain. The scoring system can be used for repeated structured re-evaluation during active observation. The statistical methodology used for its development and analysis results as being a solid and accurate tool. Despite its applicability in any case of suspected acute appendicitis it can't be considered as a substitute of the surgeon. Many times the clinical conditions and surgeons experience, even without laboratory and/or radiological examinations, can delineate the optimal management of these cases.

This study aims at presenting a new score, on a statistical basis, in the correct diagnosis of the pediatric patients with abdominal pain secondary to suspected appendiceal inflammation. The data reported is preliminary and its application for now is only retrospective. The validation of the prospective score is currently underway at our centre.

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