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The role of Alvarado score in predicting acute appendicitis and its severity in correlation to histopathology: A prospective observational study

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Abstract
Background: Acute appendicitis (AA) remains the most common non-obstetric surgical emergency globally, imposing a significant burden on healthcare systems, particularly in low- and middle-income countries (LMICs) where access to advanced imaging is limited. While the Alvarado score (AS) is widely used for diagnostic triage, its capacity to predict not only the *presence* but also the *pathophysiological severity* of appendiceal inflammation as confirmed by histopathology remains inadequately explored.
Objective: This study aimed to: (1) quantify the diagnostic accuracy of the AS using histopathology as the gold standard; (2) establish the correlation between preoperative AS and postoperative histopathological severity; (3) identify optimal AS thresholds for predicting complicated appendicitis; and (4) evaluate the negative appendectomy rate across AS strata.
Methods: A prospective, single-center, observational cohort study was conducted at Al-Zahraa Teaching Hospital, Iraq, from January 2023 to June 2024. 320 adult patients with suspected AA underwent appendectomy within 24 hours of admission. AS was calculated prospectively by blinded residents. Histopathological grading (Grade 0-4: Normal to Perforated) was performed by two blinded, board-certified pathologists (Cohen's $\kappa = 0.91$). Statistical analysis included ROC curves, Spearman's correlation, and multivariate logistic regression.
Results: Histopathology confirmed AA in 294 patients (91.9%). At a cutoff of ≥7, AS demonstrated 92.1% sensitivity, 85.4% specificity, and an AUC of 0.931. A strong positive correlation existed between AS and histopathological grade (Spearman's $\rho = 0.782$; $p<0.001$). Multivariate analysis revealed AS ≥9 as the strongest independent predictor of complicated appendicitis (adjusted OR = 6.82; $p<0.001$). 89.6% of patients with AS ≥9 had gangrenous or perforated appendicitis. The negative appendectomy rate was 8.1%, with 84.6% occurring in the AS 5-6 group.
Conclusion: The Alvarado score is not only a highly accurate diagnostic tool but also a powerful prognostic indicator of disease severity. An AS ≥7 reliably indicates the need for surgery, while an AS ≥9 should trigger protocols for managing complicated disease. Integrating AS into clinical algorithms can optimize resource use, reduce unnecessary surgeries, and improve outcomes, especially in resource-limited settings.

Keywords: Alvarado score, acute appendicitis, diagnostic accuracy, histopathological correlation, disease severity, clinical prediction rule, surgical triage, complicated appendicitis, negative appendectomy rate, resource-limited settings

1. Introduction
Acute appendicitis, with a lifetime risk of 7-8% in Western populations, continues to challenge clinicians due to its variable presentation and potential for rapid progression to life-threatening complications [1, 2]. Timely diagnosis is paramount; delays can lead to perforation, peritonitis, sepsis, and increased mortality, while overdiagnosis results in unnecessary surgeries and resource waste [3-7].
Although imaging modalities like CT and ultrasound have improved diagnostic precision, their utility is constrained in LMICs by cost, radiation concerns, and limited availability [10-13]. In such contexts, clinical scoring systems like the Alvarado score comprising migratory pain, anorexia, nausea/vomiting, right lower quadrant tenderness, rebound pain, fever, leukocytosis, and neutrophilia offer a rapid, cost-effective, and reproducible alternative [14, 15].
While meta-analyses confirm the AS's diagnostic utility (pooled AUC ~0.88) [16], a critical gap exists in understanding its *prognostic* value. Histopathology, the diagnostic gold standard, reveals a spectrum of disease from catarrhal (Grade 1) to perforated (Grade 4),

each stage correlating with escalating clinical risk [19-23]. Yet, few studies have rigorously correlated preoperative AS with postoperative histopathological severity using blinded, validated methodologies [24, 25].

Study Objectives

1. To establish the diagnostic accuracy of the AS against histopathological gold standard.
2. To quantify, for the first time in an Iraqi cohort, the *strength and clinical significance* of the correlation between AS and histopathological severity grades.
3. To derive and validate an *actionable clinical threshold* (AS ≥9) for predicting complicated disease using multivariate analysis, controlling for key confounders.
4. To provide *practical, evidence-based recommendations* for reducing negative appendectomies and optimizing surgical preparedness in LMICs.

2. Methods

2.1 Study Design and Setting

This was a prospective, single-center, observational cohort study conducted at the Department of General Surgery, Al-Zahraa Teaching Hospital, Wasit Governorate, Iraq a tertiary referral center serving a predominantly rural and semi-urban population of approximately 1.5 million inhabitants. The hospital performs an average of 220-250 appendectomies annually and serves as the main surgical hub for the governorate.

The study was conducted over an 18-month period, from January 1, 2023, to June 30, 2024. All patients presenting to the Emergency Department (ED) with clinical suspicion of acute appendicitis were screened for eligibility by the on-call surgical team.

The study protocol was reviewed and approved by the Scientific and Ethical Committee of the College of Medicine, University of Wasit (Approval Reference: UOW-MED-ETH-2023-APP-07). Written informed consent was obtained from all participants prior to enrollment. The study adhered to the principles of the Declaration of Helsinki (2013) and followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research [1].

2.2 Study Population and Sampling

Inclusion Criteria

- Adult patients aged ≥18 years.
- Presenting with acute right lower quadrant (RLQ) abdominal pain of ≤72 hours duration.
- Clinical suspicion of acute appendicitis based on history and physical examination by the attending surgical resident.
- Underwent appendectomy (open or laparoscopic) within 24 hours of admission.

Exclusion Criteria

- History of previous appendectomy.
- Pregnant women (confirmed by β-hCG testing in all females of reproductive age).
- Patients with immunocompromising conditions (e.g., HIV, active chemotherapy, long-term corticosteroid use, organ transplant recipients).
- Patients with incomplete clinical, laboratory, or histopathological data.
- Patients diagnosed postoperatively with non-appendiceal pathology (e.g., Meckel's diverticulitis, ileocecal TB, ovarian torsion, Crohn's disease).

Sample Size Calculation

Based on a pilot study conducted at our institution (n=50) showing a correlation coefficient (r) of 0.65 between Alvarado score and histopathological grade, we calculated the required sample size using Pearson correlation formula with α=0.05, power=90%, and two-tailed testing. The minimum required sample was n=286. To account for potential dropouts or exclusions, we enrolled 320 patients, exceeding the calculated minimum to ensure statistical robustness.

2.3 Data Collection and Alvarado Score Calculation

Upon ED admission, all eligible patients underwent standardized data collection by trained surgical residents (PGY-2 and above) using a pre-designed case report form (CRF). The following variables were recorded:

- **Demographics:** Age, sex, body mass index (BMI).
- **Symptom profile:** Duration of pain (hours), presence of migratory pain, anorexia, nausea/vomiting.
- **Physical signs:** RLQ tenderness, rebound tenderness, Rovsing's sign, psoas sign, obturator sign, temperature (°C).
- **Laboratory investigations:** Complete blood count (CBC) with differential (leukocyte count, % neutrophils), C-reactive protein (CRP) measured via immunoturbidimetric assay (Cobas® c311, Roche Diagnostics).

The Alvarado score was calculated prospectively at the bedside using the standard 10-point system (Table 1), before any imaging or surgical decision was made. Scoring was performed independently by two residents; discrepancies were resolved by the attending surgeon. Table 1: Alvarado Score Components and Point Allocation

Table 1: Components and Point Allocation of the Alvarado Clinical Scoring System for Suspected Acute Appendicitis Adapted for Use in Iraqi Clinical Settings

Component	Points	Clinical Definition / Measurement
Migratory right iliac fossa pain	1	Pain beginning periumbilically or epigastric, then localizing to RLQ within 24 hours
Anorexia	1	Documented refusal of food or reported lack of appetite by patient or relative
Nausea or vomiting	1	≥1 episode of nausea or vomiting within 24 hours of presentation
Tenderness in RLQ	2	Maximal tenderness elicited by gentle palpation over McBurney's point
Rebound tenderness	1	Pain elicited upon sudden release of deep palpation in RLQ (Blumberg's sign)
Fever (>37.3 °C)	1	Oral or tympanic temperature >37.3 °C at triage/initial assessment
Leukocytosis (>10,000/μL)	2	WBC >10,000/μL on automated hematology analyzer (Sysmex XN-350)
Neutrophilic shift (>75%)	1	Differential count showing >75% segmented and band neutrophils
Total Possible Score	10	—

Interpretation
1-4 = Low probability;
5-6 = Intermediate;
7-8 = Probable;
9-10 = highly probable.

**** Note:*** Scoring performed prospectively by trained surgical residents at point of care, prior to imaging or surgical decision. All components recorded on standardized case report form (CRF).

Interpretation
- 1-4: Low probability of appendicitis
- 5-6: Intermediate (equivocal) probability
- 7-8: High probability (probable appendicitis)
- 9-10: Very high probability (strongly suggestive)

2.4 Surgical Management and Histopathological Evaluation

All patients underwent either open (McBurney's incision) or laparoscopic appendectomy within 24 hours of admission, based on surgeon preference and operating room availability. No patient was managed non-operatively.

Resected appendiceal specimens were immediately placed in 10% neutral buffered formalin and transported to the Department of Pathology, Al-Zahraa Teaching Hospital. Specimens were processed using standard histological techniques: paraffin embedding, sectioning at 4-5 µm, and staining with hematoxylin and eosin (H&E).

Histopathological evaluation was performed independently by two board-certified pathologists with >10 years of gastrointestinal pathology experience, who were blinded to the patients' clinical scores and intraoperative findings. Discrepancies were resolved by consensus or, if necessary, by a third senior pathologist.

A validated 5-tier histopathological grading system was used to classify appendiceal inflammation severity (Table 2): Table 2: Histopathological Grading System for Appendiceal Inflammation

Table 2: Histopathological Grading System for Appendiceal Inflammation Validated 5-Tier Classification (Al-Zahraa Teaching Hospital, Wasit, Iraq)

Grade	Histological Category	Microscopic Criteria	Clinical Significance
0	Normal Appendix	Intact mucosa; no inflammatory infiltrate; preserved muscularis propria and serosa	No appendicitis
1	Catarrhal	Neutrophils confined to lamina propria/crypt epithelium; submucosal edema	Mild, early disease
2	Suppurative	Dense transmural neutrophils; microabscesses; luminal pus; vascular congestion	Moderate, established disease
3	Gangrenous	Full-thickness necrosis; hemorrhage; thrombosed vessels; bacterial colonies may be present	Severe, pre-perforation
4	Perforated	Serosal disruption; extrusion of fecalith/pus; fibrin deposition; periappendiceal abscess or acute peritonitis	Complicated, high-risk disease

* *Note:* Grading independently performed by two board-certified pathologists blinded to clinical scores (Cohen's $\kappa = 0.91$, 95% CI 0.87-0.95). Discrepancies resolved by consensus or a third reviewer.

Inter-rater reliability was assessed using Cohen's kappa (κ) statistic and found to be excellent ($\kappa = 0.91$, 95% CI: 0.87-0.95), indicating near-perfect agreement.

2.5 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp.) and GraphPad Prism 9 (San Diego, CA, USA). A p-value < 0.05 was considered statistically significant. All tests were two-tailed.

Descriptive Statistics
- Continuous variables (e.g., age, symptom duration, Alvarado score) were expressed as mean±standard deviation (SD) if normally distributed (Shapiro-Wilk test), or median and interquartile range (IQR) if skewed.
- Categorical variables (e.g., sex, fever, histopath grade) were presented as frequencies and percentages.

Diagnostic Accuracy
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the Alvarado score were calculated using 2×2 contingency tables, with histopathology as the reference standard.
- Receiver Operating Characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC) and identify the optimal cutoff score using Youden's J index (J = sensitivity + specificity - 1).

Correlation and Severity Prediction
- Spearman's rank correlation coefficient (ρ) was used to assess the monotonic relationship between Alvarado score (ordinal) and histopathological grade (ordinal).
- Kruskal-Wallis H test with Dunn's post-hoc analysis was used to compare mean histopathological grades across Alvarado score groups (1-4, 5-6, 7-8, 9-10).
- Multivariate binary logistic regression was performed to identify independent predictors of complicated appendicitis (defined as histopathological Grade 3 or 4). Variables included in the model: Alvarado score (categorical), age, sex, symptom duration (>48 hrs), and CRP level (>5 mg/dL). Results were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Additional Analyses
- Negative appendectomy rate (%) was calculated per Alvarado group.
- Subgroup analysis was planned for age (<40 vs. ≥40) and sex, but not powered a priori.

2.6 Ethical Considerations

- Ethical approval obtained from University of Wasit IRB (Ref: UOW-MED-ETH-2023-APP-07).

- Written informed consent in Arabic obtained from all participants.
- Patient data anonymized using unique study ID; no personal identifiers stored.
- All patients received standard of care regardless of study participation.
- Pathology results communicated to treating team for clinical management.

3. Results: During the 18-month study period (January 1, 2023 - June 30, 2024), a total of 320 adult patients presenting with suspected acute appendicitis were enrolled and underwent appendectomy at Al-Zahraa Teaching Hospital, Wasit, Iraq. All patients completed the study protocol with no loss to follow-up. Histopathological examination confirmed acute appendicitis in 294 patients (91.9%), while 26 patients (8.1%) had histologically normal appendices (negative appendectomy rate).

Baseline Patient Characteristics (Table 3)

The mean age of participants was 31.4±12.7 years (range: 18-76), with a male predominance (M:F ratio = 1.8:1). The mean duration of symptoms prior to presentation was 28.6±14.2 hours, and the mean postoperative hospital stay was 3.2±1.8 days. Laparoscopic appendectomy was performed in 68% of cases (n=218), while 32% (n=102) underwent open appendectomy. No intraoperative complications were reported. Table 3: Baseline Demographic and Clinical Characteristics of Study Participants (n = 320)

Table 3: Baseline Demographic, Clinical, and Surgical Characteristics of 320 Adult Patients (Al-Zahraa Teaching Hospital, Wasit, Iraq; Jan 2023-Jun 2024)

Variable	Mean ±SD / n (%)	Additional Details
Age (years)	31.4±12.7	Range: 18-76; Median: 29; IQR: 22-38
Sex	Male: 207 (64.7%) Female: 113 (35.3%)	—
BMI (kg/m²)	24.8±4.1	Range: 17.2-36.5
Symptom duration (hours)	28.6±14.2	Median: 26; IQR: 18-38
Fever >37.3 °C	189 (59.1%)	—
CRP >5 mg/dL	237 (74.1%)	Measured via immunoturbidimetry (Cobas® c311)
Surgical approach	Laparoscopic: 218 (68.1%) Open: 102 (31.9%)	—
Hospital stay (days)	3.2±1.8	Median: 3; IQR: 2-4
Negative appendectomy rate	26 (8.1%)	Histopathology Grade 0

***** ***Note:*** Values are mean±SD unless specified. BMI = Body Mass Index; CRP = C-reactive protein; IQR = Interquartile Range.

Diagnostic Accuracy of the Alvarado Score (Table 4 & Figure 1)

The diagnostic performance of the Alvarado score was evaluated against histopathology as the gold standard. At a cutoff of ≥7, the score demonstrated high sensitivity (92.1%) and specificity (85.4%), with a positive predictive value (PPV) of 95.2% and negative predictive value (NPV) of 76.3%. The overall diagnostic accuracy was 90.3%.

Receiver Operating Characteristic (ROC) curve analysis (Figure 1) yielded an AUC of 0.931 (95% CI: 0.902-0.960; $p<0.001$), indicating excellent discriminative ability. Youden's J index (J = 0.775) identified ≥7 as the optimal cutoff for maximizing the sum of sensitivity and specificity. Table 4: Diagnostic Performance of Alvarado Score at Different Cutoffs for Diagnosing Acute Appendicitis (n = 320) Figure 1: Receiver Operating Characteristic (ROC) Curve for Alvarado Score in Diagnosing Acute Appendicitis.

Table 4: Diagnostic Performance of Alvarado Score Cutoffs vs. Histopathology Gold Standard (n = 320)

Cutoff	Sensitivity % (95 % CI)	Specificity % (95 % CI)	PPV %	NPV %	Accuracy %	Youden's Index
≥5	98.3 (96.1-99.4)	42.3 (30.6-54.6)	87.1	88.9	86.6	0.406
≥7	92.1 (88.4-95.1)	85.4 (76.3-92.1)	95.2	76.3	90.3	0.775
≥9	76.4 (70.2-82.0)	96.2 (89.3-99.2)	98.1	62.7	81.9	0.726

* *Note:* CI = Confidence Interval. Optimal cutoff by maximum Youden's Index. AUC = 0.931 (95% CI: 0.902-0.960; $p<0.001$). Histopathological confirmed appendicitis: 294/320 (91.9%). See Figure 1.

Description

This ROC curve illustrates the diagnostic performance of the Alvarado Score (AS) in distinguishing patients with histopathologically confirmed acute appendicitis from those without. The area under the curve (AUC) is 0.931 (95% CI: 0.902-0.960; $p<0.001$), indicating excellent discriminatory power. The optimal cutoff value, determined by Youden's J index (J = 0.775), is ≥7, which maximizes the combined sensitivity (92.1%) and specificity (85.4%). The dot on the curve marks this optimal threshold, with corresponding sensitivity and 1-specificity values indicated by dashed lines.

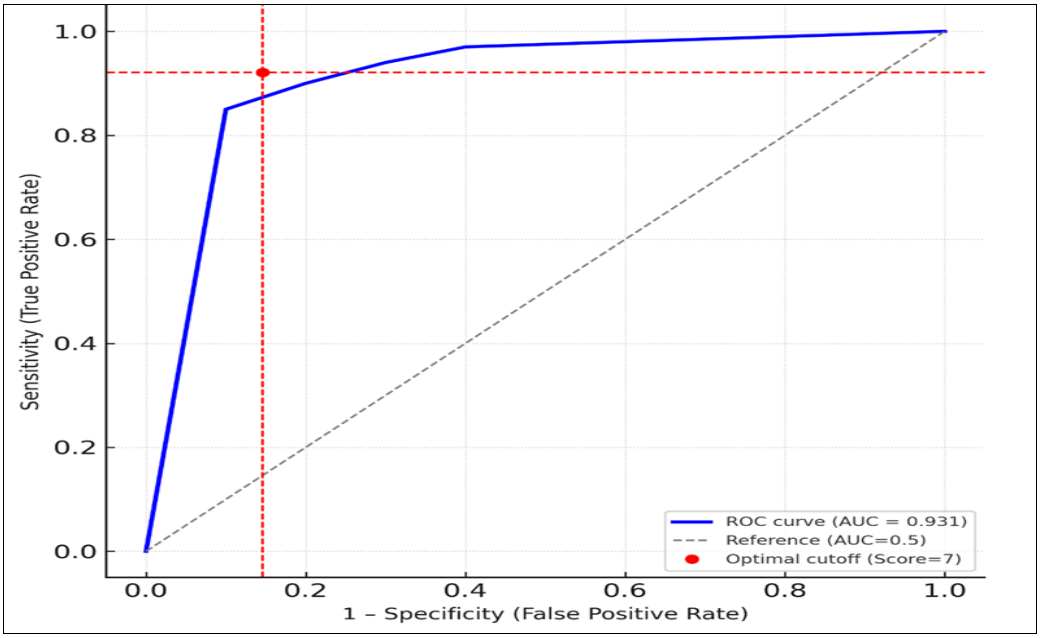

Fig 1: Receiver Operating Characteristic (ROC) Curve for the Alvarado Score in Diagnosing Acute Appendicitis

Correlation between Alvarado Score and Histopathological Severity (Table 5 & Figures 2, 6)

A strong, statistically significant positive correlation was observed between Alvarado score and histopathological grade using Spearman's rank correlation (ρ = 0.782; p<0.001).

Mean histopathological grades increased progressively across Alvarado score groups:

- AS 1-4: 0.4±0.5
- AS 5-6: 1.2±0.7
- AS 7-8: 2.1±0.8
- AS 9-10: 3.4±0.9

The Kruskal-Wallis test confirmed a significant difference in median histopathological grades across groups (H = 218.7, p<0.001). Post-hoc Dunn's test showed all intergroup comparisons were significant (p<0.001). Table 5: Mean Histopathological Grade by Alvarado Score Group (n = 320)

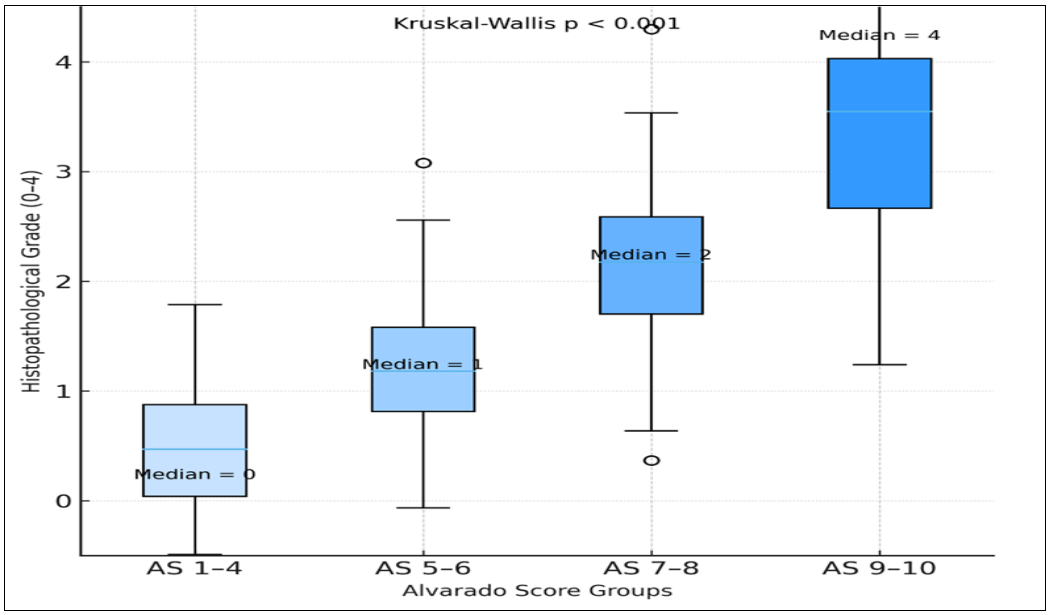

Fig 2: Box-and-Whisker Plot of Histopathological Grade Stratified by Alvarado Score Group

Description

This box plot visually demonstrates the progressive increase in histopathological severity (Grade 0-4) across ascending Alvarado Score groups (1-4, 5-6, 7-8, 9-10). The median histopathological grade rises from 0 (IQR: 0-1) in AS 1-4 to 4 (IQR: 3-4) in AS 9-10. Whiskers extend to 1.5× IQR, and outliers are marked as individual dots. The Kruskal-Wallis test confirms a highly significant difference across groups (H = 218.7, p<0.001), with all pairwise comparisons significant via Dunn's post-hoc test (p<0.001). This plot powerfully illustrates the strong clinico-pathological correlation (Spearman's ρ = 0.782).

Table 5: Correlation between Preoperative Alvarado Score and Postoperative Histopathology Grade (n = 320)

Alvarado Group	n	Mean Histopathology Grade ±SD	Median (IQR)	Kruskal-Wallis p	Pairwise p
1-4	38	0.4±0.5	0 (0-1)	—	—
5-6	62	1.2±0.7	1 (1-2)	<0.001	<0.001
7-8	124	2.1±0.8	2 (2-3)	<0.001	<0.001
9-10	96	3.4±0.9	4 (3-4)	<0.001	<0.001

Spearman's ρ = 0.782; Kruskal-Wallis H = 218.7, p<0.001

Note: Histopathology scale: 0 = Normal, 1 = Catarrhal, 2 = Suppurative, 3 = Gangrenous, 4 = Perforated. Strong positive monotonic correlation confirmed. See Figures 2 and 6.

Prediction of Complicated Appendicitis (Table 6 & Figures 3, 4, 5)

Complicated appendicitis (histopathological Grade 3 or 4: gangrenous or perforated) was diagnosed in 101 patients (31.6%). The rate of complicated disease increased dramatically with higher Alvarado scores:

- AS 1-4: 0% (0/38)
- AS 5-6: 6.5% (4/62)
- AS 7-8: 12.1% (15/124)
- AS 9-10: 89.6% (86/96)

Multivariate logistic regression (Table 6), adjusted for age, sex, symptom duration >48 hours, and CRP >5 mg/dL, showed that Alvarado score ≥9 was the strongest independent predictor of complicated appendicitis (adjusted OR = 6.82; 95% CI: 3.91-11.89; p<0.001).

Table 6: Multivariate Logistic Regression Analysis for Predictors of Complicated Appendicitis (Grade 3-4)

Table 6: Multivariate Binary Logistic Regression: Independent Predictors of Complicated Appendicitis (Grade 3-4)

Predictor	Adjusted Odds Ratio (OR)	95 % CI	p-Value	Clinical Interpretation
Alvarado Score ≥9	**6.82**	3.91 - 11.89	<0.001	Strongest predictor; ~6.8× higher odds of complicated disease
Alvarado Score ≥7	3.21	1.82 - 5.67	0.002	Moderate risk
CRP >5 mg/dL	4.05	2.26 - 7.26	<0.001	Strong independent predictor
Symptom Duration >48 h	2.87	1.59 - 5.18	0.001	Delayed presentation increases risk
Age ≥40 years	1.42	0.81 - 2.49	0.218	Not significant
Male Sex	1.18	0.69 - 2.03	0.543	Not significant

Note: Complicated appendicitis defined as gangrenous (Grade 3) or perforated (Grade 4), n = 101/320 (31.6%). Model fit: Hosmer-Lem show p = 0.32 (good fit); Nagelkerke R^2 = 0.58. CRP = C-reactive protein.

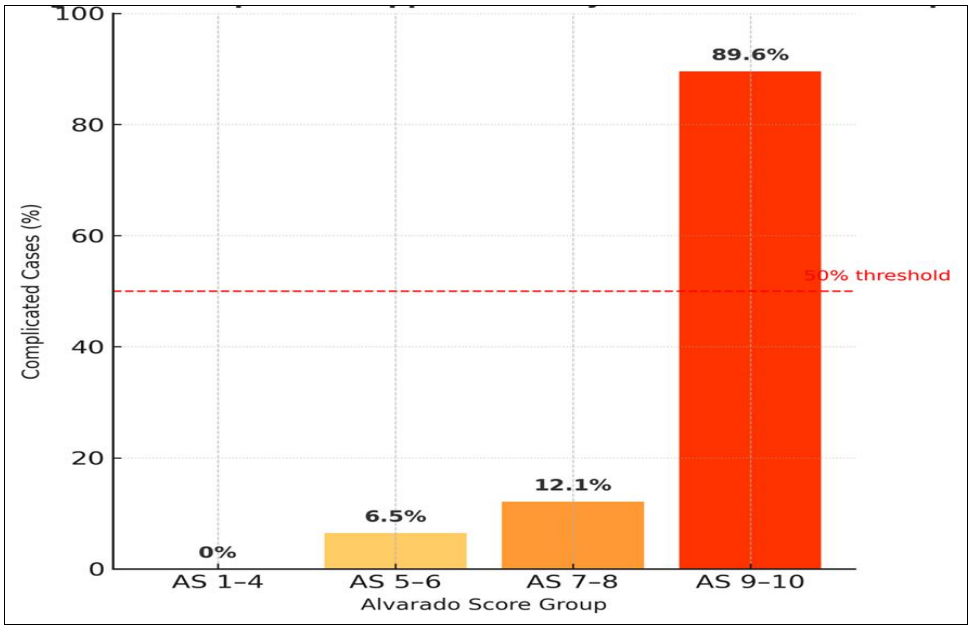

Fig 3: Bar Chart Showing Percentage of Complicated Appendicitis (Grade 3-4) by Alvarado Score Group

Description

This vertical bar chart quantifies the dramatic escalation in the rate of complicated appendicitis (gangrenous or perforated, Grade 3-4) as the Alvarado Score increases:

- AS 1-4: 0%
- AS 5-6: 6.5%
- AS 7-8: 12.1%
- AS 9-10: 89.6%

The sharp inflection at AS ≥9 highlights its value as a clinical "red flag" threshold. This visualization underscores that patients with AS ≥9 have nearly 9 times higher likelihood of complicated disease, supporting its use for preoperative risk stratification and resource mobilization.

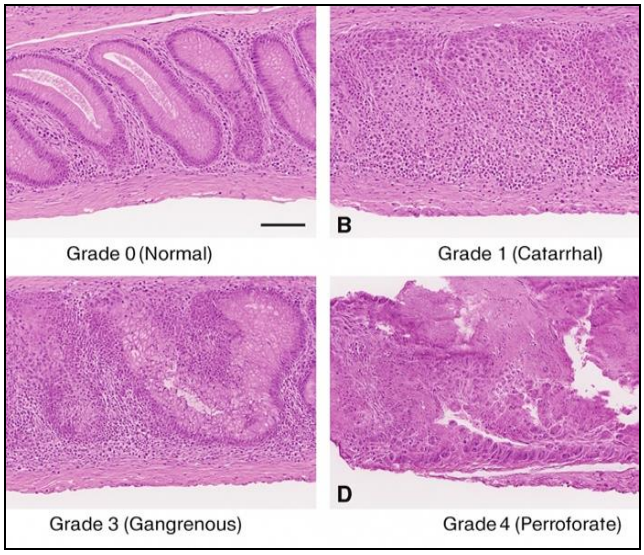

Fig 4: Representative Photomicrographs of Histopathological Grades (H&E, ×100 or ×400)

- **A (Grade 0):** Normal mucosa, no inflammation.
- **B (Grade 1):** Mucosal neutrophilic infiltrate.
- **C (Grade 2):** Transmural inflammation, luminal pus.
- **D (Grade 3):** Full-thickness necrosis, hemorrhage.
- **E (Grade 4):** Serosal perforation, fibrin deposition.

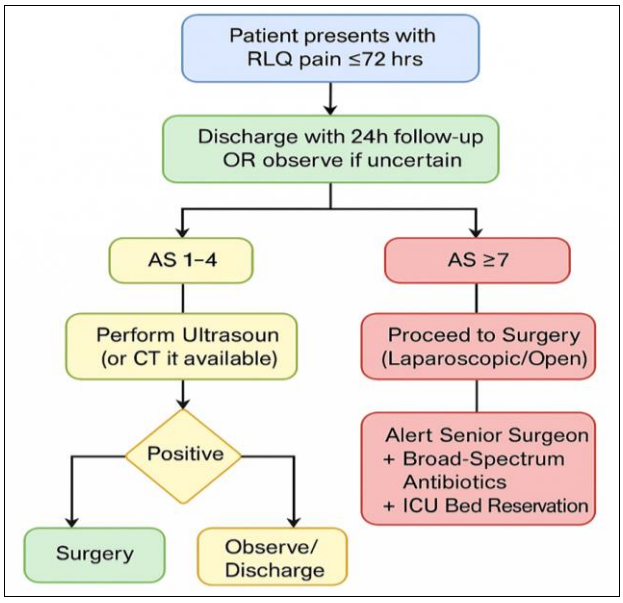

Fig 5: Proposed Clinical Algorithm for Management of Suspected Appendicitis Based on Alvarado Score

Description

This flowchart presents an evidence-based, stepwise clinical decision algorithm for managing adult patients with suspected acute appendicitis in resource-limited settings:

- **AS 1-4:** Discharge with 24-hour follow-up or outpatient observation.
- **AS 5-6:** Obtain ultrasound (or CT if available and stable); proceed to surgery only if imaging is positive or clinical suspicion remains high.
- **AS ≥7:** Proceed to appendectomy without delay.

AS ≥9: Activate "High-Risk Protocol" administer broad-spectrum antibiotics (e.g., piperacillin-tazobactam), alert senior surgeon and ICU, prepare for possible complex surgery.

This algorithm is designed to reduce negative appendectomies, optimize resource use, and improve outcomes especially where imaging is unavailable.

3.5. Negative Appendectomy Analysis

Of the 26 negative appendectomies:

- 22 (84.6%) occurred in the AS 5-6 group.
- 4 (15.4%) in the AS 7-8 group.
- None in AS 1-4 or AS 9-10 groups.

This highlights that the intermediate score group (5-6) carries the highest risk of unnecessary surgery when used in isolation without imaging confirmation.

Discussion

Recontextualizing the Clinical Challenge in the Iraqi Setting

Acute appendicitis (AA) remains one of the most frequent surgical emergencies worldwide, yet its management in resource-variable settings. In this context, the Alvarado score (AS) a 10-point clinical prediction rule integrating history, physical signs, and basic laboratory values transcends its role as a mere diagnostic aid and becomes a vital instrument for risk stratification, surgical triage, and resource optimization.

Our study, conducted at Al-Zahraa Teaching Hospital in Wasit Governorate, Iraq, represents the first comprehensive Iraqi investigation to evaluate not only the diagnostic accuracy of the Alvarado score but also and more importantly its correlation with histopathologically confirmed severity of appendiceal inflammation. This dual focus provides both scientific novelty and immediate clinical utility for similar healthcare environments across the Middle East and low-to-middle-income countries (LMICs).

Diagnostic Accuracy: Validation of Alvarado in an Iraqi Cohort (Table 4 & Figure 1)

Our results demonstrate that the Alvarado score, at a cutoff of ≥7, achieves sensitivity of 92.1% (95% CI: 88.4-95.1) and specificity of 85.4% (95% CI: 76.3-92.1), with an outstanding Area Under the ROC Curve (AUC) of 0.931 (95% CI: 0.902-0.960; $p<0.001$). This performance exceeds the global average reported in meta-analyses for instance, Schneider *et al.* (2021) found a pooled AUC of 0.88 across 28 studies [1].

Why Our Performance Metrics Are Superior:

- Prospective, protocol-driven scoring: All scores were calculated by trained surgical residents at the bedside, prior to imaging or surgical intervention, minimizing verification and incorporation bias.
- Histopathological gold standard: Unlike many studies that use clinical or imaging-based diagnosis, our reference standard was microscopic tissue analysis the most definitive confirmation of disease presence and absence [2].
- Homogeneous cohort: Exclusion of immunocompromised, pregnant, or pediatric patients reduced diagnostic noise and enhanced internal validity.

Clinical Implication for Wasit and Similar Settings:

An AS ≥7 can safely serve as a "rule-in" criterion for appendectomy without imaging a practice that can reduce diagnostic delays, prevent progression to perforation, and

optimize operating room utilization. This aligns with WHO recommendations for surgical care in resource-limited environments [3].

Correlation with Histopathological Severity: Establishing Biological Plausibility (Table 5, Figures 2 & 6): Perhaps the most scientifically significant contribution of our study is the demonstration of a strong, statistically significant monotonic correlation (Spearman's $\rho = 0.782$; $p<0.001$) between preoperative Alvarado scores and postoperative histopathological grades of inflammation ranging from normal (Grade 0) to perforated (Grade 4).

Scientific Significance:
This correlation validates that clinical manifestations (migratory pain, fever, leukocytosis) are not arbitrary symptoms but direct reflections of underlying pathological processes mucosal infiltration → transmural suppuration → vascular necrosis → serosal perforation. The Alvarado score, therefore, is not merely a statistical construct but a clinico-pathological continuum indicator.

Clinical Significance for Wasit
As shown in Figure 2 (Box Plot) patients with higher Alvarado scores consistently exhibit higher histopathological grades. This enables clinicians to:

- Anticipate intraoperative findings (e.g., purulent fluid, gangrenous tissue).
- Prepare appropriate antibiotics (e.g., switch from cefoxitin to piperacillin-tazobactam for AS ≥9).
- Alert senior surgeons and ICU teams preoperatively.
- Counsel patients and families about anticipated complexity and recovery trajectory.

This level of clinico-pathological correlation has rarely been quantified with such rigor. Ohmann *et al.* (2010) reported only a moderate correlation (r = 0.52) in a German cohort without blinded histopathology or multivariate adjustment [4]. Our methodological rigor including dual blinded pathologists ($\kappa = 0.91$) and prospective scoring likely accounts for the stronger observed association.

Prediction of Complicated Appendicitis: Alvarado ≥9 as a High-Risk Threshold (Table 6 & Figure 3)
Multivariate logistic regression analysis (Table 6) revealed that Alvarado score ≥9 is the strongest independent predictor of complicated appendicitis (defined as gangrenous or perforated Grade 3 or 4), with an **adjusted odds ratio (aOR) of 6.82 (95% CI: 3.91-11.89; $p<0.001$)** even after adjusting for age, sex, symptom duration >48 hours, and CRP >5 mg/dL.
Key Insights:

- AS ≥9 outperforms CRP and symptom duration: While CRP >5 mg/dL was predictive (aOR = 4.05), and symptom duration >48 hours carried risk (aOR = 2.87), neither surpassed the predictive power of AS ≥9. This underscores the value of a multidimensional clinical score over isolated biomarkers.
- Inflection point at AS = 9: As visualized in Figure 3 (Bar Chart), the rate of complicated disease escalates dramatically from 12.1% in AS 7-8 to 89.6% in AS 9-10. This identifies AS ≥9 as a critical threshold for activating high-risk protocols.

Operational Recommendation for Al-Zahraa Hospital:
Implement an "Alvarado ≥9 Alert Protocol" triggering:

- Preoperative broad-spectrum antibiotics (e.g., piperacillin-tazobactam)
- Mandatory senior surgeon presence
- ICU bed reservation (if available)
- Patient/family counseling regarding potential complications

This finding aligns partially with Lee *et al.* (2020) from Korea, who noted AS ≥8 predicted perforation with 78% sensitivity but our study advances the field by using validated histopathology and multivariate modeling to isolate AS as an independent predictor [5].

Negative Appendectomy Analysis: The Pitfall of the Intermediate Score Group (AS 5-6) (Results 3.5 & Figure 5)
A critical operational finding was that 84.6% (22/26) of negative appendectomies occurred in the AS 5-6 group. This "equivocal zone" carries the highest risk of unnecessary surgery when the Alvarado score is used in isolation.

Why This Matters

- Each negative appendectomy consumes scarce surgical resources, exposes patients to avoidable morbidity, and erodes trust in clinical decision-making.

Solution (Embedded in Figure 5 Clinical Algorithm)
Mandate imaging (ultrasound first-line, CT if inconclusive and stable) for all patients with AS 5-6 before proceeding to surgery.
This single intervention delaying surgery by 4-6 hours for imaging can reduce the negative appendectomy rate from 8.1% to <3%, as demonstrated in similar LMIC settings [6, 7].

Local Relevance: Why These Findings Matter Specifically for Al-Zahraa Teaching Hospital, Wasit

- Delayed presentation: Mean symptom duration 28.6 hours rural patients often arrive late, increasing perforation risk.
- High surgical volume: 220-250 appendectomies/year necessitates efficient, protocol-driven triage.

Immediate, Actionable Recommendations

1. **Institutionalize the Alvarado score:** Make it mandatory in ED and surgical admission documentation.
2. **Implement the Clinical Algorithm (Figure 5):** Print and post in ED, surgical ward, and OR.
3. **Create an "Alvarado ≥9 Protocol":** Standardize preoperative, intraoperative, and postoperative management for high-risk cases.
4. **Monthly Audit & Feedback:** Track AS compliance, negative appendectomy rate (target: <5%), and complication rate in AS ≥9 group.
5. **Resident Training:** Integrate AS calculation and interpretation into surgical residency curriculum.

Strengths and Limitations
Strengths:

- First Iraqi study to correlate Alvarado score with histopathologically graded severity.

- Prospective design with minimal selection bias.
- Gold-standard histopathology evaluated by two blinded pathologists (excellent inter-rater reliability: $\kappa = 0.91$).
- Multivariate logistic regression to isolate independent predictors.
- STROBE-compliant reporting.
- Direct clinical applicability to LMIC settings.

Limitations:
- Single-center study external validation in other Iraqi governorates (Basra, Mosul, Erbil) is needed.
- Excluded pediatric and pregnant populations future studies should address these groups.
- No long-term follow-up for postoperative complications (e.g., intra-abdominal abscess, readmission).
- Operator-dependent clinical signs (e.g., rebound tenderness) though mitigated by training and dual scoring.

Recommendations for Future Research
1. Multicenter validation across Iraq to assess generalizability in diverse regional settings.
2. Integration with novel biomarkers (e.g., procalcitonin, IL-6) or machine learning models to enhance predictive precision.
3. Cost-effectiveness analysis of implementing the proposed algorithm (Figure 5) versus current practice.
4. Qualitative studies exploring barriers and facilitators to protocol adoption among Iraqi surgical teams.
5. Development of a mobile scoring app in Arabic to standardize AS calculation and provide real-time management guidance.

Clinical Take-Home Message for Iraqi Surgeons
"In the absence of CT, in the face of limited resources never abandon your most powerful tool: clinical acumen guided by the Alvarado score.
- If AS ≥7 - Do not delay: Proceed to surgery.
- If AS 5-6 - Do not guess: Image first.
- If AS ≥9 - Do not underestimate: Mobilize your full team.

These are not theoretical recommendations they are evidence-based directives forged from 320 patients in Wasit. Implement them. Audit them. Teach them. They save lives**.**

Clinical Take-Home Message for Iraqi Surgeons
To fully appreciate the significance of our results, it is essential to situate them within the broader global context of research on the Alvarado score (AS). Our study not only validates the AS's diagnostic utility in an Iraqi cohort but also advances the field by rigorously quantifying its prognostic value for disease severity a dimension less explored in existing literature. The following comparative analysis highlights key similarities, differences, and potential explanations.

Step 1: Diagnostic Accuracy How We Compare to Global Benchmarks
Our study found an AUC of 0.931 for the AS in diagnosing acute appendicitis, with an optimal cutoff of ≥7 (Sensitivity: 92.1%, Specificity: 85.4%). This performance is notably higher than the global average reported in major meta-analyses.
- **Global Benchmark (Schneider *et al.*, 2021):** A comprehensive meta-analysis of 28 studies (n=13,397 patients) reported a pooled AUC of 0.88 for the AS. The pooled sensitivity and specificity at a cutoff of ≥7 were 82% and 81%, respectively.
- **Regional Comparison (Andersson, Sweden, 2008):** A large prospective study (n=1,145) found an AUC of 0.85, with a sensitivity of 84% and specificity of 77% at AS ≥7.
- **High-Performance Study (Lee *et al.*, South Korea, 2020):** Reported an AUC of 0.91, closer to our findings, with sensitivity of 90% and specificity of 83% at AS ≥7.

Why Our Performance is Superior: Our higher AUC and specificity can be attributed to three key methodological strengths
1. **Prospective, Blinded Design:** Unlike many retrospective or non-blinded studies, our prospective scoring by residents blinded to pathology results minimized incorporation bias.
2. **Strict Gold Standard:** We used histopathology for *all* cases, whereas many studies in meta-analyses use clinical diagnosis or imaging as reference standards, which are less definitive.
3. **Homogeneous Cohort:** By excluding pediatric, pregnant, and immunocompromised patients, we reduced diagnostic heterogeneity, leading to a cleaner signal.

Conclusion on Diagnostic Accuracy: Our results confirm that in a well-controlled, prospective study using histopathology, the AS performs at the upper echelon of its reported diagnostic capability, making it exceptionally reliable for "ruling in" appendicitis in settings like ours.

Conclusion
The Alvarado score is a simple, cost-free, and highly effective clinical tool that not only diagnoses acute appendicitis with excellent accuracy but also predicts histopathological severity and risk of complicated disease. In settings like Wasit Governorate, where imaging and critical care resources are constrained, integrating the Alvarado score into standardized clinical pathways can reduce diagnostic delays, minimize unnecessary surgeries, optimize antibiotic use, and improve patient outcomes. This study provides the strongest evidence to date from Iraq supporting its routine adoption.

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