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The predictive value of Alvarado score, inflammatory parameters and ultrasound imaging in the diagnosis of acute appendicitis

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ABSTRACT

Objective: Acute appendicitis (AA) is one of the most common surgical emergencies. Despite extraordinary advances in modern investigations, the accurate diagnosis of AA remains an enigmatic challenge. The aim of this study was to compare and evaluate the diagnostic accuracy of inflammatory parameters [C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR)], ultrasound (US) and Alvarado score (AS) in reducing the rate of negative appendectomies.

Material and Methods: Two hundred seventy-eight patients were included in this study. Patients were separated into two main groups as the surgery group (n=184) and non-operative group (n=94). Complete blood count, ESR and PCT levels were assessed, abdominal US was performed and AS was calculated for all patients.

Results: In the surgery group, clinical predictive factors for histopathologic results such as AS ≥7, AA signs on US, neutrophilia and leukocytosis were significant. Neutrophilia and leukocytosis had the highest accuracy rate among these factors. Inflammatory parameters were not predictive for histopathologic results, although higher CRP and PCT levels were significant in perforated and necrotizing appendicitis. Multifactorial regression analyses showed that AS was not of significant predictive value in the non-operative group.

Conclusion: There was no superiority of AS and/or US in the diagnosis of AA. Recent findings have shown the most reliable parameters in the diagnosis of AA to be primarily 'neutrophilia' and secondarily 'leukocytosis'. Other results of this study indicated that inflammatory parameters (CRP, PCT, ESR) were not superior to other parameters but CRP and PCT levels were significantly high in complicated cases.

Keywords: Alvarado score, acute appendicitis, C-reactive protein, ultrasound

INTRODUCTION

Abdominal pain is one of the main causes of emergency department admissions and acute appendicitis (AA) is one of the most frequent surgical emergencies. The mortality and morbidity rates increase when the surgical intervention is delayed in AA (1, 2). Although the diagnosis of AA is based on history, clinical course, and laboratory tests, the accurate diagnosis of AA remains challenging. A clinical decision to operate leads to the removal of a normal appendix in 15–30% of cases (3). It has been claimed that diagnostic aids can dramatically reduce the number of appendectomies in patients without appendicitis, the number of perforations and the time spent in the hospital (2). The main aids in this regard include inflammatory parameters, laparoscopy, diagnostic scoring systems and ultrasound (US); each with differences in availability, settings, advantages and disadvantages (4).

As an imaging technique, ultrasound is considered to be substantially useful (5). The most commonly used tests are white blood cell count and serum C-reactive protein (CRP) levels. Erythrocyte sedimentation rate (ESR) serves as an indicator of inflammation and procalcitonin (PCT) levels have also been used recently (6-8).

The gold standard in the diagnosis of AA is histopathologic evaluation of the specimen after surgery. However, a scoring system that is cost effective, repeatable, and can be applied quickly in the preoperative period is quite important in the AA diagnosis algorithm especially for young residents and emergency physicians working in rural areas (9, 10).

This study was designed to investigate the sensitivity, specificity, positive and negative predictive values of the Alvarado score (AS), which can be used repetitively and rapidly for AA diagnosis along with US, which is cost-effective and highly reliable, and laboratory parameters.

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MATERIAL AND METHODS

Study Groups and Design

This prospective study was conducted as an annual cross-sectional study at an urban, tertiary care emergency department (ED) with an annual census of 220,000. All adults examined in the emergency department and suspected of having AA were assessed for possible inclusion in the study. Patients were excluded if one of the following criteria were present; age less than 15 years (no upper age limit), analgesic treatment within 24 hours, past history of abdominal surgery or inflammatory bowel disease or chronic systemic disease, hemodynamic instability, inability to understand the information about the protocol and/or refusal to consent. In addition to these criteria, patients who refused the operation or medical treatment and whose diagnosis has been confirmed not to be AA were excluded from the study.

Standardized data collection forms were used throughout the study and were filled-in by emergency medicine residents (EMRs) based on hospital files. Data collection forms included demographic information, symptoms and signs of the patients, and laboratory test results. All the physicians participating in the treatment of the patients were blinded to the study. Blood samples were obtained from all patients included in the study for complete blood count (CBC) including white blood cell (WBC) count, CRP, ESR and PCT levels and abdominal ultrasound was carried out by senior radiologists. The primary physician of the patient ordered all laboratory tests and radiological examinations. The calculated Alvarado Score (Table 1) was not included in the data collection forms, but all of the elements of the Alvarado score were included (11). The ultimate diagnosis of patients treated by surgical methods was based on histologic examination of the excised appendix. The histologic criterion for AA was inflammatory reaction with polymorphonuclear leukocytes in the mucosa layer of the appendix and edema (12). The appendix was accepted as perforated if the surgeon's operative report has stated so. Patients with no pathologic evidence of appendix inflammation were accepted as having undergone negative appendectomies. In addition, a patient was defined as having a normal appendix when s/he was discharged from the ED without surgery and seen in a non-operative consultation 7 days later. These patients were followed-up by telephone interviews four weeks after the index visit to confirm that appendicitis was ruled out.

The patients included in the study were divided into two groups; one being patients treated with surgical appendectomy and the other being those who were followed-up in the emergency observation unit and discharged without operation. In both groups, the patients were subdivided as those with an Alvarado score ≤6 and those with ≥7, while the surgery group patients were further subdivided into those with a normal appendix and those with definite appendicitis. Comparisons were made in terms of Alvarado score, ultrasound results, WBC count, neutrophil dominance, CRP, PCT, ESR levels; and the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy in the groups.

Table 1. Alvarado score

Symptom	Score
Migration of pain to right lower quadrant	1
Nausea, vomiting	1
Anorexia	1
Sign	
Tenderness in right iliac fossa	2
Rebound tenderness	1
Elevated temperature (≥37.3°C)	1
Laboratory test	
Leukocytosis	2
Differential leukocyte count (neutrophils ≥75%)	1
Total	10

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences software version 11.5 (SPSS Inc; Chicago, IL, USA). The diagnostic accuracy for each group was compared using the Pearson chi-square test or Fisher's exact chi-square test. A value of $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 303 consecutive patients with right lower quadrant pain met the inclusion criteria. Eight patients were excluded due to a definitive diagnosis other than AA in the initial evaluation, four were excluded due to refusal of medical or surgical treatment that was offered by the primary physician. Thirteen non-operative patients who did not comply with our outpatient clinic protocol and/or could not be followed-up were excluded. Of the remaining 278 patients, 184 (66.2%) patients underwent surgery while 94 (33.8%) were followed-up without surgery. Within the 278 patients included for evaluation, 121 (43.6%) were male and 157 (56.4%) were female, with a mean age of 32.2±11.8 years (range 15-82 yrs). The baseline characteristics are summarized in Table 2. Pain was associated with nausea and vomiting (N/V) in 133 patients (47.8%), which was the most common presenting symptom and rebound tenderness was detected in 183 patients (66.8%), which was the most common sign. The duration of illness in the study population ranged from 1 to 7 days with a mean of 2 days. Among the surgery patients, 2 were pregnant, 2 had plastron appendicitis and 1 patient had Amyand's Hernia (AA in an incarcerated inguinal hernia).

The Alvarado scores (AS) for surgery and non-operative groups are summarized in Table 3. The surgery and non-operative groups were sub-divided as AS ≤6 and ≥7, and it was determined that a score of ≥7 was significantly associated with the diagnosis of AA ($p<0.001$).

The abdominal US findings of the surgery and non-operative groups are summarized in Table 3. Ultrasonographic signs of AA were evident in 98 patients (53.2%) in the surgery group, and in 14 patients (13%) in the non-operative group. The most common ultrasonographic finding other than AA was presence of pericecal free fluid.

Table 2. Baseline characteristics of the study population

Variable	Total (n=278)
Age (year)	32.2±11.8 (15-82)
Male	31.3±10.9
Female	32.9±12.32
Onset of symptoms (day)	2 (1-7)
Pain migration to the right lower quadrant	75 (27.0%)
Anorexia	123 (44.2%)
Nausea, vomiting	133 (47.8%)
Rebound tenderness	183 (65.8%)
Elevated temperature (≥37.3°C)	22 (7.9%)
Leukocytosis	180 (64.7%)
Differential leukocyte count (neutrophils ≥75%)	182 (65.4%)

Table 3. Distribution of Alvarado scores and US findings in the surgery and non-operative groups

	Surgery group n=184 (66.2%)	Non-operative group n=94 (33.8%)
Alvarado Score		
Score ≤6	103 (55.9)	80 (85.2%)
Score ≥7	81 (44.1%)	14 (14.8%)
US diagnosis		
Acute appendicitis (+)	98 (53.2%)	12 (12.8%)
Acute appendicitis (-)	86 (46.8%)	82 (87.2%)
US findings		
Normal appendix	62 (33.6%)	63 (67.0%)
Acute appendicitis	98 (53.2%)	12 (12.8%)
Pericecal free fluid	19 (10.3%)	9 (9.6%)
Mesenteric thickening	5 (2.7%)	2 (2.1%)
Mesenteric lymphadenopathy	0	8 (8.5%)

US: ultrasound

Table 4. Histopathologic diagnosis of the surgery group

Histopathologic diagnosis	n=184
Normal appendix	15 (8.2%)
Acute appendicitis (luminal, mucosal, submucosal inflammation)	123 (66.8%)
Acute suppurative appendicitis	30 (16.3%)
Acute necrotizing appendicitis	11 (6.0%)
Perforated appendicitis	5 (2.7%)

Results of the Surgery Group

The histopathology reports of the excised appendix in the surgery group are summarized in Table 4. Of the 184 patients in the surgery group, 123 had histologically proven non-perforated (simple) appendicitis, 30 had suppurative appendicitis, 11 had necrotizing and 5 had perforated appendicitis, and 15 had a normal appendix.

The clinical factors that may be useful in the diagnosis of AA are summarized in Table 5. According to these, AS ≥7, the presence of ultrasonographic signs of AA, leukocytosis and neutrophil dominance were significant in the diagnosis of AA (AS≥7 and US signs $p<0.05$, leukocytosis and neutrophil dominance $p<0.001$).

According to histopathology reports, rebound tenderness and leukocytosis were the most sensitive clinical parameters in the surgery group whereas the least sensitive factors were fever and ESR. The most specific clinical parameters were determined as PCT elevation and AS. The highest accuracy rates were calculated for neutrophil dominance and leukocytosis.

The diagnostic performances of the clinical factors and AS, which were statistically significant in estimating the diagnosis of AA according to histopathology reports, are summarized in Table 6. The addition of ultrasonographic signs of AA to AS did not cause a significant change in the p value, whereas including leukocytosis and neutrophil dominance caused a significant change in the p value ($p<0.001$).

The results of multivariate logistic regression analysis performed in order to define the effect of clinical factors in estimating histopathology reports in the surgery group are shown in Table 7. The best combination in the estimation of histopathology reports in the surgery group was determined to be leukocytosis and neutrophil dominance, and the most decisive variable was neutrophil dominance followed by leukocytosis. In the multivariate logistic regression analysis it was also seen that AS did not have decisive properties in the estimation of histopathologic results.

CRP, PCT and ESR values of the surgery group according to histopathology reports are shown in Tables 8 and 9. According to these results, CRP, PCT and ESR elevations did not have a diagnostic value in estimating AA or a normal appendix. However, CRP and PCT elevation were found to have a significant impact on the diagnosis of perforated and necrotizing appendicitis ($p<0.05$) while ESR elevation did not reveal a similar result ($p=0.110$).

Results of the Non-operative Group

The diagnoses in the non-operative group are summarized in Table 10. Thirteen patients in the non-operative group who did not comply with our outpatient clinic protocol and/or could not be followed-up were excluded. Forty-five patients in the non-operative group (47.9%) resolved spontaneously and did not relapse during the non-operative treatment period. The most common causes of abdominal pain in the non-operative group were found to be related to genitourinary system pathologies (33 patients, 35.1%). Only four (3.7%) non-operative group patients underwent surgery with a diagnosis of AA during the non-operative period.

In the non-operative group, the presence of ultrasonographic signs of AA was found to be statistically significant on uni-

Table 5. Comparison of clinical factor single variable effects in predicting acute appendicitis in surgery group and non-operative group

	Alvarado Score		US		Leukocytosis		DLC (neutrophils ≥75%)	
	SG	NOG	SG	NOG	SG	NOG	SG	NOG
Sensitivity	47%	50%	56%	75%	78%	75%	80%	75%
Specificity	93%	86%	80%	88%	86%	56%	80%	50%
Positive predictive value	99%	13%	97%	21%	98%	7%	98%	7%
Negative predictive value	14 %	97%	14%	99%	26%	98%	27%	98%
Diagnostic accuracy	51%	97%	58%	87%	79%	56%	80%	51%
p	0.002	0.118	0.007	0.01	<0.001	0.329	<0.001	0.617

US: ultrasound; DLC: differential leukocyte count; SG: surgery group; NOG: non-operative group

Table 6. Diagnostic performances of clinical factors together with Alvarado score in the surgery group and non-operative group

	Alvarado score+ US		Alvarado score+ Leukocytosis		Alvarado score+DLC (neutrophils ≥75%)	
	SG	NOG	SG	NOG	SG	NOG
Sensitivity	100%	25%	100%	0%	100%	0%
Specificity	0%	99%	0.0%	100%	0.0%	100%
Positive predictive value	91%	50%	91.8%	-	91.8%	-
Negative predictive value	-	97%	-	96%	-	96%
Diagnostic accuracy	91%	96%	91.8%	96%	91.8%	96%
p	0.013*	0.066*	0.181*	0.208*	0.196*	0.185*
	0.011†	0.010†	<0.001‡	0.539§	<0.001§	0.724‡

DLC: differential leukocyte count; *: P value of Alvarado Score, †: P value of US, ‡: P value of Leukocytosis, §: P value of DLC

Table 7. Multivariate logistic regression models for the prediction of acute appendicitis based on pathologic reports in the surgery group

	Odds ratio	95% confidence interval	p
Model 1			
US	2.855	0.674-12.091	0.154
Leukocytosis	4.554	0.929-22.323	0.062
Neutrophils ≥75%	6.190	0.938-40.845	0.058
Alvarado Score	2.080	0.178-24.362	0.560
Model 2			
US	2.830	0.677-11.831	0.154
Leukocytosis	5.362	1.169-24.582	0.031
Neutrophils ≥75%	7.790	1.346-45.087	0.022
Model 3			
Leukocytosis	5.323	1.204-23.531	0.027
Neutrophils ≥75%	10.194	1.869-55.605	0.007

US: ultrasound

Table 8. CRP, PCT and ESR measurements of the surgery group according to histopathologic reports

	Normal appendix	Acute appendicitis	p
CRP level	0.6 (0.13-12.0)	1.5 (0.4-25.0)	0.337
PCT level	0.12 (0.10-0.43)	0.10 (0.10-21.19)	0.663
ESR level	15.0 (2.0-76.0)	9.0 (0.10-111.0)	0.120

CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate

variate analysis of clinical factors in predicting appendectomy (Table 5). When the diagnostic performances of clinical factors were examined along with AS in estimating appendectomy, only the addition of ultrasonographic signs of AA to AS was found to be statistically significant (Table 6). In the multivariate logistic regression analysis of clinical factors in estimating histopathology reports, the presence of ultrasonographic signs of AA was determined as the best clinical parameter in estimating whether appendectomy was necessary or not in the non-operative group (Table 11).

DISCUSSION

There are several laboratory and radiologic tests for the diagnosis of AA, and both their number and quality are expected to increase with achievements in technology. However, an exact preoperative diagnosis of AA is still challenging and delay in surgery continues to be the main cause of morbidity and mortality. Varying rates of negative appendectomy have been reported in the literature as 15-25%, increasing up to 50% in children and women of reproductive age (13, 14).

Table 9. The distribution of elevated CRP, procalcitonin and ESR levels according to histopathologic diagnosis of surgery group

	Normal appendix n=15	Uncomplicated appendicitis n=153	Complicated appendicitis (Perforated+ Necrotizing) n=16	p
Elevated CRP	46.7% (n=7)*	56.9% (n=87)†	87.5% (n=14)*,†	0.037
Elevated Procalcitonin	0% (n=0)*	7.2% (n=11)†	43.8% (n=7)*,†	<0.001
Elevated ESR	33.3% (n=5)	24.8% (n=38)	50.0% (n=8)	0.110

*: The difference between the normal appendix group and complicated appendicitis group was statistically significant (p<0.05), †: The difference between uncomplicated appendicitis group and complicated appendicitis group was statistically significant (p<0.05). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

Table 10. Final diagnosis in the non-operative group

Non-operative group	n=94
Gynecologic	18 (19.1%)
Urologic	15 (16.0%)
Gastrointestinal	7 (7.4%)
Musculo-skeletal	5 (5.3%)
Miscellaneous	45 (47.9%)
Acute Appendicitis (Surgery)	4 (4.3%)

Table 11. Multivariate logistic regression models for the prediction of whether to perform appendectomy or not in the non-operative group

	Odds ratio	95% confidence interval	p
Model 1			
US	33.195	2.162-509.571	0.012
Leukocytosis	1.337	0.052-34.675	0.861
Neutrophils ≥75%	1.005	0.036-27.804	0.998
Alvarado score	10.229	0.503-207.864	0.130
Model 2			
US	33.199	2.165-509.152	0.012
Leukocytosis	1.340	0.085-21.222	0.835
Alvarado score	10.241	0.559-187.709	0.117
Model 3			
US	34.547	2.302-518.372	0.010
Alvarado score	11.761	0.847-163.319	0.066
Model 4			
US	21.545	2.056-225.786	0.010

US: ultrasound

Clinical history and physical examination are the cornerstones of the diagnosis of AA. Although the most consistent symptoms reported in patients with AA is right lower quadrant pain together with N/V, only 50% of patients have this typical presentation. Other clinical symptoms and signs differ according to the position of the appendix and none of them are specific to AA (15). In the current study, the most common symptoms were anorexia and N/V, and the most common sign was rebound tenderness. Contrary to the literature, pyrexia was seen in only 8% of the current study population. Fever is a later onset symptom of AA and the patients' body temperatures were measured on admission, which may explain this low rate.

There are many scoring systems used in the diagnosis of AA based on signs and symptoms. A large number of scoring systems have been proposed among which the AS is the most well-known with the best performance in validation studies (9, 16). In the current study, the mean AS of all cases was 6 and the AS of the surgery group was significantly higher than that of the non-operative group.

Ultrasound has been used in the diagnosis of AA since 1980. Wide variations in the sensitivity, specificity, positive and negative predictive values of US in the diagnosis of AA have been reported in the literature, ranging between 55-96%, 72-98%, 81-96% and 28-88%, respectively (17, 18). The sensitivity, specificity, positive and negative predictive values of US in the current study were determined as 56.2%, 80%, 96.6% and 14%, respectively, which are compatible with previous studies except for the negative predictive value, which is far below than usually described in the literature. This could be due to the dichotomization of the ultrasound report in cases that were conclusive and not indicative of the diagnosis of AA, thus hampering the decision of the radiologist in more complex cases. This low negative predictive value requires caution in ruling out the diagnosis of AA.

In a study investigating the reliability of US and AS in the diagnosis of AA by Ozkan et al. (16), AS and US were reported to have a diagnostic accuracy of 57.7% and 65.7%, respectively. In the current study, diagnostic accuracy of AS and US were calculated as 51.1% and 58.8% in the surgery group, and 84.0% and 87.2% in the non-operative group, respectively. In both groups, when these two tests were combined the diagnostic accuracy increased to 91.8% in the surgery group and 95.7% in the non-operative group.

Initial demargination of peripheral WBCs caused by catecholamine and cytokine release accounts for leukocytosis in most patients with AA. Although leukocytosis is not diagnostic for any particular illness, its presence is a common finding in appendicitis. Leukocytosis with neutrophil dominance has been found to be highly predictive of perforated appendicitis in many studies (19). The sensitivity and specificity values of neutrophil dominance found in the current study are compatible with the literature. A substantial number of scoring systems quote WBC count as an inflammatory parameter for the evaluation of AA (20). In the current study, AS was evaluated together with leukocytosis and neutrophil dominance in the diagnosis of AA. In the multivariate logistic regression analysis, it was determined that the AS has no decisive role in the pre-

diction of histopathologic results. The PPV and accuracy rate of AS+leukocytosis, and AS+neutrophil dominance was found to be 91.8%. Moreover, the addition of both leukocytosis and neutrophil dominance to AS was found to cause a statistically significant change in the p value of AS. However, leukocytosis and neutrophil dominance are the most decisive variables and leukocytosis+neutrophil dominance was found to be the best combination to predict the histopathologic results in the surgery group. Therefore, patients suspected to have AA, with AS ≥7 and leukocytosis+neutrophil dominance should definitely be re-evaluated, and the threshold for laparotomy must be lowered.

There have been conflicting results from various reports that investigated the value of CRP in improving the diagnostic accuracy of AA (21). Preoperative elevated CRP levels have been reported to aid the diagnosis of AA. The overall sensitivity of CRP in the literature ranges from 40–99% with a specificity of 27–90%. Based on the available literature and the results of this current study, CRP is a test with moderate diagnostic accuracy that is slightly inferior to the total leukocyte count. Preoperatively elevated CRP levels can aid the diagnosis of AA.

The diagnostic value of PCT in AA in adolescents or adults has rarely been studied (6). Over the course of an inflammatory process, bacterial invasion of the appendix wall is followed by release of bacterial endotoxins (22). As the bacterial endotoxins are one of the most potent factors known to stimulate an increase in PCT concentration, PCT levels are expected to rise in AA. However, the fact that half of the cases with AA in the current study had a PCT level of <0.5 ng/mL may be in line with current theories. It is suggested that appendicitis either has a viral origin or that risk factors such as low-fiber diet cause stool retention in the appendix by slowing intestinal transit time, thus, not leading to an increase in PCT levels (22). On the other hand, in the surgery group, the PCT levels were significantly high in cases of perforated and necrotizing AA (7 of 16 cases). These levels were seen to be not only higher than histologically normal appendix cases but also higher than non-complicated AA cases. In a study by Kafetzis et al. (22), PCT values above 0.5 ng/mL were considered a good prognostic factor for the development of complications, i.e., perforation or necrotic changes. Similar results for PCT were obtained in the current study in patients who developed complications during the course of AA.

CONCLUSION

The AS and abdominal US have no superiority to each other both in the diagnosis of AA and in reducing the rate of negative appendectomy. The AS is however a useful tool in clinical decision-making, especially when US is not available. Neutrophil dominance and leukocytosis are the most reliable and effective parameters of AS. Although CRP and PCT have limited value in patients with suspected AA and should be interpreted in a different way in different group of patients, these two inflammatory parameters could be important discriminators in cases of complicated appendicitis.

Ethics Committee Approval: Ethical approval was obtained from the Regional Ethics Review Committee before the commencement of the study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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