ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

The Predictive Value of Ultrasound, Alvarado Score, and C-Reactive Protein in Pediatric Appendectomy Outcomes

Ultrason, Alvarado Skoru ve C-Reaktif Proteinin Pediatrik Appendektomilerdeki Prediktör Değeri

Ali Çelik[1], Mehmet Altuntaş[1]

ABSTRACT

Aim: This retrospective study aimed to investigate the combined accuracy of appendix diameter, C reactive protein, and Alvarado score in classifying patients with negative appendectomy and acute appendicitis.

Material and Methods: This descriptive observational cohort study research was conducted at the Emergency Department of a Training and Research Hospital between November 2017 and April 2019. We included the data of appendicitis cases aged under 18 years in this retrospective study and gathered data on patients` demographics, preoperative laboratory values, signs, symptoms, and final pathological diagnosis, retrospectively. Then, cases were divided into acute appendicitis or negative appendectomy groups according to formal pathology reports.

Results: The final study population consisted of 60 patients; the negative appendectomy rate was 25%. The diagnostic accuracy of the multivariate model`s involving CRP, Alvarado score, and appendix diameter was 93.3%, with a sensitivity and specificity of 93.3% for identifying acute appendicitis (+LR: 14 and -LR: 0.07). Applying the model could have prevented 93.3% of negative appendectomy cases (25% to 1.7%) from undergoing unnecessary surgery in our cohort.

Conclusion: In conclusion, CRP, Alvarado score, or appendix diameter should not be used individually to diagnose AA in children. However, combining these variables can increase the accuracy of acute appendicitis diagnosis and may provide a significant reduction in negative appendectomy rates.

Keywords: Appendicitis, Alvarado score, appendix diameter, C-reactive protein, lymphoid hyperplasia, negative appendectomy

ÖZ

Amaç: Bu retrospektif çalışma, negatif apendektomili ve akut apandisitli hastaları sınıflandırmada apendiks çapı, C reaktif protein ve Alvarado skorunun birleşik doğruluğunu araştırmayı amaçladı.

Gereç ve Yöntemler: Bu tanımlayıcı gözlemsel kohort çalışması, Kasım 2017 ile Nisan 2019 tarihleri arasında bir Eğitim ve Araştırma Hastanesi Acil Servisinde yürütülmüştür. Çalışmaya 18 yaş altı apandisit olguları dahil edilmiş ve hastaların demografik özellikleri, laboratuvar ölçümleri, semptom, bulgu ve nihai patoloji raporlarına ilişkin veriler retrospektif olarak toplanmıştır. Daha sonra olgular resmi patoloji raporlarına göre akut apandisit veya negatif apendektomi gruplarına ayrılmıştır.

Bulgular: Nihai çalışma popülasyonu 60 hastadan oluşuyordu ve negatif apendektomi oranı %25 idi. CRP, Alvarado skoru ve apendiks çapı verilerini içeren çok değişkenli modelin tanısal doğruluğu %93.3, akut apandisit tanımlamada duyarlılık ve özgüllüğü %93.3 idi (+LR: 14 ve -LR: 0.07). Modeli uygulamanın, kohortumuzdaki negatif apendektomi vakalarının %93,3'ünü (%25 ila %1,7) gereksiz cerrahiden kurtarabileceği görülmüştür.

Sonuç: Sonuç olarak, CRP, Alvarado skoru veya apendiks çapı çocuklarda AA tanısında tek başına kullanılmamalıdır. Ancak bu değişkenlerin birlikte kullanımı apandisit tanısının doğruluğunu artırabilir ve negatif apendektomi oranlarında önemli bir azalma sağlayabilir.

Anahtar Kelimeler: Akut apandisit, Alvarado skoru, apandiks çapı, C-reaktif protein, lenfoid hiperplazi, negatif apendektomi

Received: January 16, 2022 Accepted: Arpil 21, 2022

[1] Recep Tayyip Erdogan University Training and Research Hospital, Department of Emergency Medicine, Rize, Turkiye.

Corresponding Author: Ali Celik, MD ***Address:*** Recep Tayyip Erdogan University Training and Research Hospital, Department of Emergency Medicine, Rize, Turkiye.

Phone: +905442936191 ***E-mail:*** dralicelik.88@gmail.com

Atıf için/Cited as: *Celik A, Altuntas M.* The Predictive Value of Ultrasound, Alvarado Score, and C-Reactive Protein in Pediatric Appendectomy Outcomes. Anatolian J Emerg Med 2022;5(3):109-115. https://doi.org/10.54996/anatolianjem.1058404

Introduction

Acute appendicitis (AA) remains one of the most common surgical emergencies of all ages. The expected lifetime risk of appendicitis is stated to be about 8% (1). In most cases, the ideal treatment option is an appendectomy, which places a significant burden on healthcare systems. With the progress in diagnosis, severe complications have decreased. Despite pre-surgical diagnostic imaging tools, negative appendectomy (NA) cases, mostly lymphoid hyperplasia (LH), has grown as a novel dilemma at a rate of up to 25% (2). In this regard, conservative treatment (CT) with antibiotics has become a better approach for uncomplicated cases. However, antibiotics are still preferred in limited circumstances, due to the high recurrence rate of up to 40% and potential institutional disparities (3).

Many diagnostic tools exist for identifying appendicitis, such as clinical decision rules (CDRs) settled by laboratory parameters, physical examination findings, and patients` symptoms. Leucocyte counts and C-reactive protein (CRP) measures are widely used but non-specific laboratory markers of acute appendicitis. The Alvarado Score (AS) and Pediatric Appendicitis Score (PAS) are extensively utilized CDRs with adequate sensitivity for appendicitis but lack specificity. Ultrasonography (US) is a useful imaging modality for suspected pediatric appendicitis without radiation exposure. The American College of Radiology (ACR) positioned the US as the initial imaging for children with suspected appendicitis (4). In the sonographic examination, a fluid-filled, non-compressible appendix with a diameter of 6 mm is recognized as AA. However, US also lacks sufficient specificity, and viewing the appendix is not feasible in all cases.

This study hypothesized that the combination of CRP, CDRs (AS or PAS), and appendix diameter (AD) would provide more reliable diagnostic accuracy regardless of the severity of appendicitis. Consequently, the study aimed to investigate the predictive performance of CRP, CDRs, and appendix diameter (AD), both independently and mutually.

Material and Methods

Design, location, and study period

This retrospective observational study was performed after obtaining approval from the hospital authorities, and the patients` consents were waived (Date: 06.01.2021 Number: E-64247179-799). This study was conducted at an academic ED between November 2017 and April 2019. The total volume of patients under 18 years at the ED during the study period was 16029.

Patient selection and data collection

The patients diagnosed with acute appendicitis under the age of 18 years old who presented to the ED were included in our study. The patients who underwent elective surgery and other surgical procedures or were transported to another hospital before surgery, those treated without surgical intervention, and those who had inconclusive pathology reports were excluded from the study. We gathered data on patient demographics, preoperative laboratory values, signs and symptoms in ED, and final pathological diagnosis. After collecting the data needed, AS and PAS were calculated according to defined previously in the literature (5).

Statistical analysis

The summary statistics were reported as median with interquartile range (IQR) and percentages (%), as appropriate. The Shapiro-Wilk test and histograms were conducted to identify the distribution patterns of continuous variables. Mann-Whitney U test was used to compare continuous variables, and Pearson's chi-square test was performed for categorical variables. Odds ratios (OR) of univariate analyses with 95% confidence intervals (CI) and Wald test statistics were recorded. Then, the goodness-of-fit measures of regression models and collinearity issues between variables were examined for multivariate analysis. The correlation coefficient value > 0.6, tolerance value < 0.1, and variance inflation factor (*VIF*) > 10 for a variable resulted in it being removed from the regression model. Then, the receiver operating characteristic (ROC) curve analysis was performed to identify cut-offs for true AA compared to a normal appendix. Contingency tables were used for the fitted regression model`s diagnostic utility metrics following. In all tests, $p < 0.05$ was accepted as the statistically significant cut-off value. We performed statistical analysis using Jamovi software (version 1.1.5.0; https://jamovi.org) and Statistical Package for Social Sciences (SPSS version 26). *The STARD 2015 guidelines for reporting diagnostic accuracy studies* were used as a reference while preparing for this report (7).

Results

During the study period, a total number of 87 patients were diagnosed with acute appendicitis, and 27 cases were excluded (16; treated conservatively, 5; transferred to another hospital, 6; without enough data). Finally, 60 patients were included in the statistical analysis. 45 (75%) patients had pathologically confirmed AA (**Figure 1**).

The patients` median age was 13 (IQR: 5), and 39 patients (65%) were male. No statistically significant difference was found between groups concerning age or sex. ($X^2_{(1)} = 1.20$, *p=0.27*; $U_{(15, 45)} = 334.5$, *p= 0.96, respectively*). CRP and WCC levels were significantly higher in AA cases than among the lymphoid hyperplasia (LH) group ($U_{(15, 45)} = 148.5$, ***p = 0.001***; $U_{(15, 45)} = 195$, ***p < 0.01***; respectively). The patients of the AA group had higher AS, PAS, and AD than in the LH group ($U_{(15, 45)} = 148.5$, ***p= 0.001***; $U_{(15, 45)} = 188.5$, ***p<0.01***; $U_{(15, 45)} = 100.5$, ***p<0.001***; respectively) (**Table 1**).

	Appendicitis –	Appendicitis +		Univariate regression analysis OR (95 % CI) *		Multivariate regression analysis OR (95 %CI) *	
	n = 15	n = 45				Model 1	Model 2
Male, n (%)	8 (53.3 %)	31 (68.9 %)	p=0.27	1.97 (0.59-6.40) NS	p=0.28	0.39 (0.04-4.43) NS	removed
CRP$^{\geq 0.8}$, n (%)	4 (26.7 %)	38 (84.4 %)	**p< 0.001**	14.9 (3.68-60.50) ***	**p< 0.001**	13.74 (1.31-151.1) *	8.58 (1.28-57.4) *
Age, median (IQR)	12 (11-15)	13 (9-15)	p=0.965	0.97 (0.83-1.13) NS	p=0.73	1.04 (0.71-1.43) NS	removed
AS, median (IQR)	5 (4- 5.5)	7 (6- 8)	**p= 0.001**	1.90 (1.22-2.96) **	**p= 0.001**	6.16 (1.35-27.03) *	2.27 (1.24-4.17) **
PAS, median (IQR)	6 (5- 7)	7 (6- 8)	**p= 0.009**	1.42 (1.01-2.01) *	**p= 0.036**	0.39 (0.11-1.35) NS	removed
AD, median (IQR)	6.5 (6.1- 6.9)	8.1 (7.9- 10)	**p< 0.001**	3.18 (1.54-6.50) **	**p< 0.001**	4.53 (1.46-14.73) **	4.36 (1.50-12.6) **

CRP: C- reactive protein, AD: appendix diameter, AS: Alvarado Score, PAS: Pediatric Appendicitis Score,CRP$^{\geq 0.8}$: dichotomous data of CRP according to 0.8 mg/dl cut off, IQR: interquartile range, P value: by Mann-Whitney U and Pearson's X^2 test, NS: nonsignificant (p>0.05), OR: Odds ratio, CI: Confidence interval, LR test: Omnibus Likelihood ratio test statistics and p value, *: p value (*: p<0.05, **: p<0.01, ***: p<0.001) of Wald test statistics of logistic regression analysis

Table 1: Baseline characteristics of variables

In this study, it is evaluated whether these four variables (CRP, AD, and CDRs (AS or PAS)) together create a new predictive score to find out AA. CRP values were transformed into a dichotomous version according to the 0.8 mg/dl cut-off calculated with ROC analysis to get an easily calculatable score. 38 (84.4%) cases in the AA group showed positive CRP values and 4 patients (26.7%) in the LH group with respect to the new cut-off value, indicating a statistically significant difference. We also performed univariate regression analyses that revealed significant predictive abilities for CRP, AS, PAS and AD to discriminate AA cases from LH cases (**Table 2)**.

Following the univariate regression analyses, correlation analyses were performed to prevent multi-correlation and no significant correlation was detected between variables except for AS and PAS. A strong correlation existed between AS and PAS (Spearman ***r: 0.87***, ***p < 0.0001***). Moreover, PAS revealed no meaningful predictive performance to differentiate AA in the multivariate logistic regression model including AS, CRP, and AD (OR: 0.39 (CI95%: 0.11-1.35), *p= 0.13*) or within the model excluding AS (OR: 1.63 (CI 95%: 0.96-2.77), *p= 0.07*). Consequently, PAS was removed from the final multivariate model. As a result, the multivariate logistic regression model including all variables minus PAS was able to differentiate the AA cases from the LH cases ($X2_{(5)} = 37.5$, ***p < 0.0001***). However, the backward procedures involving the removal of age and sex did not cause a significant change in pseudo R^2 (Nagelkerke's R^2: 0.688 to 0.688; McFadden's: 0.556 to 0.555) and provided a decrease in Bayesian Information Criterion (BIC; 54.5 to 46.4) and Akaike Information Criteria (AIC: 41.9 to 38.0). These results pointed out no difference between the two models in terms of predictive ability. Therefore, the final model was formed by CRP, AS, and AD parameters. According to the regression analysis, the patients with positive CRP (≥ 0.8 mg/dl) were 8.5 times more likely to have AA than negative ones. The model also showed that each one-mm increase in appendix diameter cause a 436 % increase in the likelihood of appendicitis.

Metrics	Value	95% CI		Appendicitis +	Appendicitis -	Total
Sensitivity	93.3%	81.7 – 98.6		42	1	
Specificity	93.3%	68.1 – 98.8	**Predicted +**	(RT: 95.6%)	(RT: 4.4%)	43
+ LR	14	2.1 – 93.15		(CT: 95.6%)	(CT: 13.3%)	(CT: %75)
- LR	0.07	0.02 – 0.2		3	14	
+PV	97.7%	86.3 – 99.6	**Predicted -**	(RT:13.3%)	(RT: 86.7%)	17
-PV	82.35%	60.8 – 93.4		(CT: 4.4%)	(CT: 86.7%)	(CT: %25)
Accuracy	93.3%	83.8 – 98.2	Total	45 (RT: 75%)	15 (RT: 25%)	60

+ LR: Positive Likelihood Ratio, - LR: Negative Likelihood Ratio, +PV: Positive Predictive Value, -PV: Negative Predictive Value, RT: Raw Total, CT: Column Total.

Table 2: Diagnostic metrics of final multivariate logistic regression model and 2x2 classification table of patients

In addition, one point increase in Alvarado Score provides a 227% rise in the likelihood of appendicitis. As a result, the final model accurately labeled 93.3 % of cases in our study. The final model equation was formed as below:

$$P = \frac{1}{1+e(-16.099 + (0.820 \times \mathbf{AS}) + (1.471 \times \mathbf{AD}) + (2.149 \times [0 \text{ if } CRP<0.8\ mg/dl,\ \ 1 \text{ if } \geq 0.8 \text{mg/dl}])}$$

According to final model equation of multivariate analysis, a simplified score was generated as: **[AS + (2 × AD) + (4 × {0; if CRP<0.8, 1 if ≥0.8}]**. Then, the diagnostic accuracy metrics for variables and the final model distinguishing AA were figured out with the use of the optimal cut-off values calculated through ROC analysis. The predictive performance of the final model (cut off ≥ 22.8) expressed a sensitivity of 93.3%, a specificity of 93.3%, a positive likelihood ratio (+LR) of 14, a negative likelihood ratio (-LR) of 0.07 and the area under the curve (AUC) was 0.942 (**Table 2-3)**. To predict acute appendicitis, AD had a slightly better diagnostic performance with an AUC of 0.851 compared to AS (0.780) and CRP (0.780). According to the data, both AS and PAS showed similar specificity (93.3%) and respective PPV of 92.9% and 94.1% at the cut-off point of 7. Also, based on the original ruling out cut-offs, AS had a sensitivity of 77.8%, an NPP of 52.4% and PAS had a sensitivity of 88.9%, an NPP of 28.6%. AS had statistically insignificant but slightly better predictive performance compared to PAS (AUC difference: 6%, (95% CI: -0.08% to 13%); Delongs' test, *p=0.084*). The predictive performance of variables and final model were summarised in **Table 3**, and ROC curve analysis comparisons of the final model, and variables were shown in **Figure 2.**

Discussion

This report studied a multivariate model including a combination of CDRs (AS and PAS), radiological, and laboratory findings to predict AA. The final multivariate model including these variables showed a diagnostic accuracy of 93.3% with a sensitivity of 93.3% and a specificity of 93.3%. Depending on a -LR of 0.07, a +LR of 14, low false negative (6.7%), and low false-positive rate (6.7%), we could recommend the model to rule in or out for acute appendicitis in children.

Previous studies showed that AS and PAS have high sensitivity but low specificity, limiting their use (7). In literature, various optimal cut-offs for these scores were reported in the diagnosis of AA (8, 9). In the prospective cohort study of Wu et al., AUCs of Alvarado score were observed higher than PAS (10). Systematic reviews and meta-analysis suggested that the typical AS is valuable in children to rule out AA (AS< 5; -LR: 0.04- and sensitivity: 0.99) (5, 11). Nevertheless, one of these concluded that the standard PAS cut-offs were inaccurate in distinguishing AA (PAS≥ 8; +LR: 8.1, PAS< 4; -LR: 0.13) (5). In our cohort, AS (≥5) and PAS (≥6) could not show acceptable diagnostic performance based on the best cut-off points calculated by ROC analysis. At the cut-off point of 8, the maximum +LR for AS and PAS were observed (+LR: 4.3, +LR: 5.3; respectively). The patients with an AS <3 or a PAS<4, both have a -LR of 0.16. These results are partially correlated with the current literature. AS and PAS appeared as only mediocre tests; they are not accurate enough for ruling in or out AA in children.

Metric	Model prediction	Appendix diameter	Alvarado score	PAS	C-reactive protein
AUC ±SE	0.942 ± 0.037	0.851 ± 0.061	0.780 ± 0.073	0.721 ± 0.076	0.780 ± 0.076
(95% CI)	(0.871- 1.000)	(0.731- 0.971)	(0.636- 0.924)	(0.571- 0.870)	(0.633- 0.927)
Cut off value	22.8	7.1 mm	5	6	0.8 mg/dl
Sensitivity (%)	93.3	88.9	88.9	86.7	84.4
Specificity (%)	93.3	80	46.7	33.3	73.3
+ PV (%)	97.7	93	83.3	79.6	90.5
- PV (%)	82.4	70.6	58.3	45.5	61.1
+ LR	14	4.44	1.6	1.3	3.2
- LR	0.07	0.13	0.23	0.4	0.21
P value	p< 0.0001***	p< 0.0001***	p= 0.0001**	p= 0.0018**	p= 0.0001**

SE: standard error, PAS: Pediatric Appendicitis Score, AUC: Area Under Curve, +PV: Positive predictive value, -PV: Negative predictive value, + LR: Positive likelihood ratio

Table 3: *Area under the curve measures and cut off values of receiver operating characteristic curve for prediction pathologically positive appendicitis*

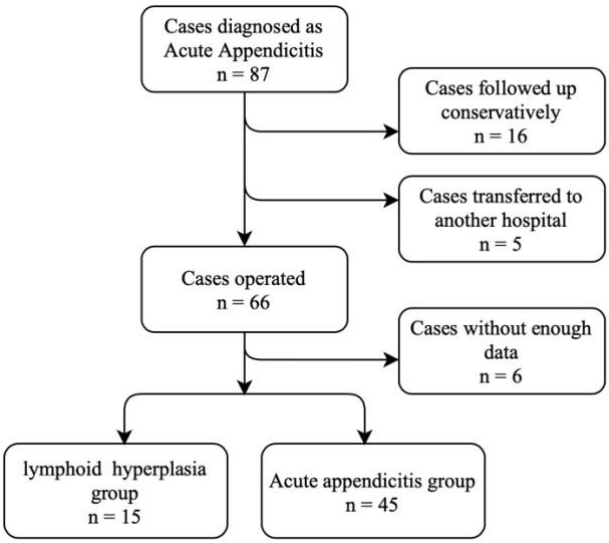

Figure 1: Flow chart of patients` selection and outcome.

C-reactive protein, leukocytes, and neutrophils are widely investigated laboratory markers in AA. They have been reported as predictors of appendicitis; however, they are not accurate for diagnosing or ruling out AA on their own (12-14). According to a recent meta-analysis, only a combination of CRP (≥ 3 mg/dl) and WCC (≥ 12000) achieved a +LR of 4.36. In the same report, WCC < 10000 showed the best value of -LR (0.21) but not enough to rule out AA (5). Another recent study that included 1391 patients reported that a combination of CRP, WCC, and leucocytosis has a strong discrimination ability (14). This study analyzed only CRP as a predictor of AA as the Alvarado score included the others. We observed a +LR of 3.2 for CRP (≥ 0.8 mg/dl) which is consistent with current literature (15). Therefore, CRP was not precise enough to rule in AA.

In the modern era, presurgical radiologic imaging is now routine in most circumstances. US is positioned as a first-line imaging tool for suspicion of AA in children; however, the accuracy of US is strongly related to operator experience and patients` body status (4). In this regard, several studies reported different results of the diagnostic metrics for the diagnosis of acute appendicitis (8, 15-22). Also, it was reported that repeated US protocols, US plus PAS or AS, and US in selected patient groups were able to reach the sensitivity up to 100% (7, 8, 15, 18, 20, 22-24). It is a known fact that larger appendix diameters (non-compressible, greater than 6 mm) increase the likelihood of appendicitis (15, 20, 23). However, Wu et al. suggested that lymphoid hyperplasia might be observed in cases that have a non-compressible appendix 6-8 mm in diameter (19). In our cohort, appendix diameter less than 6 mm significantly rule out appendicitis (-LR:0.0, NPV:100%, sensitivity: 100%) but not specific enough to differentiate NAs alone (specificity: 20%, PPV: 79%). According to ROC analysis, AD greater than 7.1 mm is the best cut-off with limited diagnostic accuracy (+LR:4.4, -LR:0.13). Multivariate analysis showed that each 1 mm increase in AD raises the likelihood of AA by 4.36 times (OR: 4.36) and a 1 mm decrease provides a 78% reduction to harbor appendicitis (OR: 0.22) which is compatible with current literature (16). Several reports have suggested that using CT over US could minimize the number of negative appendectomies (1, 7, 20, 24). However, US first protocols using CDRs are extensively favored in many centers to avoid radiation exposure (1, 7, 17, 21, 25). In this work, we established that PAS, AS, AD, and CRP, individually, and AS, AD, and CRP in combination, are valuable predictors of appendicitis.

In our cohort, applying the model that included these variables could have saved 14 (93.3% of NA group) cases from avoidable surgeries and the negative appendectomy rate (NAR) would have been significantly reduced (25% to 1.7%).

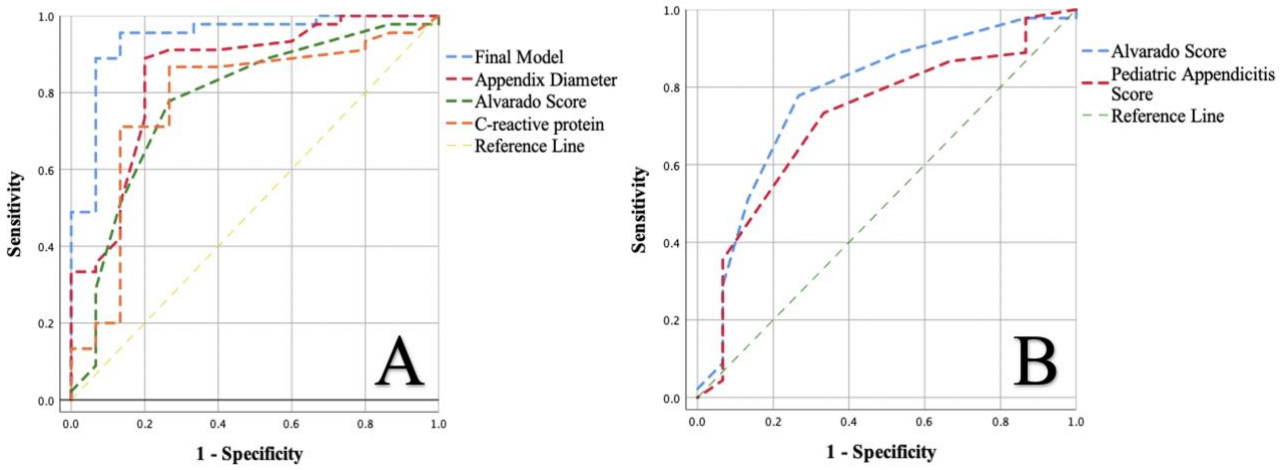

Figure 2: Receiver operating characteristic curve of multivariate regression model prediction, CRP, AD, and AS for acute appendicitis: A. Comparison of ROC curves between AS- PAS: B.

Moreover, none of the three false-negative cases had signs of complicated or even suppurative appendicitis. Therefore, we could suggest using the model in the decision-making of the treatment strategy.

Limitations

This study's first and foremost limitation was its retrospective nature, which may result in bias, especially in collecting data. The lack of an external or internal validation cohort because of the small sample size is the second most mattering limitation that might cause optimism about our findings. As such, the results should be validated in larger cohorts before accepting them globally. Third, this study's NAR was slightly higher than the rate in the current literature. However, this is thought to not be an actual limitation for this study, as cases of lymphoid hyperplasia have been accepted as negative appendicitis and several studies have reported similar or even higher NARs (normal appendix and lymphoid hyperplasia) (1, 7, 23). Meanwhile, the post-ultrasound NAR is known to be higher than the post-CT NAR (17). Furthermore, a conservative follow-up is also an important factor in decreasing NAR, but this may not be feasible in settings with limited resources. There were only two paediatric surgeons in the study's institute and the related region during the study period. Hence, surgical treatment was selected as a safer and more definitive choice in most cases.

Conclusion

In conclusion, C-Reactive Protein, AS, PAS, or appendix diameter should not be used individually to diagnose AA in children. However, using them together can aid the diagnosis or exclusion of acute appendicitis and may provide a significant reduction in the negative appendectomy rate.

Conflict of Interest: The authors declare no conflict of interest regarding this study.

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contribution: Contributions of authors were listed in brackets following the associated sections of the study: Literature search (AÇ), study design (AÇ, MA), supervision and quality control (AÇ), data collection (MA), statistical analyses (AÇ), drafting the manuscript (AÇ). All authors were concerned in the writing and crucial revision of the manuscript and approved the last version. AÇ and MA take the whole responsibility for the paper.

Acknowledgements: We thank Nazmiye Çelik from Penn State University (PA, USA) Engineering Science and Mechanics Department for her support with the statistical analyses and typesetting. And we also thank Haldun Akoğlu from Marmara University Faculty of Medicine, Department of Emergency Medicine, for his valuable support in statistical and methodological issues.

Ethical Statement: Approval was obtained from Rize Scientific Research Review Commission (Date: 06.01.2021 Number: E-64247179-799). All authors declared that they follow the rules of Research and Publication Ethics.

References

1. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. The Lancet. 2015;386(10000):1278-87.
2. Akbulut S, Koc C, Sahin TT, Sahin E, Tuncer A, Demyati K, et al. Determination of factors predicting acute appendicitis and perforated appendicitis. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2021;27(4):0-. https://doi.org/10.14744/tjtes.2020.60344.
3. Salminen P, Tuominen R, Paajanen H, Rautio T, Nordström P, Aarnio M, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. Jama. 2018;320(12):1259-65.
4. Koberlein GC, Trout AT, Rigsby CK, Iyer RS, Alazraki AL, Anupindi SA, et al. ACR Appropriateness Criteria® Suspected Appendicitis-Child. Journal of the American College of Radiology. 2019;16(5):S252-S63.
5. Ebell MH, Shinholser J. What are the most clinically useful cutoffs for the Alvarado and Pediatric Appendicitis Scores? A systematic review. Annals of emergency medicine. 2014;64(4):365-72. e2.
6. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ (Clinical research ed). 2015;351:h5527. https://doi.org/10.1136/bmj.h5527.
7. Kim SH, Choi YH, Kim WS, Cheon J-E, Kim I-O. Acute appendicitis in children: ultrasound and CT findings in negative appendectomy cases. Pediatric radiology. 2014;44(10):1243-51.
8. 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. Academic Emergency Medicine. 2017;24(5):523-51.
9. Goldman RD, Carter S, Stephens D, Antoon R, Mounstephen W, Langer JC. Prospective validation of the pediatric appendicitis score. The Journal of pediatrics. 2008;153(2):278-82.
10. Wu H-P, Yang W-C, Wu K-H, Chen C-Y, Fu Y-C. Diagnosing appendicitis at different time points in children with right lower quadrant pain: comparison between Pediatric Appendicitis Score and the Alvarado score. World journal of surgery. 2012;36(1):216-21.
11. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Medicine. 2011;9(1):139. https://doi.org/10.1186/1741-7015-9-139.
12. Yang J, Liu C, He Y, Cai Z. Laboratory Markers in the Prediction of Acute Perforated Appendicitis in Children. Emergency medicine international. 2019;2019.
13. Sengul S, Guler Y, Calis H, Karabulut Z. The Role of Serum Laboratory Biomarkers for Complicated and Uncomplicated Appendicitis in Adolescents. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP. 2020;30(4):420-4.
14. Chiang JJ, Angus MI, Nah SA, Jacobsen AS, Low Y, Choo CS, et al. Time course response of inflammatory markers in pediatric appendicitis. Pediatric Surgery International. 2020;36(4):493-500.

15. Kabir SA, Kabir SI, Sun R, Jafferbhoy S, Karim A. How to diagnose an acutely inflamed appendix; a systematic review of the latest evidence. International Journal of Surgery. 2017;40:155-62. https://doi.org/https://doi.org/10.1016/j.ijsu.2017.03.013.
16. Gee KM, Jones RE, Babb JL, Preston SC, Beres AL. Clinical and Imaging Correlates of Pediatric Mucosal Appendicitis. The Journal of surgical research. 2019;242:111-7. https://doi.org/10.1016/j.jss.2019.04.039.
17. Lee J, Ko Y, Ahn S, Park JH, Kim HJ, Hwang Ss, et al. Comparison of US and CT on the effect on negative appendectomy and appendiceal perforation in adolescents and adults: A post-hoc analysis using propensity-score methods. Journal of Clinical Ultrasound. 2016;44(7):401-10.
18. Toprak H, Kilincaslan H, Ahmad IC, Yildiz S, Bilgin M, Sharifov R, et al. Integration of ultrasound findings with Alvarado score in children with suspected appendicitis. Pediatrics International. 2014;56(1):95-9. https://doi.org/https://doi.org/10.1111/ped.12197.
19. Xu Y, Jeffrey RB, DiMaio MA, Olcott EW. Lymphoid Hyperplasia of the Appendix: A Potential Pitfall in the Sonographic Diagnosis of Appendicitis. AJR American journal of roentgenology. 2016;206(1):189-94. https://doi.org/10.2214/ajr.15.14846.
20. Mittal MK, Dayan PS, Macias CG, Bachur RG, Bennett J, Dudley NC, et al. Performance of ultrasound in the diagnosis of appendicitis in children in a multicenter cohort. Academic Emergency Medicine. 2013;20(7):697-702.
21. Gurien LA, Smith SD, Dassinger MS, Burford JM, Tepas JJ, Crandall M. Suspected appendicitis pathway continues to lower CT rates in children two years after implementation. The American Journal of Surgery. 2019;218(4):716-21.
22. Alter SM, Walsh B, Lenehan PJ, Shih RD. Ultrasound for diagnosis of appendicitis in a community hospital emergency department has a high rate of nondiagnostic studies. The Journal of emergency medicine. 2017;52(6):833-8.
23. Aydin S, Tek C, Ergun E, Kazci O, Kosar PN. Acute appendicitis or lymphoid hyperplasia: how to distinguish more safely? Canadian Association of Radiologists Journal. 2019;70(4):354-60.
24. Terasawa T, Blackmore CC, Bent S, Kohlwes RJ. Systematic review: computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. Annals of internal medicine. 2004;141(7):537-46.
25. Schoel L, Maizlin, II, Koppelmann T, Onwubiko C, Shroyer M, Douglas A, et al. Improving imaging strategies in pediatric appendicitis: a quality improvement initiative. The Journal of surgical research. 2018;230:131-6. https://doi.org/10.1016/j.jss.2018.04.043.