

Effect of Alvarado Score on the Negative Predictive Value of Nondiagnostic Ultrasound for Acute Appendicitis

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Abstract

Background: The purposes of this study were to calculate the negative predictive value (NPV) of nondiagnostic ultrasound (US) in patients with suspected appendicitis and to identify the clinical factors that were associated with the nondiagnostic US. **Methods:** We conducted a retrospective review of 412 patients who had graded-compression appendiceal US performed during January 2017 and December 2017. The NPV of the nondiagnostic US in combination with clinical parameters was calculated. Multivariate regression analysis was used to determine the independent predictors for the nondiagnostic US. **Results:** The US exam was nondiagnostic in 64.8% of the patients, giving an NPV of 70.8%. The NPV of nondiagnostic US increased to 96.2% in patients who had an Alvarado score of <5. The patients who did not have migratory pain, did not have leukocytosis, and had a pain score of <7 were more likely to have a nondiagnostic US study ($P < 0.001$). **Conclusion:** Alvarado score had an inverse effect on the NPV of nondiagnostic appendiceal US. Patients who had nondiagnostic US and Alvarado score of <5 were very unlikely to have appendicitis. Active clinical observation or re-evaluation rather than immediate computed tomography may be a safe alternative approach in these low-risk patients. However, the Alvarado score itself was not a predictive factor of nondiagnostic US. The absence of migratory pain, absence of leukocytosis, and low pain score were the independent predictors of nondiagnostic appendiceal US.

Keywords: Alvarado score, appendicitis, negative predictive value, nondiagnostic ultrasound, ultrasound

INTRODUCTION

Early diagnosis and prompt treatment of acute appendicitis are important to reduce morbidity and mortality from perforation and abscess formation.^[1] Although computed tomography (CT) is considered to be a modality of choice due to its excellent diagnostic performance,^[2,3] there is growing concern about ionizing radiation exposure as well as contrast-induced nephropathy in patients who have a CT scan.^[4,5] Moreover, CT scan may not be generally available in a resource-limiting situation. Therefore, graded-compression ultrasound (US) has been suggested as the first imaging test and followed by selective CT if the US is nondiagnostic or equivocal.^[6,7]

In clinical practice, 65%–71% of all US examinations fail to demonstrate the appendix or cannot demonstrate the whole length of appendix.^[8–11] This condition is commonly

regarded as a nondiagnostic US examination. In these patients, the decision to perform a CT scan may be very challenging. A combination of US findings and the clinical predictive score would be helpful for the patient triage to CT scan, which can help to make effective use of both imaging modalities.

The purposes of this study were

1. To calculate the negative predictive value (NPV) of nondiagnostic US alone and when it is combined with the clinical parameters, particularly the Alvarado score
2. To identify the clinical factors that were associated with nondiagnostic US in patients with suspected appendicitis.

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MATERIALS AND METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Committee on Human Rights Related to Research Involving Human Subjects (ID 06-61-73). The informed consent was waived. The records of 502 patients who had graded-compression appendiceal US from January 2017 to December 2017 were retrieved from our radiology database. Ninety patients were excluded because of inaccessible follow-up medical records ($n = 45$) and incomplete medical records ($n = 45$).

The medical and pathology records were reviewed for patient age, gender, weight, body mass index, duration of symptoms, Alvarado score, surgical diagnosis, pathological diagnosis, and patient disposition. The Alvarado score is a diagnostic score that is based on the symptoms (migratory pain, anorexia, nausea, and/or vomiting), signs (tenderness, rebound tenderness, and elevated body temperature), and laboratory findings (leukocytosis and left shift).^[12] One point was given to the presence of each indicator, except two points for tenderness and leukocytosis, making a total score of 10. A higher score means a higher probability of appendicitis.

The imaging studies were reviewed for US visualization of appendix, relevant US findings, US diagnosis, other imaging modalities performed, and their impression. The definitive diagnosis of appendicitis was based on the surgical pathology in patients who had surgery and on abdominal CT or clinical follow-up at 3 months after emergency department (ED) admission for those who did not have surgery.

All US examinations were performed with one of the two US systems: Aplio 500 system (Toshiba Medical Systems, Tokyo, Japan) with curved transducer (C6-2 MHz) and linear-array transducer (L14-3 MHz or L11-3 MHz) and Xario 200 scanner (Toshiba Medical Systems, Tokyo, Japan) with curved transducer (C6-1 MHz) and linear-array transducer (L14-5 MHz or L11-4 MHz). The standard US protocol includes a general scan of the right-sided abdomen and the pelvis using a curved transducer. Later, graded-compression US was performed using a linear-array transducer. This technique involved the examiners gently compressing the linear transducer using both hands, simulating deep palpation of the abdomen.^[13] The adjunctive maneuvers (posterior manual compression and left posterior oblique positioning) were also performed if the appendix was not visualized on supine scan.^[14,15] Between 8 am and 4 pm, a radiology trainee performed the US study under the direct supervision of the attending staff, whereas an on-call senior radiology trainee performed the US study during after-hours. The after-hours study was later reviewed and finalized by the attending staff on the following day. The visualization of the appendix was determined by the US operator at the time of the study. The appendiceal US report was categorized into

1. Diagnostic study (positive or negative for appendicitis)
2. Nondiagnostic study.

The diagnostic criteria for acute appendicitis include enlarged (outer-to-outer wall diameter >6 mm) and noncompressible appendix, hyperechoic change of periappendiceal fat, appendicolith, periappendiceal fluid, and appendiceal wall hyperemia [Figure 1].^[16]

Categorical data were expressed as count and percentage. Continuous data were summarized as mean and standard deviation or median and range. The sensitivity, specificity, NPV, and positive predictive value (PPV) with a 95% confidence interval (CI) were calculated. The assessment of differences was performed by using the Chi-square test or Fisher's exact test for categorical data and by student *t*-test or Mann–Whitney *U* test for continuous data. The variables noted to have differences in the Chi-square test or Mann–Whitney *U* test were used as dependent variables in univariate logistic regression analysis. Variables with a $P \leq 0.05$ were considered to be statistically significant, and then, stepwise multivariate logistic regression analysis was used to determine independent factors. All statistical analyses were performed using STATA version 13 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

Among 412 patients enrolled, 282 (68.4%) were female. The age ranged from 3 to 91 years (mean age of 43 years). One hundred and ten (26.7%) US examinations were performed by staff radiologists and the rest 302 (73.3%) US examinations were performed by radiology trainees. The demographic characteristics are summarized in Table 1.

Surgical pathology was able to confirm acute appendicitis in 215 (52%) patients. The rest of 197 (48%) patients did not have appendicitis on either follow-up imaging or clinical records. One hundred and forty-five patients (35.2%) had positive US for appendicitis. Among these, 137 patients (94.5%) had appendicitis (true-positive) and eight patients (5.5%)

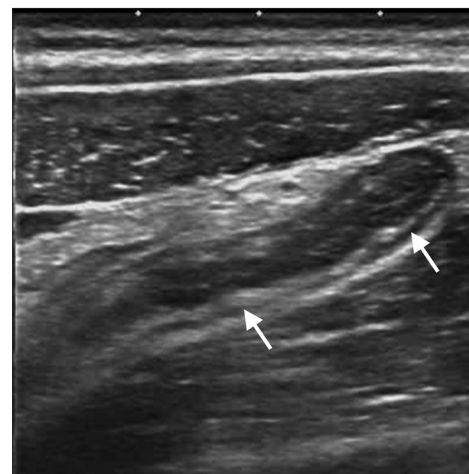


Figure 1: Acute appendicitis in a 20-year-old man. A graded compression sonogram showing an 8-mm noncompressible appendix (white arrows) with hyperechoic change of the surrounding fat

did not have appendicitis (false-positive). Two out of eight patients had ruptured diverticulitis ($n = 1$) and nonspecific right lower quadrant (RLQ) inflammation ($n = 1$). The other six patients had lymphoid hyperplasia. The US results were deemed nondiagnostic in 267 (64.8%) patients, of which 78 patients (29.2%) had appendicitis confirmed on pathology.

The US had an overall sensitivity of 63.7% (95% CI: 56.9%–70.2%), specificity of 95.9% (95% CI: 92.2%–98.2%), PPV of 94.5% (95% CI: 89.4%–97.6%), and NPV of 70.8% (95% CI: 64.9%–76.2%) for the diagnosis of acute appendicitis. The US studies performed by staff radiologists had higher sensitivity than the examinations performed by radiology trainees (76.2% vs. 58.6%; $P < 0.05$), but both of them had comparable specificity (95.7% vs. 96%), PPV (96% vs. 93.7%), and NPV (75% vs. 69.6%). Several clinical and laboratory parameters were analyzed to assess the effect on NPV of nondiagnostic US, as shown in Table 2.

Table 1: Baseline characteristics of the patients

Parameters	n (%)
Female	282 (68.4%)
Male	130 (31.6%)
Mean age, year (SD)	43 (19.7)
Mean weight, kg (SD)	60.9 (14.2)
Mean BMI, kg/m ² (SD)	23.8 (4.7)
Median duration of symptoms, hour (range)	24 (1-336)
Leukocytosis	290 (70.4%)
Fever	123 (29.9%)
RLQ pain	412 (100%)
Migratory pain	138 (33.5%)
Anorexia	141 (34.2%)
Nausea/vomiting	237 (57.5%)
Alvarado score	
0-4	60 (14.5%)
5-6	157 (38.1%)
7-8	156 (37.9%)
9-10	39 (9.5%)

SD: Standard deviation, BMI: Body mass index, RLQ: Right lower quadrant

When integrated with Alvarado score, the overall NPV of nondiagnostic US was 96.2% (95% CI: 86.8%–99.5%) in patients with Alvarado score of <5 and decreased to 74.1% (95% CI: 64.8%–82.0%) in patients with Alvarado score of 5–6, 58.4% (95% CI: 47.5%–68.8%) in patients with Alvarado score of 7–8, and 38.9% (95% CI: 17.3%–64.3%) in patients with Alvarado score of 9–10.

Female gender, absence of migratory pain, absence of anorexia, absence of leukocytosis, Alvarado score of <7 , and pain score of <7 were significantly associated with nondiagnostic US on univariate analysis. These variables were entered into a multivariate regression model. The absence of migratory pain, absence of leukocytosis, and pain score were the independent predictors of nondiagnostic US on multivariate analysis, as shown in Table 3.

DISCUSSION

The overall NPV of nondiagnostic US in our study was 70.8% which was lower than 84.5% reported by Cohen *et al.*^[1] Their study was performed in the pediatric population which usually has smaller body habitus and a lesser amount of adipose tissue. These two factors may increase the visualization of the appendix, therefore giving the higher NPV.

We found that the low clinical likelihood for acute appendicitis had an inverse effect on the NPV of nondiagnostic US. The NPV of nondiagnostic US increased to 89.3% in patients without leukocytosis and increased to 96.2% in patients with an Alvarado score of <5 . Based on the proposed clinical decision rule to rule out appendicitis in patients with nondiagnostic US,^[17] the patients with nondiagnostic US can be discharged from the ED and followed up in the following day if they had fewer than two of the following factors: male gender, migration of pain to the RLQ abdomen, vomiting, and white blood cell (WBC) count higher than $12 \times 10^9/L$. The NPV of this rule was 84% in patients with inconclusive US. The absence of these factors would give the possible maximal Alvarado score of 6, which yielded an NPV of 74.1% in our study.

Table 2: Negative predictive value of nondiagnostic ultrasound in different clinical scenarios

Scenarios	All studies			Studies performed by radiologists			Studies performed by trainees		
	Studies (n)	True-negative (n)	NPV (95% CI)	Studies (n)	True-negative (n)	NPV (95% CI)	Studies (n)	True-negative (n)	NPV (95% CI)
Overall	267	189	70.8 (64.9-76.2)	60	45	75 (65.8-82.4)	207	144	69.6 (65.4-73.5)
No fever	194	142	73.2 (66.4-79.3)	44	36	81.8 (66.8-91.3)	150	106	70.7 (62.6-77.7)
No migratory pain	203	162	79.8 (73.6-85.1)	49	39	79.6 (65.2-89.3)	154	123	79.9 (72.5-85.7)
No anorexia	185	140	75.7 (68.8-81.7)	37	30	81.1 (64.3-91.4)	148	110	74.3 (66.4-81.0)
No nausea/vomiting	119	83	69.7 (60.7-77.8)	22	16	72.7 (49.6-88.4)	96	67	69.8 (59.4-78.5)
No leukocytosis	103	92	89.3 (81.7-94.5)	29	27	93.1 (75.8-98.8)	74	65	87.8 (77.7-93.9)
Alvarado score ≤ 4	52	50	96.2 (86.8-99.5)	14	14	100 (73.2-100)	38	36	94.7 (80.9-99.1)
Alvarado score 5-6	108	80	74.1 (64.8-82.0)	22	17	77.3 (54.2-91.3)	86	63	73.3 (62.4-82.0)
Alvarado score 7-8	89	52	58.4 (47.5-68.8)	18	12	66.7 (41.2-85.7)	71	40	56.3 (44.1-67.9)
Alvarado score 9-10	18	7	38.9 (17.3-64.3)	6	2	33.3 (6.0-75.9)	12	5	41.7 (16.5-71.4)

NPV: Negative predictive value, CI: Confidence interval

Table 3: Univariate and multivariate analyses of predictors for nondiagnostic ultrasound

Predictors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	Adjusted OR (95% CI)	P
Female gender	1.73 (1.12-2.67)	0.014	-	-
Migratory pain	3.41 (2.20-5.29)	<0.001	2.53 (1.58-4.07)	<0.001
Anorexia	1.56 (1.02-2.39)	0.042	-	-
Leukocytosis	4.75 (2.67-8.45)	<0.001	3.48 (1.85-6.54)	<0.001
Alvarado score	2.37 (1.55-3.61)	<0.001	-	-
Pain score	2.17 (1.42-3.32)	<0.001	2.14 (1.35-3.40)	<0.001

US: Ultrasound, OR: Odds ratio, CI: Confidence interval

We suggest that the integration of US results and clinical data has a significant impact on US performance and patient disposition. An Alvarado score of 5 was described as a useful clinical prediction rule to “rule out” appendicitis in all patient groups.^[18] The appendix tends to have a normal size and the signs of inflammation are not evident in the patients who had low Alvarado score and nondiagnostic US.^[19] An immediate CT scan may be avoided in these patients with an Alvarado score of <5 to reduce unnecessary radiation and iodinated contrast exposure.^[1,9,20]

Shah *et al.* studied 318 patients with nonvisualized appendix who had short-interval CT following the US. Appendicitis was diagnosed in 16% of their study population and only 0.6% had other important CT findings which required urgent surgery.^[21] They suggested serial physical examination, active clinical observation, and correlation with laboratory findings to further triage the patients.^[21] In our study, a second-line CT scan was performed in 25 patients who had nondiagnostic US and Alvarado score of <5. Only two of them had confirmed acute nonperforated appendicitis on both CT scan and pathology results. Neither of them had leukocytosis.

The incidence of appendicitis in our study was 52.2% which was slightly higher than previously reported data of 43%.^[22] The sensitivity, specificity, PPV, and NPV in our study were also comparable to previous data in 2010,^[22] which suggests a consistent diagnostic performance at our institution.

The relative chance of nondiagnostic US in patients who did not have migratory pain, who did not have leukocytosis, and who had pain score of <7 were 2.53, 3.48, and 2.14 times higher than those of their counterparts, respectively. Seventy-six percent of patients who had nondiagnostic US did not have migratory pain, 39% did not have leukocytosis, and 53.9% had pain score of <7. The migratory pain to the RLQ abdomen is regarded as a classic sign of appendicitis with a sensitivity of 43%, specificity of 84%, and NPV of 80%.^[17] This sign can be absent due to anatomical variation of the appendix or due to extreme patient age with atypical presentations.^[23] WBC count can also serve as a useful inflammatory biomarker for appendix inflammation. Previous literature found that patients who had normal appendix had lower WBC count than those

with inflamed or complicated appendix.^[24,25] The migratory pain had a negative likelihood ratio of 0.52, while an elevated WBC count (i.e., leukocytosis) had a negative likelihood ratio between 0.26 and 0.51 in the diagnosis of appendicitis.^[26,27] We postulated that the patients without migratory pain and leukocytosis were unlikely to have inflamed appendix, therefore reducing the chance of having diagnostic US results. The incidence of nondiagnostic US in our study was 64.8% which was at the lower end among the reported incidence of 65%–71%.^[8-11,19] The trend toward a lower nondiagnostic rate in our study might be related to the better US machine and the use of adjunctive US techniques. Nevertheless, the overall sensitivity of the US in our investigation is relatively low (64%). This lower sensitivity may be related to the US examiners' experience level. In 73% of our cases, the US examinations were performed by senior radiology trainees who had 2–3 years of US experience (approximately 200–300 abdominal scans). It was unclear if the US operators had performed adjunctive maneuvers correctly, or they had used other indirect supportive signs of appendicitis.^[28] Moreover, the higher sensitivity of previous studies may be related to publication bias (underreport studies with poor US sensitivity).

Several limitations should be noted. This study was conducted in a single academic center which could limit the generalization of the result. There was a lack of pathological proof in patients who did not have surgery. We considered these patients true negative after the follow-up records were reviewed up to 3 months after the initial ED admission. Some patients with overt clinical signs of appendicitis may proceed directly to the surgery without imaging workup. There was a relatively low number of patients with low Alvarado score which could limit the potential impact of our study. We did not assess the outcome of nondiagnostic US such as perforation rate, length of hospital stay, or total time from ED arrival to the final diagnosis.

CONCLUSION

The patients who had nondiagnostic US and Alvarado score of <5 were unlikely to have acute appendicitis. Active clinical observation or re-evaluation rather than immediate CT may be a safe alternative approach in a resource-limiting situation. Patients who did not have migratory pain, did not have leukocytosis, and had pain score of <7 were more likely to have nondiagnostic US. Validation of this data with a larger prospective study will aid the clinicians in the selection of imaging options in appendicitis.

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Conflicts of interest

There are no conflicts of interest.

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