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ABDOMINAL IMAGING

ORIGINAL ARTICLE

The role of CT in decision for acute appendicitis treatment

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PURPOSE
Acute appendicitis is the most common cause of acute abdomen requiring surgery. Although the standard treatment has been surgery, it has been seen in recent years that treatment is possible with antibiotics and non-operative observation. In this study, our aim is to determine whether the computed tomography (CT) findings in patients diagnosed with acute appendicitis can be used for directing treatment.

METHODS
A retrospective analysis was conducted on 138 patients with acute appendicitis who underwent CT between 2015 and 2019. In this study, medical treatment group (n=60) versus surgical treatment group (n=78) and successful antibiotic treatment group (n=23) versus unsuccessful antibiotic treatment group (n=14) were compared. Appendiceal wall thickness, appendiceal diameter, the severity of mural enhancement, intra-abdominal free fluid, the severity of periappendiceal fat stranding, size of pericecal lymph node, appendicolith, adjacent organ findings, and the CT appendicitis score of groups were compared with Pearson Chi-square and Mann–Whitney U tests. Multivariable logistic regression was used to identify predictors of surgical treatment, expressed as odds ratios (ORs) with 95% CIs. Diagnostic efficacies of appendiceal diameter, the CT appendicitis score, and the developed model were quantified by receiver operating characteristic curves.

RESULTS
Appendiceal diameter ($P < .001$), adjacent organ findings ($P=0.041$), the CT appendicitis score ($P < .001$), the severity of periappendiceal fat stranding ($P=.002$), appendicolith ($P=.001$), and intra-abdominal free fluid ($P < .001$) showed statistically significant differences between the medical and surgical treatment groups. According to the logistic regression test, if the patients are with appendiceal diameter ≥13 mm (OR=5.1, 95% CI: 1.58-16.50), appendicolith (OR=4, 95% CI: 1.17-13.63), and intra-abdominal free fluid (OR=3.04, 95% CI: 1.28-7.20), surgeons should prefer surgical treatment. The area under the curves for the CT appendicitis score, the appendiceal diameter, and the model were 0.742 (95% CI: 0659-0824), 0.699 (95% CI: 0.613-0.786), and 0.745 (95% CI: 0.671-0.819), respectively. As the successful and unsuccessful medical treatment groups were compared, the only significant parameter was the severity of mural enhancement ($P=.005$).

CONCLUSION
CT findings may be helpful in patients with uncomplicated acute appendicitis whose treatment surgeons are indecisive about. We can recommend surgical treatment in cases with appendix diameter ≥13 mm, intra-abdominal free fluid, appendicolith, high CT appendicitis score, and severe mural enhancement.

Acute appendicitis is the most common cause of acute abdomen requiring surgical treatment. The lifelong risk of acute appendicitis is approximately 6%-7%. Appendicectomy has been the standard treatment of acute appendicitis since it was first reported by McBurney in 1889, and the general acceptance since the 19th century has been that in the absence of surgery, the disease often progresses from uncomplicated to perforated appendicitis.[1] The shift in surgical technique from open to laparoscopic appendicectomy has resulted in reduced length of hospital stay and morbidity and earlier postoperative recovery, but irrespective of the technique, there are risks associated

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with appendicectomy, including surgical site and intra-abdominal infections, incisional hernia, and peritoneal adhesions.[2-4] Therefore, there is increasing interest in a more conservative approach such as treating appendicitis with antibiotics alone, and randomized controlled trials have been performed in recent years in which antibiotic therapy has been evaluated, and meaningful results have been obtained.[5-9] With these developments in recent years, different treatment approaches have emerged. A case diagnosed with uncomplicated acute appendicitis by imaging methods can be treated with antibiotics or surgery.[10] But, there is still controversy about which treatment should be applied for uncomplicated acute appendicitis.[11] In the present study, we aimed to predict the treatment by comparing the computed tomography (CT) findings of the patients with uncomplicated acute appendicitis evaluated by surgeons and treated with antibiotics or surgery.

Methods

Patients

This study was approved by Marmara University institutional ethics committee (Protocol number: 09.2019.476, on May 3, 2019). As the present study was retrospective, we did not seek informed consent. The medical records and contrast-enhanced CT images of 987 adult patients with suspected acute appendicitis between the period of April 2015 and March 2019 were retrieved following a lexicon search tool function by searching for keyword phrases such as "appendix," "inflamed appendix," and "acute appendicitis." Due to the following reasons, 849 patients were excluded from the study: patients with lack of treatment information, CT findings compatible with perforated appendicitis, patients under 18 years of age, who had non-contrast-enhanced abdominal CT, and who had dementia or psychiatric disorders and other diseases that indirectly affect CT findings of acute appendicitis (pelvic inflammatory disease, inflammatory bowel disease, and malignancy). Finally, a total of 138 patients (101 men and 37 women; age range 18-68 and median age 30) were included in the study. Seventy-eight patients treated with appendectomy formed the surgical treatment group, whereas 60 patients treated with antibiotics formed the medical treatment group. Every patient in the medical treatment group was given IV ciprofloxacin–metronidazole or ceftriaxone–metronidazole at the emergency room, followed by 10 days of oral amoxicillin–clavulanic acid or ciprofloxacin–metronidazole. So to evaluate the success of medical treatment, information was obtained from the patients via phone following their posttreatment as of at least 6 months. Twenty-three patients were excluded either owing to lack of follow-up (n = 17) or patients' lack of completing the minimum required duration of 6 months posttreatment (n = 6). Twenty-three patients who completely recovered having received antibiotic therapy and whose acute appendicitis did not relapse during at least 6 months of follow-up represented the successful medical treatment group; 14 patients who were operated due to recurrent acute appendicitis in follow-up represented the unsuccessful medical treatment group (Figure 1).

CT imaging

A high-resolution CT scan was performed in all patients with 128 and 256 slice multidetector row CT scanners (Somatom Definition Flash 256 CT and Somatom Definition AS 128 CT). The acquisition parameters were as follows: tube voltage, 120 kV; tube current, automatic current modulation (CARE Dose 4D); mAs, 250; pitch, 0.6; slice thickness, 5 mm; collimation, 32 × 1.2; reconstruction interval, 5 mm. Patients were scanned in the supine position and during breath hold. Images were acquired from the dome of the diaphragm through the pubic symphysis. All patient received IV contrast material. Non-ionic iodinated contrast agent (300 mg/100 mL) was injected at a rate of 2.5 mL/s and 1.5 mL/kg through an intravenous catheter placed in the antecubital fossa with a scanning delay of 60 seconds. Oral contrast material was not used in CT examinations.

Image analysis and study design

All CT examinations were interpreted by 2 radiologists (C.C.K. with 4 years of abdominal imaging experience and D.T. with 30

Main points

- Although medical treatment has proven to be a successful method of treatment of uncomplicated acute appendicitis, there is still controversy over which treatment to apply.
- It is intended that the computed tomography (CT) appendicitis score, which carries the information of all CT parameters, gives us an idea about the severity of acute appendicitis, such as the Alvarado score.
- CT findings may be helpful in acute appendicitis cases about whose treatment surgeons are indecisive, and surgical treatment may be preferred in patients with appendiceal diameter ≥13 mm, intra-abdominal free fluid, appendicolith, high CT appendicitis score, and severe mural enhancement.

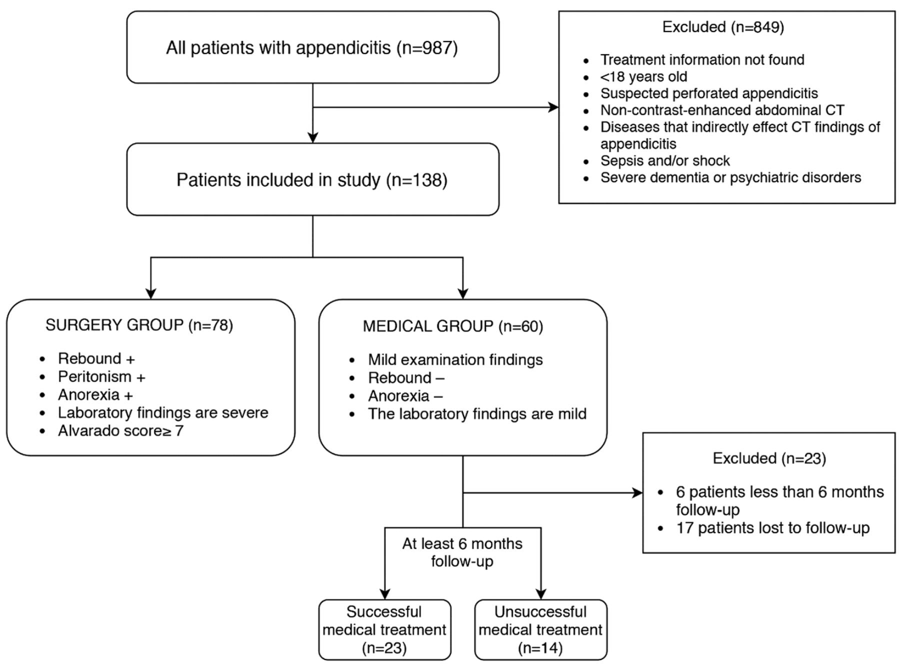

Figure 1. Derivation of the study population. CT, computed tomography.

years of abdominal imaging experience) in consensus. The following parameters were evaluated: (1) the severity of mural enhancement, (2) wall thickness of appendix, (3) adjacent organ findings, (4) appendicolith, (5) intra-abdominal free fluid, (6) appendix diameter, (7) maximum size of pericecal lymph node, (8) the severity of periappendiceal fat stranding, and (9) the CT appendicitis score.

While *the severity of mural enhancement* was evaluated, it was compared with the density of the right external iliac artery. If the severity was lower, it was stated as "mild," and if it was equal or more pronounced, it was stated as "severe." The severity of mural enhancement was graded as 1 (mild) and 2 (severe) (Figure 2). *Wall thickness of the appendix* was measured from where it was the thickest by using axial, coronal, and sagittal planes. Wall thickness of the appendix was graded as 0 (<3 mm) and 1 (≥3 mm) (Figure 3). *The diameter of the appendix* was measured from where it was the widest by using axial, coronal, and sagittal planes. The diameter of the appendix was graded as 1 (≤9 mm), 2 (10-12 mm), and 3 (≥13 mm) (Figure 4). If there was *intraluminal appendicolith* or *intra-abdominal free fluid*, it was graded as 1, if not, it was graded as 0. When evaluating *the periappendiceal lymph nodes*, we measured the size of the long axis of the largest lymph node. The size of the periappendiceal lymph nodes was graded as 1 (≤10 mm) and 2 (>10 mm). *The adjacent organ finding* is the reactive wall thickening of the cecum, colon, and ileal loops around the course of the appendix. If there was an adjacent organ finding, it was graded as 1, if not, it was graded as 0. *The severity of periappendiceal fat stranding* was graded as 0 (none), 1 (mild), and 2 (severe). If it spread more than 1.5 cm from the appendix, it was considered as "severe" (Figure 5). *The CT appendicitis score* was calculated by summing these grades of all the evaluated parameters (Table 1). We intended to have an idea about the severity of acute appendicitis with the CT appendicitis score, which carries the information of all variables evaluated in CT.

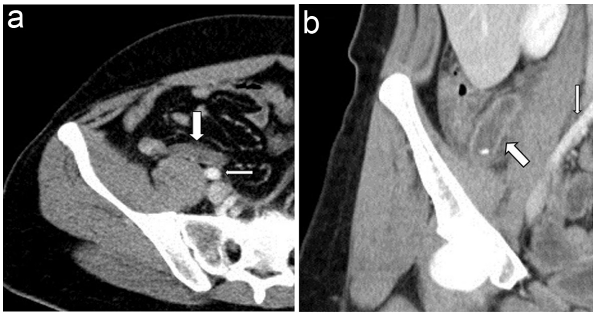

Figure 2. Example of the severity of mural enhancement. On contrast-enhanced abdominal CT scans, if the severity of mural enhancement (*thick arrow*) was less pronounced **(a)** than the right external iliac artery (*fine arrow*), it was graded as 1. If the severity of mural enhancement (thick arrow) was equal or more pronounced **(b)** than the right external iliac artery (*fine arrow*), it was graded as 2. CT, computed tomography.

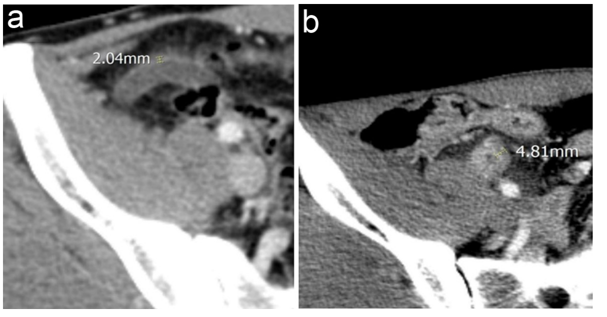

Figure 3. Example of the wall thickness of the appendix. On contrast-enhanced abdominal CT scans, it was graded as 0 while the wall thickness of the appendix was below 3 mm **(a)** and 1 if 3 mm or above **(b)**.

Statistical analysis

Statistical analysis was performed using Stata 15.1 statistics program package for Windows. Continuous variables were described as median and interquartile range. Categorical variables were presented by frequencies and percentages. Categorical variables were analyzed by Pearson Chi-square test or Fisher exact test, and continuous variables were analyzed by Mann–Whitney U test. A *P*-value < .05 was considered statistically significant. Backwards binary logistic regression analysis, in which surgical or medical treatment outcomes were dependent variables and data obtained from CT were independent variables, were used to determine the parameters that lead to surgical treatment. Results of univariate and multivariate analysis have been detailed with *P*-value, 95% CIs, and the odds ratio (OR). Diagnostic efficacies of appendiceal diameter, the CT appendicitis score, and developed model were quantified by receiver operating characteristic (ROC) curves. Positive likelihood ratios were used to determine the optimal cut-off value. The areas under the ROC curves were compared with the Delong test.

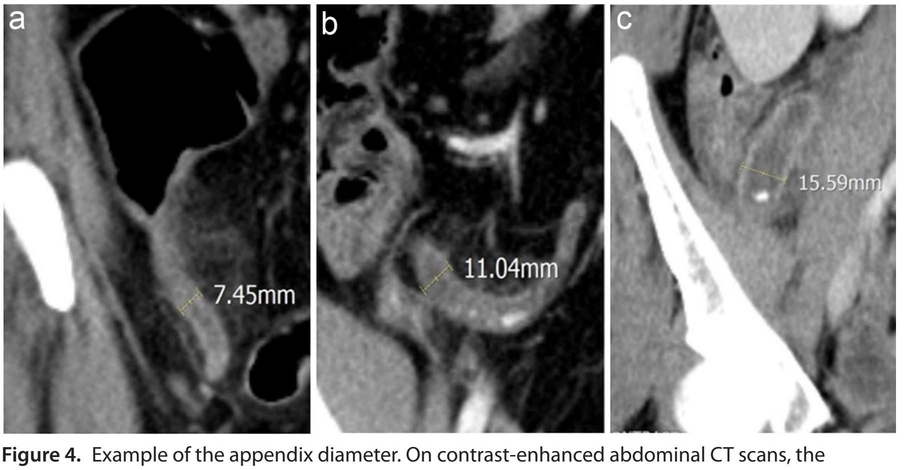

Figure 4. Example of the appendix diameter. On contrast-enhanced abdominal CT scans, the diameter of the appendix lumen was measured and it was graded as 1 (≤9 mm) **(a)**, 2 (10-12 mm) **(b)**, and 3 (≥13 mm) **(c)**.

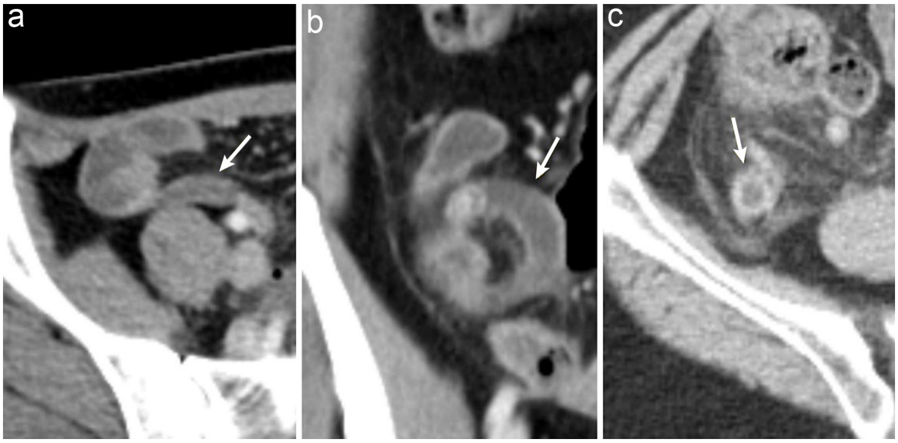

Figure 5. Example of the severity of periappendiceal fat stranding. On contrast-enhanced abdominal CT, the severity of periappendiceal fat stranding was graded as 0 (none) **(a)**, 1 (mild) **(b)**, and 2 (severe) **(c)**.

Results

Baseline patient characteristics were summarized in Table 2. Median (interquartile range) age was 30 (24-34) years, and 27% of study participants were female. Physical findings of patients were right lower quadrant tenderness (89%), nausea or vomiting (69%), anorexia (67%), and rebound (54%). Median (interquartile range) duration of symptoms was 12 (7-18) h, median white blood cell count was 13.6 (10.7-16.8) × 10^9/L, median C-reactive protein was 13.4 (3.44-46.4) mg/L, and median neutrophil percentage was 78.4% (70.8-84.7).

Among the evaluated parameters, the adjacent organ finding (*P*=.041), appendicolith (*P*=.001) and intra-abdominal free fluid (*P* < .001), the diameter of the appendix (*P* < .001), the severity of periappendiceal fat stranding (*P*=.002), and the CT appendicitis score (*P* < .001) (Figure 6) showed significant differences between surgical and medical treatment groups. ROC analysis was executed to evaluate the performance of the diameter of the appendix and the CT appendicitis score as a predictor of surgical treatment, which demonstrated that areas under the curve (AUC) ± standard errors were 0.699 ± 0.044 (95% CI: 0.613-0.786, *P* < .001) and 0.742 ± 0.042 (95% CI: 0.659-0.824, p<0.001), respectively (Table 3) (Figure 7). The diameter of appendix being ≥13 mm directs surgeons to surgical treatment with 39.74% sensitivity and 93.33% specificity (63.04% correctly classified, positive likelihood ratio=5.96; negative likelihood ratio=0.65). The CT appendicitis score ≥8 directs surgeons to surgical treatment with 78.21% sensitivity and 63.33% specificity (71.74% correctly classified, positive likelihood ratio=2.13; negative likelihood ratio=0.34) (Table 3).

Univariate logistic regression was performed for the 5 variables that were significantly different between the groups (adjacent organ finding, appendicolith, intra-abdominal free fluid, appendiceal diameter, and the severity of periappendiceal fat stranding). The adjacent organ finding and the severity of periappendiceal fat stranding were not significant on univariate analysis, so the other 3 variables were included in a multivariable model (Table 4). All 3 variables contributed significantly to the multivariable model (appendicolith: OR=4 (95% CI: 1.17-13.63), intra-abdominal free fluid: OR=3.04 (95% CI: 1.28-7.20), appendiceal diameter ≥13 mm: OR=5.1 (95% CI: 1.58-16.50), *P* < .001). In the model in which all 3 findings are positive, surgeons may prefer surgical treatment with 69.23% sensitivity and 71.67% specificity (70.29% correctly classified, positive predictive value=76.06%; negative predictive value=64.18%). The area under the ROC curve ± standard error for this model was 0.745 ± 0.038 (95% CI: 0.671-0.819, *P* < .001) (Table 3) (Figure 7). There were 11 patients all of whom had surgery in the study population meeting all 3 criteria. There were 67 patients meeting no criteria, 24 (36%) of whom had surgery. There was no significant difference in AUC values from ROC curves created for appendiceal diameter, the CT appendicitis score, and the model (*P*=.379).

In the second part of the study, the patients who were treated with antibiotics were followed up for at least 6 months and the recurrence rate was determined. Besides, the CT findings of successful and unsuccessful medical treatment groups were compared. The only significant parameter was the severity of mural enhancement with a *P*-value of .005. ROC analysis was used to evaluate the strength of the CT appendicitis score on the success of medical treatment, which demonstrated

Table 1. CT appendicitis score table

	0	1	2	3
Severity of mural enhancement		Mild	Severe	
Wall thickness of appendix	<3 mm	≥3 mm		
Intraluminal appendicolith	–	+		
Intra-abdominal free fluid	–	+		
Appendiceal diameter		≤9 mm	10-12 mm	≥13 mm
Maximum size of pericecal lymph node		≤10 mm	>10 mm	
Adjacent organ findings	–	+		
Severity of periappendiceal fat stranding	–	Mild	Severe	

CT, computed tomography.

Table 2. Demographics and clinical findings at presentation in 138 patients

Patient characteristics	Results
Age	30 (24-34)
Female*	37 (27%)
Physical findings	
RLQ tenderness*	123 (89%)
Rebound*	74 (54%)
Nausea/vomiting*	95 (69%)
Anorexia*	92 (67%)
Duration of symptoms (hours)	12 (7-18)
Inflammatory markers	
WBC count (×10^9/L)	13.6 (10.7-16.8)
CRP (mg/L)	13.4 (3.44-46.4)
% neutrophils	78.4 (70.8-84.7)

*Data are presented as median (interquartile range) or n (%).
RLQ, right lower quadrant; WBC, white blood cell; CRP, C-reactive protein.

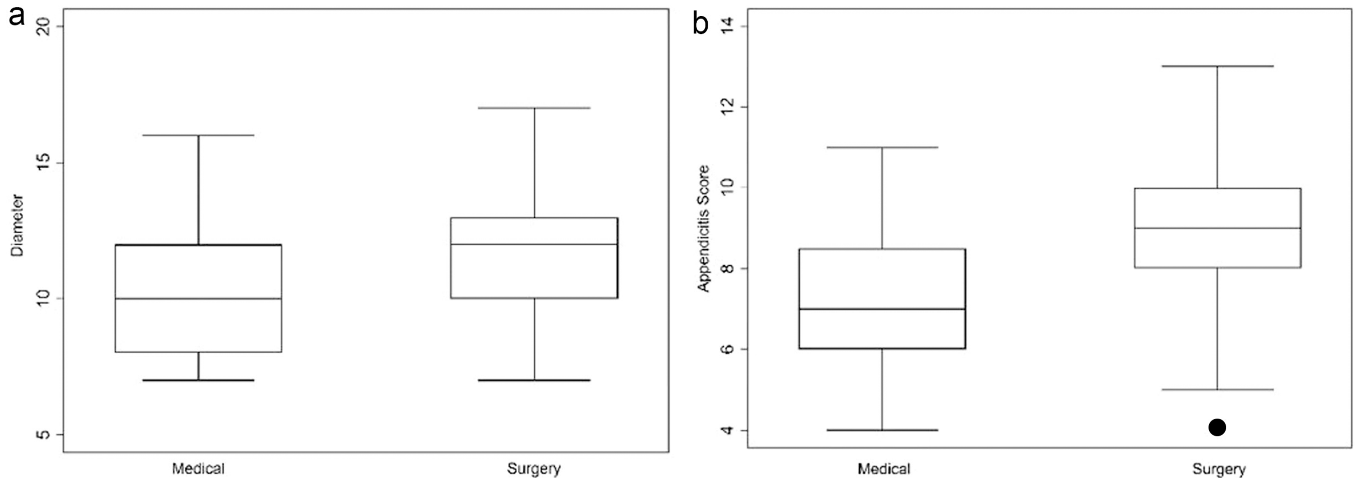

Figure 6. Box and whisker plots show the distribution of the appendix diameter **(a)** and the CT appendicitis score **(b)** in surgical and medical treatment groups.

that AUC ± standard error was 0.609 ± 0.094 (95% CI: 0.423-0.794, *P*=.101) (Table 3) (Figure 7). The CT appendicitis score ≥7 indicates that medical treatment will fail with 78.57% sensitivity and 60.87% specificity (67.57% correctly classified, positive likelihood ratio=2.007; negative likelihood ratio=0.352) (Table 3).

Discussion

Although the accepted standard treatment of acute appendicitis is appendectomy, medical treatment has also proven to be a successful method in recent studies. Acute appendicitis severity varies in a spectrum of early acute appendicitis with mild symptoms and complicated appendicitis with abscess formation. Complicated appendicitis with abscess formation is treated with IV antibiotic treatment, percutaneous abscess drainage, and interval appendectomy. Acute appendicitis cases in early perforation are treated with IV antibiotics and appendectomy urgently. Patients with mild clinical symptoms during the early acute appendicitis period are treated just with antibiotics. However, since most acute appendicitis patients are in the middle of this spectrum, there is still an ongoing controversy over which treatment should be applied.[11] Our aim in this study is to guide the treatment by depending on CT findings of patients with uncomplicated acute appendicitis.

In the literature, studies upon the subject are mostly about clinical and laboratory findings. There is no consensus among studies, including radiological results.

In general, in previous studies, regardless of the severity of clinical findings, antibiotic treatment was given to the patients with uncomplicated acute appendicitis and then successful and unsuccessful medical treatment groups were compared. Unlike the studies conducted previously, in the present study, firstly surgical and medical treatment groups and then successful and unsuccessful medical treatment groups were compared because of the fact that surgical treatment is preferred in cases of severe acute appendicitis in our hospital. When surgical and medical treatment groups were compared, appendicolith, adjacent organ findings, intra-abdominal free fluid, the diameter of the appendix, the severity of periappendiceal fat stranding, and the CT appendicitis score showed considerable differences. There is 1 study in the literature comparing surgical and medical treatment groups, and as a result, only the presence of appendicolith demonstrated a significant difference in both groups.[12] However, in this study, the selection of the initial treatment was left to the patient's voluntary preference rather than the surgeon's decision, whereas in our study, the surgeon selected the initial treatment according to the severity of the patient's clinical and examination findings. The different results between the studies might stem from the diversity in the approaches toward patient groups mentioned above.

Surgeons use the Alvarado scoring system when determining the surgical treatment in acute appendicitis. The Alvarado scoring system, which reflects a kind of appendicitis severity, is based on laboratory values, symptoms, and findings of physical examination. In our hospital, surgeons prefer surgical treatment in patients with the Alvarado score ≥7. In the present study, all evaluated parameters were graded according to their severity, and these grades were

Table 3. Results of ROC curve analysis, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio and determination of cut-off values

Variables	AUC (95% CI)	SE	P	Cut-off point	Sensitivity	Specificity	+LR	–LR
Appendiceal diameter	0.699 (0.613-0.785)	0.044	<.001	≥13 mm	39.74%	93.33%	5.96	0.65
CT appendicitis score 1	0.742 (0.659-0.824)	0.042	<.001	≥8	78.21%	63.33%	2.13	0.34
CT appendicitis score 2	0.609 (0.423-0.794)	0.094	.101	≥7	78.57%	60.87%	2.01	0.35
Model	0.745 (0.671-0.819)	0.038	<.001		69.23%	71.67%	2.44	0.43

CT appendicitis score 1 (comparison of medical treatment and surgical treatment groups), CT appendicitis score 2 (comparison of successful and unsuccessful medical treatment groups).
ROC, receiver operating characteristic curve; AUC, area under the curve; SE, standard error; +LR, positive likelihood ratio; –LR, negative likelihood ratio; CT, computed tomography.

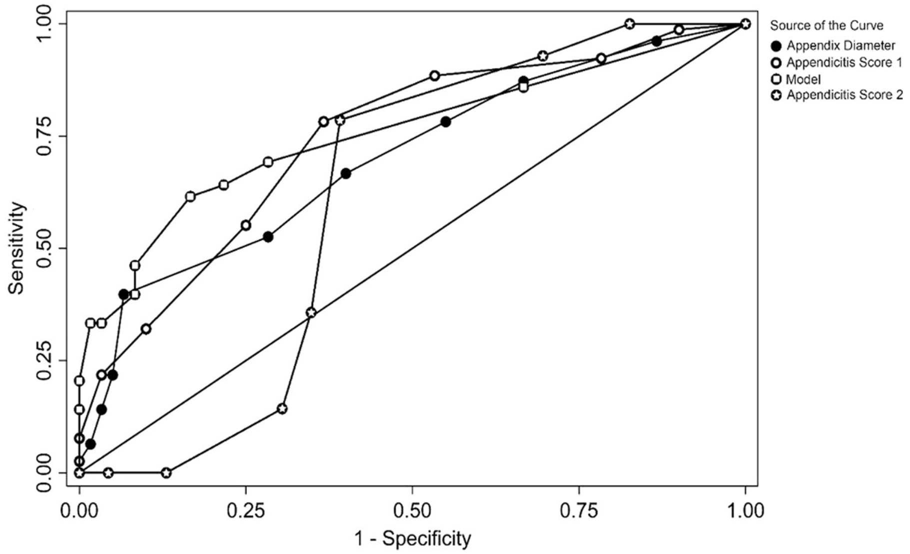

Figure 7. ROC analysis of appendiceal diameter, appendicitis score 1 (comparison of medical treatment and surgical treatment groups), model, and appendicitis score 2 (comparison of successful and unsuccessful medical treatment groups). ROC, receiver operating characteristic curve.

summed so as to obtain the CT appendicitis score. It is intended that the CT appendicitis score, which carries the information of all parameters, gives us an idea about the severity of acute appendicitis, such as the Alvarado score. To our knowledge, there has been no such radiological evaluation in the literature so far. In our statistical analysis, the CT appendicitis score showed a significant difference between the surgical and medical treatment groups ($P < .001$). The CT appendicitis score ≥8 indicates that surgeons may prefer surgery with 78.21% sensitivity and 63.33% specificity. Considering the retrospective nature of this study, we could not compare the Alvarado score and the CT appendicitis score. Future larger studies are needed to compare these both scoring systems.

Surgery can be preferred with 69.23% sensitivity and 71.67% specificity in the model generated with parameters (diameter ≥13 mm, appendicolith, and intra-abdominal free fluid) that are found to be significant while comparing surgical and antibiotic treatment groups.

In our study, while successful and unsuccessful medical treatment groups were compared, the severity of mural enhancement indicated a noticeable difference. In the literature, there are studies in which the presence of appendicolith ($P = .019$)[12] and appendix diameter ($P = .031$)[13] showed significant differences. In a study with pediatric cases, there was no radiological finding that demonstrated a significant difference between successful and unsuccessful medical treatment groups.[14] The incompatibility within these results of the studies may be due to the possible differences in antibiotic administration routes (oral/IV), the type of antibiotic, the duration of treatment, and the approaches of the surgeons to the treatment.

Table 4. Univariate and multivariable predictors of surgical treatment

	Univariate analysis			Multivariable analysis		
Independent variables on CT scan	OR	95% CI	P	OR	95% CI	P
Appendix diameter						
10-12 mm	1.64	0.74-3.63	.220	-	-	-
≥13 mm	12.31	3.69-41.08	.001	5.1	1.58-16.50	.006
Adjacent organ findings	2.24	1.02-4.90	.622	-	-	-
Severity of periappendiceal fat stranding						
Mild	0.45	0.70-2.89	.401	-	-	-
Severe	1.58	0.25-10.20	.626	-	-	-
Intraluminal appendicolith	5.85	1.90-18.03	.002	4	1.17-13.63	.027
Intra-abdominal free fluid	4.02	1.82-8.86	.001	3.04	1.28-7.20	.011

According to the studies, the recurrent disease in medical treatment patients was usually in the first 6 months, whereas the rate of recurrent disease was only 3% during the 6-month to 2-year period.[13] Therefore, we have determined the follow-up period as at least 6 months. The follow-up period and the recurrence rates of the previous studies seem to have been 17% at 2 years, 21% at 4 years, 26% at 1 year, and 44% at 6 months.[13-16] Also, in a randomized controlled study, the recurrent disease rate was 27.3% at 1 year, 34% at 2 years, 35.2% at 3 years, 37.1% at 4 years, and 39.1% at 5 years.[5-7,9] In our study, the rate of recurrent disease was 38% after at least 6 months of follow-up and was found to be higher than previous studies. The highest follow-up period in our study was 4 years. If all patients had been followed up for 4 years, a higher rate of recurrent disease could have been achieved. This variability in the results of the studies can be explained by differences in antibiotic administration routes (IV/oral), type of antibiotic (amoxicillin–clavulanate, ceftriaxone–metronidazole, ciprofloxacin–metronidazole, ertapenem, or cefdinir–metronidazole), and duration of treatment. Performing the treatment entirely by IV route can be a factor that positively affects the success of medical treatment. Furthermore, the severity of acute appendicitis in patients may vary in each study; therefore, the response to the treatment may also be different. Since the recurrence rate rises as the follow-up time increases, it is natural that our study has high recurrence rates compared to the other studies with short follow-up time.

The study has several limitations. First, it is a retrospective analysis from a single center. Second, a limited number of cases of successful and unsuccessful medical treatment were available, which precluded a proper analysis of predictors in this subset. Third, in evaluating the presence of intra-abdominal free fluid, the minimal free fluid that can be seen due to ovulation in young female patients created limitation. Fourth, the severity of the mural enhancement was visually evaluated, and quantitative analysis was not performed. Fifth, assessment of oral contrast agent passage into the appendix lumen is helpful in the interpretation of acute appendicitis; however, oral contrast material was not used in CT protocol in this study. Sixth, there are the differences in the approaches of the surgeons to the treatment (since treatment decision is not based on objective criteria), the antibiotic administration routes, the type of antibiotic, and the duration of treatment.

In conclusion, although the recurrence rate in acute appendicitis cases treated with antibiotics is higher in our study than the other studies, we believe that antibiotic treatment is an alternative to surgery for uncomplicated acute appendicitis cases. CT findings may be helpful in acute appendicitis cases about whose treatment surgeons are indecisive. We can recommend surgical treatment in patients with appendix diameter ≥13 mm, intra-abdominal free fluid, appendicolith, high CT appendicitis score, and severe mural enhancement. Larger studies are needed for a more thorough assessment.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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